First-episode affective psychoses: exploring specific clinical features in order to adapt early intervention strategies

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First-episode affective psychoses: exploring specific clinical features in order to adapt early intervention strategies

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Prof. Clarisse Dromain

« C'est une maladie naturelle à l'homme que de croire qu'il possède la vérité. »

- Blaise Pascal -

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Thesis abstract (English)

Backgroung: Affective psychosis is a conceptual grouping used in clinical practice that lacks strong scientific basis. It includes patients who, in addition to psychosis, have a mood disorder. While early intervention has shown great efficacy, it mainly focuses on schizophrenia spectrum disorders, neglecting the affective forms of psychosis. Thus, this PhD thesis aims to study the relevance of the concept of affective psychosis in early intervention and its usefulness in developing stratification strategies. **Method:** These aims are addressed in two ways through four chapters, first through a literature review and then in the frame of three prospective studies conducted in a sample a first episode psychosis patients treated at the Treatment and early intervention in psychosis programme (TIPP) in Lausanne (Switzerland). The first chapter investigates literature on first-episode affective psychoses, outlining its specific clinical features and challenges. The second chapter explores the differences between affective and non-affective psychosis patients. The third chapter explores to which degree the various diagnostic categories included in the affective psychosis subgroup have sufficient commonalities to justify this grouping. Finally, the fourth chapter explores premorbid-based stratification strategies within affective psychoses to identify subgroups of patients that may require specific early intervention strategies. **Results:** Studies 1, 2, and 3 confirm the relevance of using the conceptual grouping of affective psychoses. Study 4 shows that the concept of affective psychoses regroups patients with various premorbid profiles that may require specific pharmacological and psychosocial treatment adjustment. **Conclusion:** This PhD thesis provides further evidence for the need of developing research in early intervention using the concept of affective psychosis, and points out clinical characteristics that may be used as therapeutic targets to develop adapted early intervention strategies for these patients.

Thesis abstract (French)

Contexte : Le terme psychose affective désigne un concept utilisé dans la pratique clinique mais qui manque d'une base scientifique solide. Ce concept regroupe des patients qui ont une psychose et une perturbation de l'humeur. Bien que l'intervention précoce ait démontré une grande efficacité, celle-ci s'est focalisée sur les troubles du spectre schizophrénique, négligeant les formes affectives. Cette thèse de doctorat a donc pour objectifs d'étudier l'intérêt du concept de psychose affective dans l'intervention précoce et son utilité pour développer des stratégies de stratification. **Méthode :** Ces objectifs sont adressés de deux manières à travers 4 chapitres, premièrement à travers une revue de littérature, ensuite dans le cadre de trois études prospectives conduites dans un échantillon de patients 1er épisode traités au programme de traitement et intervention précoce dans la psychose (TIPP) à Lausanne (Suisse). Le 1er chapitre investigue la littérature scientifique sur le 1er épisode de psychose affective, ses caractéristiques cliniques et enjeux. Le 2ème explore les différences entre les patients avec une psychose affective ou non-affective. Le 3ème explore à quel degrés les catégories diagnostiques variées inclues dans le sous-groupe de psychose affective ont suffisamment de points commun pour justifier ce regroupement. Enfin, le 4ème explore des stratégies de stratification au sein des psychoses affectives sur la base des facteurs prémorbides pour identifier des sous-groupes de patients pouvant nécessiter des stratégies d'intervention précoce spécifiques. **Résultats :** Les études 1, 2 et 3 confirment la pertinence d'utiliser le concept de psychoses affectives. L'étude 4 a montré que le concept de psychoses affectives permet d'identifier des profils prémorbides variés de patients pouvant bénéficier d'ajustements spécifiques de traitement. **Conclusion :** Cette thèse a mis en évidence la nécessité de développer des recherches sur l'intervention précoce utilisant le concept de psychose affective et a mis en lumière des indices cliniques pouvant faire l'objet de cibles thérapeutiques afin de développer des stratégies d'intervention précoce adaptées pour ces patients.

1. Introduction

Affective psychoses challenge the classical categorical diagnostic classification considering the overlap between psychotic and mood disorders. Early intervention strategies also challenge categorical classifications based on prototypical forms of disorders identifiable in chronic states. Such identification issues are thus particularly problematic when it comes to the early phase of affective psychoses. Therefore, early interventions strategies have widely been developed within a dimensional perspective that tend to include larger spectrums of disorders. However, these early intervention programmes are based on the rationale of adapted and personalized intervention strategies further highlighting the usefulness of identifying subgroups of patients with specific needs. This PhD thesis addresses four main questions: First, does the literature suggest that these patients have specific needs and outcome; second, are patients with affective psychosis significantly different from patients with non-affective psychosis on the basis of premorbid and clinical features; third, is this group composed of diagnoses that have sufficient commonalities to make such conceptual grouping relevant; and fourth, can we use the affective psychosis concept to develop stratification strategies on the basis of premorbid characteristics.

In this introduction, we present the concepts of (1) affective psychoses, (2) early intervention, (3) first-episode affective psychoses and its identification issues, followed by (4) the aims of the PhD project. We then report the results of the studies addressing these aims in four chapters: (1) A narrative review of intervention in first-episode affective psychoses; (2) Exploring the clinical relevance of a dichotomy between affective and non-affective psychosis: Results from a first-episode psychosis cohort study; (3) Affective psychoses as a conceptual grouping in early psychosis: homogenous or heteronomous clinical features?; (4) Subtyping based on premorbid profile: A strategy to personalize treatment in first-episode affective psychosis.

Finally, we discuss the findings considering strengths and limitations of these studies, and suggest future developments.

1.1. *The concept of affective psychosis*

Individual with affective psychoses are the target population of this project, and more precisely the early phase of their illness. The objective of this section is to introduce: 1) the concept of affective psychosis from its early definition to its current use; 2) the specific challenges of early intervention associated with this clinical entity; and 3) to what extent this project addresses important and original nosological issues that are relevant in clinical practice.

The affective and non-affective psychosis dichotomy emerged with Kraepelin (Chia et al., 2019; Kraepelin, 1903) to clinically differentiate schizophrenia (*dementia praecox*) and psychotic mood disorders (*manic-depressive insanity*). Indeed, the *dementia praecox* category gathered paranoid, catatonic and hebephrenic syndromes described as expressing dull mood and apathy, while the *manic-depressive insanity* category included bipolar disorder and recurrent depressive disorders, major clinical forms with depressive and/or manic disturbance (Kendler, 2020; Kraepelin, 1903; Reddy, 2012). Affective psychosis nowadays refers to psychotic patients who, in addition to positive psychotic symptoms, display mood syndrome, either in the form of manic or depressive syndromes, or of a combination of both (Strakowski et al., 1998). This group of psychoses includes two affective disorders, namely major depressive disorder with psychotic symptoms (MDP) and bipolar I disorder (BD) with psychotic symptoms, as well as schizoaffective disorder (SAD; Bergé et al., 2016; see table 1 for the DSM-IV diagnostic criteria that we will use in this project; Lambert, Conus, Lambert, & McGorry, 2003; Proctor, Mitford, & Paxton, 2004), a psychotic disorder with mood disturbance. Individuals with a diagnosis of affective psychosis represent a significant proportion (~30%)

of all psychotic patients (Proctor et al., 2004). However, although the concept of "affective psychosis" is applied in clinical settings and discussed in scientific publications, it currently lacks a clear and strong scientific basis (Chia et al., 2019; Conus & McGorry, 2002).

Table 1. DSM-IV criteria for the diagnoses of schizoaffective disorder, major depressive disorder with psychotic features, and bipolar disorder with psychotic features

Schizoaffective disorder	**Major depressive disorder with psychotic features**	**Bipolar disorder I or II with psychotic features**
A. An uninterrupted period of illness during which, at some time, there is either a Major Depressive Episode, a Manic Episode, or a Mixed Episode concurrent with symptoms that meet Criterion A for Schizophrenia. **Note:** The Major Depressive Episode must include Criterion A1: depressed mood.	A. Presence of at least a single Major Depressive Episode.	A. Currently (or most recently) in a Manic/Mixed/Depressive Episode. A. Presence (or history) of one or more Major Depressive Episodes
B. During the same period of illness, there have been delusions or hallucinations for at least 2 weeks in the absence of prominent mood symptoms.	B. The Major Depressive Episode is not better accounted for by Schizoaffective Disorder and is not superimposed on Schizophrenia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder Not Otherwise Specified.	B. There has previously been at least one Major Depressive Episode, Manic Episode, or Mixed Episode. B. Presence (or history) of at least one Hypomanic Episode
C. Symptoms that meet criteria for a mood episode are present for a substantial portion of the total duration of the active and residual periods of the illness.	C. There has never been a Manic Episode, a Mixed Episode, or a Hypomanic Episode. **Note:** This exclusion does not apply if all of the manic-like, mixed-like, or hypomanic-like episodes are substance or treatment induced or are due to the direct physiological effects of a general medical condition.	C. The mood episodes in Criteria A and B are not better accounted for by Schizoaffective Disorder and are not superimposed on Schizophrenia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder Not Otherwise Specified. C. There has never been a Manic Episode, or a Mixed Episode
D. The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.		D. The mood symptoms in Criteria A and B are not better accounted for by Schizoaffective Disorder and are not superimposed on Schizophrenia, Schizophreniform Disorder, Delusional Disorder, or Psychotic Disorder Not Otherwise Specified. E. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. *Specify current or most recent episode*
Specify type: **Bipolar Type:** if the disturbance includes a Manic or a Mixed Episode (or a Manic or a Mixed Episode and Major Depressive Episodes) **Depressive Type:** if the disturbance only includes Major Depressive Episodes	**Severe With Psychotic Features:** Delusions or hallucinations. If possible, specify whether the psychotic features are mood-congruent or mood-incongruent: **Mood-Congruent Psychotic Features:** Delusions or hallucinations whose content is entirely consistent with the typical depressive themes of personal inadequacy, guilt, disease, death, nihilism, or deserved punishment. **Mood-Incongruent Psychotic Features:** Delusions or hallucinations whose content does not involve typical depressive themes of personal inadequacy, guilt, disease, death, nihilism, or deserved punishment. Included are such symptoms as persecutory delusions (not directly related to depressive themes), thought insertion, thought broadcasting, and delusions of control.	**Severe With Psychotic Features:** Delusions or hallucinations. If possible, specify whether the psychotic features are mood-congruent or mood-incongruent: **Mood-Congruent Psychotic Features:** Delusions or hallucinations whose content is entirely consistent with the typical manic or depressive themes. **Mood-incongruent Psychotic Features:** Delusions or hallucinations whose content does not involve typical manic or depressive themes. Included are such symptoms as persecutory delusions (not directly related to grandiose or depressive themes), thought insertion, and delusions of being controlled.

The lack of a strong scientific basis for the concept of "affective psychosis" raises the question as to whether this is an arbitrary clinical construct defining a convenient grouping of diagnostic categories, or an evidence-based clinical entity that may be identifiable and useful to develop intervention guidelines (Borsboom, 2008). Although previous studies used this concept to investigate outcomes and even proposed some specific clinical guidelines for such patients (Aas et al., 2011; Kovasznay et al., 1997; Lambert et al., 2003; Strakowski et al., 1998), there are relatively few studies on this topic, especially in the early stage of illness. To our knowledge, only few studies have addressed the conceptual issue of the existence or not of such a clinical entity based on scientific evidence (Brockington et al., 1979; Kendell & Gourlay 1970). These two studies have tried to identify a dichotomy in psychotic patient samples but found mixed results, suggesting that there was no clear dichotomy between affective and non-affective psychoses. However, these results should be taken with caution as these studies were based on heterogeneous samples of patients admitted to hospital at different stages of illness. Furthermore, one of these studies was cross sectional and therefore did not explore the dynamic of the illness (Kendell & Gourlay, 1970), and the others included outcome variables from a follow-up assessment done at very variable time points (Brockington, Kendell, & Leff, 1978; Brockington, Kendell, Wainwright, Hillier, & Walker, 1979). This is critical, considering that longitudinal follow-up of multiple psychopathological factors seems crucial to characterize and identify the complex clinical picture of such mental disorders (Arrasate et al., 2014; Craddock & Owen, 2007). Accordingly, robust evidence to support or reject such a dichotomy would require a longitudinal and systematic assessment of psychopathology in a representative sample of patients.

Previous findings from studies addressing the nosological issues of the psychosis spectrum suggested there may be a continuum between schizophrenia and BD (Cheniaux et al., 2008; Craddock, O'Donovan, & Owen, 2009; Ivleva et al., 2010; Moller, 2003), with a large number of

patients (45% of cases) standing in the middle of this continuum, expressing mixed forms of the disorders and displaying heterogeneous clinical presentation (Cheniaux et al., 2008; Keshavan et al., 2011). While this dimensional perspective on psychotic and mood disorders enables the inclusion of mixed forms of the disorders, it fails to provide clear stratification tools and subtypes useful for clinical practice. This is particularly important considering the wide range of patients in the middle of the continuum with various clinical phenotypes. Such a dimensional perspective, though important to explore the etiopathogenesis of mental disorders, might therefore be limited for the development of clinical guidelines (Craddock & Owen, 2007).

In sum, the relevance of the concept of affective psychosis currently lacks strong scientific evidence. Grouping patients with mood and psychotic features who belong to different diagnostic categories, may however be useful for clinical purposes in order to stratify patients on the psychosis spectrum, and thus to develop interventions adapted to their specific needs. This might be particularly relevant for early intervention, that we will introduce in the next section, where boundaries between diagnostic categories are blurred (McGorry, 1994; McGorry et al., 1995).

1.2. *Early intervention in psychosis*

The objective of this section is to introduce the concept of early intervention in psychosis, its characteristics, and challenges. This section places special emphasis on presenting the stratification issues in clinical settings of early intervention that will be addressed in this project. We will then focus on the specificities of early intervention in first-episode affective psychoses.

Early intervention programmes for psychosis have been developing over the last three decades. More and more specialized programmes have been implemented with the aim to reduce the duration of untreated psychosis (DUP) and in order to improve prognosis. Pre-psychotic manifestation of subthreshold symptoms, which might lead to more severe mental disorders (Eaton, Badawi, & Melton, 1995; Garety & Rigg, 2001) as well as the few years after the first-episode, defined as the first onset of florid psychotic symptoms (disorganization, hallucinations, delusion) sustained for more than a week (Krebs et al., 2014) and the three to five years following the onset, constitute the main periods targeted in early intervention. Indeed, the first few years of illness constitute a "critical period" for preventing chronicity and for developing interventions to promote sustained remission (Birchwood, Todd, & Jackson, 1998). Intensive and specialized interventions in the early phases of psychosis have shown to improve symptomatic and functional outcomes, increase satisfaction and engagement in care, as well as to reduce the risk of relapse (Fusar-Poli, McGorry, & Kane, 2017). Their effectiveness is also known to be better than treatment as usual regarding several outcomes in early psychosis such as adherence to treatment, number of hospitalizations, comorbid substance misuse, functional and symptomatic recovery and involvement in school/work (Correll et al., 2018; Craig et al., 2004; McGorry, Killackey, & Yung, 2007; Petersen et al., 2005).

Although specialized and integrated early intervention programmes improve care in psychosis, there are still some challenges to resolve. These include improving relapse prevention, long-term maintenance of treatment benefits, and the identification of patient groups with specific treatment needs in order to develop more adapted interventions. Early identification is particularly crucial in order to introduce appropriate treatment and care as soon as possible (McGorry, 2002). However, classical categories of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) are based on chronic states, giving pictures of prototypical forms of illness, notwithstanding unclear boundaries between disorders in the early stages (McGorry, 1994; McGorry et al., 1995). While the "psychosis" umbrella is used to facilitate detection rather than "schizophrenia" (Driessen, Gunther, Bak, van Sambeek, & van Os, 1998), there are still some stratification issues due to unspecific onset, especially among those with mood syndrome who sometimes experience a very long delay before the introduction of appropriate treatment (Baethge et al., 2003; Egeland, Blumenthal, Nee, Sharpe, & Endicott, 1987; Fusar-Poli et al., 2017; Post et al., 2003). A large number of patients expressing mixed forms of illness, combining psychotic and mood features, have thus challenged the classical categorical perspective on psychotic disorders (Keshavan et al., 2011; Thaker, 2008). This suggests the need to further investigate mixed clinical phenotypes combining both categorical and dimensional measures to catch the complexity of the early course of psychotic disorders (Craddock & Owen, 2007; Keshavan et al., 2011; Thaker, 2008)

In sum, early stratification and introduction of optimal treatment is the major goal of early intervention in psychosis. The first-episode of psychosis, and the first 2 to 5 following years, constitute a critical period during which early intervention programmes have shown great effectiveness on the course of illness to prevent chronicity. However, differentiating affective psychoses at the onset may be challenging, especially among mixed forms of the illness with unspecific onset. This will be the focus of the next section.

1.3. *First-episode affective psychoses and its stratification and diagnostic issues*

Early intervention may face specific challenges when dealing with first-episode affective psychoses. Focusing on first-episodes is an opportunity to intervene as soon as the illness is declared in order to prevent relapse, and chronicity. This section outlines the challenges of intervention and stratification in first-episode affective psychoses, and the gaps in the current literature, which the current project will take significant steps to address.

First-episode affective psychoses can be defined as the first clear and sustained manifestation of psychotic symptoms combined with a depressive and/or manic syndrome (Krebs et al., 2014; Strakowski et al., 1998). The diagnosis of a first-episode affective psychosis is challenging, firstly because the clinical features of non-affective and affective psychoses may not be specific at onset which may lead to a preliminary diagnosis of a psychotic disorder not otherwise specified (Fusar-Poli et al., 2017), and secondly because early manifestation of affective psychoses are often atypical (Berk et al., 2007). For example, the diagnosis of BD is especially challenging considering its insidious onset often observed during adolescence or early adulthood with low specific symptoms like depression, sleep disturbance, energy fluctuation or irritability, and atypical mania like dysphoric or mixed forms (Berk et al., 2007). Consequently, it remains difficult to correctly stratify affective psychoses early on. Furthermore, the presence of a mood disorder in addition to psychotic symptoms may have an impact on treatment response and the evolution of the disorder, which suggests that specific treatment strategies may be required to treat affective psychoses (Fusar-Poli et al., 2017). Studying first-episode affective psychoses thus offers an opportunity to explore determinants of outcomes without the impact of relapses and long-term medication after several years of illness

like in chronic states, and it may enable the development of early intervention strategies that would fit to such neglected group.

While first-episode psychoses have been widely explored in schizophrenia, affective psychoses remain largely neglected (Berk et al., 2007; Chia et al., 2019; Conus & McGorry, 2002; Taylor, Bressan, Pan, & Brietzke, 2011). This is a major source of concern considering that patients with affective psychosis are at high risk of suicidal behaviour, multiple relapses and non-adherence to treatment (Bergé et al., 2016; Berk et al., 2007; Bowtell et al., 2018). For example, a recent prospective study reported 50% of suicidal behavior in patients with first-episode affective psychosis at 12 months follow-up (Coentre et al., 2021), and 43% of relapse in first-episode psychosis patients after 2 years of follow-up (Bergé et al., 2016). Furthermore, while syndromic recovery is often achieved early after the onset of affective psychosis, symptomatic and functional recovery may be poor (Conus et al., 2006; Strakowski et al., 1998; Tohen, Strakowski, et al., 2000). Indeed, Strakowski et al. (1998) reported that only 35% of patients achieved functional recovery at 12 months follow-up after a first hospitalization for affective psychosis. Similarly, in another 12-month prospective study, showed that while 90% of patients with first-episode mania achieved syndromic recovery, 61% of them failed to get back to their previous level of functioning. Even after 24 month follow-up, functional recovery was 2.6-2.7 times less likely than syndromic recovery in patients with a first-episode of major affective disorder with psychotic features (Tohen, Hennen, et al., 2000). Research to improve our understanding of patients with affective psychosis is therefore crucial in order to develop early intervention and preventive strategies for this particularly sensitive population.

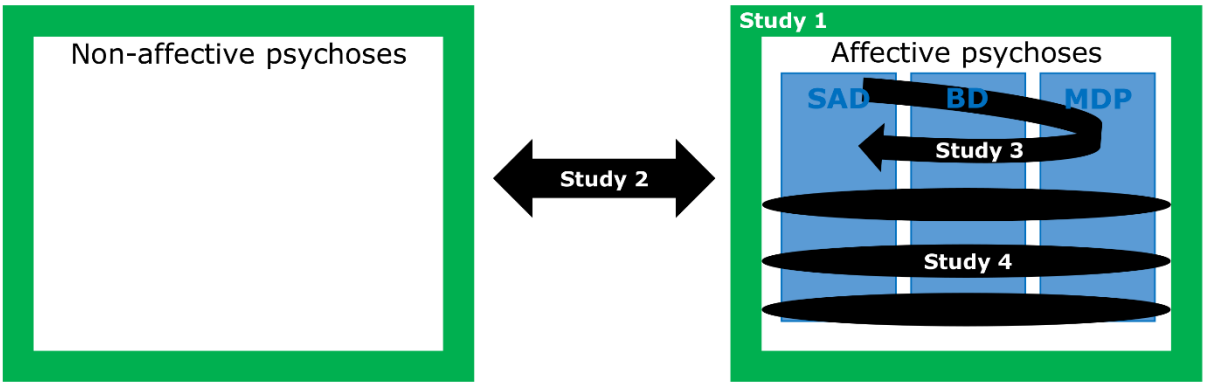
Studies on first-episode affective psychoses mainly focused on first-episode mania (Chang et al., 2016; Conus & McGorry, 2002; Ratheesh et al., 2017; Strakowski, McElroy, Keck, & West, 1996), highlighting impairments in

premorbid adjustment (Ratheesh et al., 2017), and difficulties to fully recover (Conus & McGorry, 2002). Affective psychoses may, however, be characterized by manic and/or depressive syndrome associated with psychotic symptoms (Strakowski et al., 1998; Tohen, Strakowski, et al., 2000). Past studies on first-episode affective psychoses focused almost exclusively on patients who express full-blown manic syndrome, thus neglected to include, SAD and MDP who did not express mania. It is worth noting that depressive and manic symptom dimensions may also co-occur, which can worsen prognosis and decrease patients' quality of life and functioning (Bauer, Simon, Ludman, & Unützer, 2005). Unfortunately, the current literature lacks studies that take the co-occurrence of depressive and manic symptom dimensions in first-episode affective psychoses into account. It thus suggest that it would be important to study affective psychoses including both depressive and manic subthreshold symptoms. In addition, the co-occurrence of mood and psychotic symptoms may be particularly important to study in the early course of affective psychoses to stratify patients, considering their relative duration is at the basis of the differential diagnosis between BD and SAD.

In sum, studying first-episode affective psychoses is an opportunity to pave the way to the development early intervention in a relatively neglected area of research. Poor symptomatic and functional outcomes, as is often the case, is a clear incentive for developing such specialized interventions for affective psychoses. However, current literature on first-episode affective psychoses lacks studies investigating the comprehensive spectrum of mood syndromes associated with psychotic features including both depressive and manic dimensions. Therefore, in order to develop effective early intervention programmes, it would be crucial to study first-episode affective psychoses with all its associated dimensions, either depressive, mixed or manic.

1.4. *Aims of the project*

Literature on early intervention in psychosis stresses the importance of conducting research on first-episode psychoses in order to develop clinical strategies that can prevent a chronic state from emerging. The need for clear identification guidelines for intervention in this field highlights the importance of such development. Considering the lack of a strong scientific basis for the concept of affective psychoses, we would like to address its clinical relevance in early intervention, considering, first its specific clinical features and the treatment challenges it generates, second the clinical differences between affective and non-affective psychosis, third the degree of commonalities between diagnostic categories included within the affective psychosis sub-group. Fourth, we would like to investigate its usefulness in stratification to identify subgroups of patients that may require specific early intervention strategies (see figure 1).



Note. SAD = Schizoaffective disorder; BD = Bipolar disorder I; MDP = Major depressive disorder with psychotic features.

Figure 1. Illustration of the conceptualisation of the studies to explore the clinical relevance of the concept of affective psychoses in early intervention and its usefullness in clinical settings

The identification of clinical differences between affective and non-affective psychoses groups, as well as the study of the homogeneity within the affective psychoses group, may address the issue of the clinical relevance of a dichotomy within psychoses, and the pertinence of gathering diagnostic categories under the "affective psychosis" umbrella, including not only manic but also depressive and mixed states.

In addition, we would like to explore if patients stratification is possible within first-episode affective psychoses patients at baseline and based on clinical characteristics readily available to clinicians. Such stratification may pave the way for developing adapted early intervention strategies while overcoming stratification and diagnostic challenges in the early phase of affective psychoses. We will conduct clinical prospective studies in a cohort of first-episode psychosis patients treated at a specialized early psychosis intervention programme (the Treatment and Early Intervention in Psychosis Programme; TIPP) that has been implemented by Lausanne University Hospital's Department of Psychiatry in 2004 (Baumann et al., 2013; Conus & Bonsack, 2004). Patients entering the programme are aged 18–35, reside in the Lausanne catchment area and have crossed the psychosis threshold according to the Comprehensive Assessment of At-Risk Mental States scale's (CAARMS; Yung et al., 2005) *Psychosis Threshold* subscale. This project may therefore identify important clinical targets for specialized intervention, based on psychopathological characteristics that are accessible to clinicians.

Finally, considering that manic and depressive symptoms could alternate and possibly co-occur, along with additional psychotic symptoms, we find it relevant to consider the longitudinal dynamic of symptoms by following the course of sub-groups of patients in the early phase of illness. Therefore, in order to better characterize the first-episode affective psychoses group, the studies of this PhD thesis will explore the dynamics of symptom dimensions over time. This is an original and pertinent approach considering that, to our knowledge, studies on first-episode affective psychoses have neither explored the dynamics of symptom dimensions over time, nor included both depressive and manic forms of psychosis. Moreover, studying psychotic and mood symptoms dimensionally, and including them even if they are only at subthreshold level and do not allow a diagnosis of depression or mania, may enable a more accurate longitudinal modelling. Such dimensional approach would improve our ability to investigate and stratify patients that do not

express a full-blown manic syndrome in the early course of affective psychoses.

2. Results

The thesis' objectives are addressed in four successive chapters. The first chapter, based on a narrative review, synthesizes and discusses the main findings and gaps in the literature on early intervention in first-episode affective psychoses. The second chapter addresses the clinical differences between affective and non-affective psychoses, focusing especially on the relevance of such a dichotomy in the early phase of illness. The third chapter explores the clinical relevance of the concept of affective psychosis in the early course of illness from the angle of the presence or not of a certain degree of commonalities in patients belonging to the diagnostic categories included in this concept. Finally, chapter four explores the relevance of a stratification of patients based on patients' premorbid characteristics to develop adapted intervention strategies in first-episode affective psychoses. Below is a summary of the methods and results relevant to each of the chapters.

Chapter 1. A narrative review of intervention in first-episode affective psychoses (Appendices)

This chapter presents a narrative review of the current literature on intervention in first-episode affective psychoses, with the objective of addressing the relevance of the concept of "affective psychosis" in early intervention. The selected studies were examined considering the following main topics of early intervention: diagnostic categorization, premorbid factors, intervention, duration of untreated illness, neurobiology and neurocognition. Our findings from the literature suggests that many characteristics of patients justify to consider this sub-grouping. We found that the concept of affective psychoses includes different diagnoses depending on the authors, especially regarding SAD which is not always included. Nevertheless, this review revealed specific psychopathological and neurocognitive characteristics in affective psychoses that may justify specialized intervention and suggests that the concept of affective psychosis is therefore relevant for early intervention. However, literature on this topic remains sparse, suggesting the need for further investigation, especially studies in first-episode cohorts including every diagnosis included under the affective psychoses umbrella, including SAD, MDP, BD.

Personal contribution: I was personally involved in the conceptualization of the study. I worked with a librarian to develop the search strategies, undertook the publications selection process, then extracted the data, and synthesized the key results stemming from all the studies included. I finally wrote the review as first author.

Chapter 2. Exploring the clinical relevance of a dichotomy between affective and non-affective psychosis: Results from a first-episode cohort study (Appendices)

The objective in this chapter was to explore the clinical relevance in early intervention of a dichotomy between affective and non-affective psychoses. A sample of 330 first-episode psychosis patients treated at our early intervention programme was studied prospectively. Our findings showed that patients with an affective psychosis were more likely to be female and had a shorter DUP than those with a non-affective psychosis. We also observed that positive symptoms remained lower over the 36-month follow-up in the affective group. The affective psychosis group also showed a significantly better insight after 6 months follow-up, and a higher degree of variability of manic symptoms. The affective and non-affective groups did not differ regarding negative and depressive symptoms. The environmental quality of life and insight recovery were better in the affective psychosis group at 36 months follow-up. This study suggests the affective and non-affective groups differ regarding the course of illness and outcome, which suggests the need for specific treatment adjustment. It therefore provides support to the utility of a dichotomy between affective and non-affective psychoses in early intervention.

Personal contribution: I conceptualized the study, performed the statistical analyses in collaboration with P. Golay, and wrote the paper as first author.

Chapter 3. Affective psychosis as a conceptual grouping in early psychosis: homogenous or heteronomous clinical features? (Appendices)

After exploring if sufficient differences justified a dichotomy between affective and non-affective psychoses in chapter 2, we explore, in chapter 3, if, within the affective psychoses subgroup, there is a sufficient degree of homogeneity between diagnostic subgroups to justify grouping them together. Through a prospective study in a sample of 77 first-episode affective psychoses patients, we addressed, through Bayesian statistical methods, the issue of homogeneity within the group. Our analysis revealed an important number of commonalities between diagnoses within the affective psychosis subgroup regarding several socio-demographic variables and outcome characteristics. Moreover, no significant differences could be observed regarding the course of positive and manic symptoms. However, general and negative symptoms were more severe in SAD than BD patients during the first 18 months, as well as depressive symptoms during the first year. SAD patients displayed as well more difficulty to achieve functional recovery as well as to get back to work after discharge than the two other groups. Despite these differences and considering the similarities between SAD, MDP, and BD, developing clinical guidelines in early intervention using the affective psychosis grouping seems relevant and may be more achievable than relating to each psychopathological dimension However, the poorer prognosis of SAD regarding functioning may require specific attention and some complementary therapeutic approach.

Personal contribution: I conceptualized the study, performed the statistical analyses in collaboration with P. Golay, and wrote the paper as first author.

Chapter 4. Subtyping based on premorbid profile: a strategy to personalize treatment in first-episode affective psychosis? (Appendices)

In this chapter we investigate an alternative way to identify groups within first-episode affective psychoses, exploring the specific course of illness and needs of patients on the basis of information that may be available to clinician at entry to the programme, such as premorbid and baseline clinical characteristics. In order to do so, we conducted a prospective study in a sample of 74 first-episode affective psychoses using latent class analysis (LCA).

Our results revealed three different groups within affective psychoses that were independent of diagnostic categories. The first group, composed of a majority of women, included patients with later onset of psychosis, and more severe depressive symptoms in the first 6 months, in contrast with the two other groups that revealed more severe manic symptomatology over the 36 months follow-up and an earlier onset of psychosis. Despite good symptomatic recovery, this group had difficulties in getting back to work at follow-up. The two latter groups differed regarding premorbid adjustment, psychiatric history and exposure to traumatic events. The group where patients displayed exposure to numerous serious antecedents had the worst prognosis (higher rate of hospitalizations and poorer global recovery, especially regarding return to work and to premorbid level of adjustment. This study provides further evidence of poor functional recovery in the early phase of affective psychoses. It also proposes an alternative way to stratify patients within affective psychosis based on premorbid characteristics; the distinct course and outcome characteristics of these groups suggest they may require specific treatment adjustment. This premorbid subtyping could therefore be used as a complement to the diagnosis, which is often difficult to determine at an early stage, in order to propose treatments that are better fitted to the needs of patients. .

Personal contribution: I conceptualized the study, conducted the statistical analyses in collaboration with P. Golay, and wrote the paper as first author.

3. Discussion and future perspectives

This thesis addresses the relevance of the concept of affective psychosis in the field of early intervention and explored the elements that may justify the development of specific treatment strategies for such patients. An important strength of our work is that it is based on the prospective follow-up of patients over three years of treatment.

More precisely, our aims were to study (1) the relevance of the concept of affective psychosis in early intervention, especially its specific clinical features and challenges (Study 1), its clinical differences compared to non-affective psychosis (Study 2), and the degree of homogeneity of the diagnostic categories included within such conceptual grouping (Study 3); (2) its usefulness in developing stratification strategies based on clinical factors accessible to clinicians at entry, especially premorbid characteristics, in order to develop adapted early intervention strategies (Study 4). Study 1, 2 and 4 have already been published in peer-reviewed journals. Study 3 is currently under review.

In this section, we discuss the main findings of the studies of this PhD thesis, especially the extent to which these results show that affective psychosis is a relevant concept in early intervention, and how such a concept can be used to stratify patients with specific needs. Strengths and limitations of this project are then highlighted, followed by suggestions for future developments.

3.1. Affective psychosis, a relevant concept to develop treatment strategies targeted to patients with a combination of a mood disorder and psychotic features

This thesis provides several pieces of evidence supporting the relevance of the conceptual grouping of affective psychoses in the early phase of such disorders. First, study 1 highlights the relevance of developing early intervention in first-episode affective psychoses. Indeed, developing early

intervention targeting such a sensitive population seems crucial considering the high risk of chronicity due to multiple relapses which can induce severe deficits (Conus, 2010). In addition, despite a good syndromic recovery, poor functional and symptomatic recovery has been observed (Studies 1 & 4; Conus et al., 2006; Salvadore, Drevets, Henter, Zarate, & Manji, 2008; Tohen, Hennen, et al., 2000; Tohen, Strakowski, et al., 2000). This population also require a focus on other therapeutic targets than reducing symptoms to favor long-term remission. For example, targeting neurocognition (processing speed, verbal working memory), trauma or comorbidities like substance abuse may be particularly important to develop care in first-episode affective psychoses (Study 1; Berk et al., 2007; Buck et al., 2020; Conus, 2010; Daglas et al., 2017; Daglas et al., 2014; Lee et al., 2014; Olvet, Burdick, & Cornblatt, 2013; Torrent et al., 2018).

Second, developing specific early intervention strategies for affective psychoses may be relevant considering several specificities compared to the non-affective psychoses (Study 1). For example, contrary to the non-affective psychoses, the clinical presentation of affective psychoses overlaps between mood and schizophrenia spectrum disorders such that both psychotic and mood dimensions should be considered in pharmacological treatment (Berk et al., 2007; Conus, 2010). Psychoeducation, which is particularly important in improving adherence to treatment, has also its specific challenges in this population considering false apparent good evolution of affective psychoses due to good syndromic recovery. Thus, in our narrative review (Study 1), we suggested that early intervention strategies should be adapted to deal with the specific clinical features and challenges of early affective psychoses.

Moreover, study 2 provides evidence that the use of a dichotomy between affective and non-affective psychoses might be relevant to develop an adapted early intervention strategy for affective psychoses. Our results show several clinical differences between first-episode affective and non-affective psychoses groups. While only duration of untreated psychosis

(DUP) and sex differed between groups at entry, the course of illness diverged all over the duration of the specialized early intervention programme, despite the personalized treatment adjustments inherent in such programme. Therefore, considering the clinical differences between affective and non-affective groups despite an adapted early intervention programme, it seems justified to develop a specific early intervention strategy targeting the needs of affective psychoses.

However, study 2 also reveals mixed results, highlighting some elements not allowing a clear dichotomy between affective and non-affective psychoses. For example, our findings reveal no differences between groups in the course of depressive or negative symptoms all throughout the 36-month follow-up, nor regarding symptoms and functioning at 2-month follow-up. Our findings thus also suggest that the affective psychosis concept encompasses patients that may be too heterogeneous. We therefore investigated the homogeneity of the diagnostic categories gathered under the affective psychoses umbrella (Study 3). Our findings revealed that SAD, BD and MDP had many similarities regarding premorbid characteristics, clinical evolution, and outcome. Therefore, clinical features in the early course of illness of the diagnostic categories within affective psychoses seemed homogeneous enough to justify the use of such conceptual grouping. Taken together, study 2 and 3 shows that the concept of affective psychoses may be relevant to gather patients with specific needs in a larger category that would be easier to stratify early on, contrary to the diagnoses requiring a lengthy process (Malhi, Green, Fagiolini, Peselow, & Kumari, 2008).

Nevertheless, study 3 also shows some differences between diagnostic categories. The SAD group in particular had worse outcome than the BD group. However, in the course of illness, we could only observe a difference regarding negative and general symptomatology during the first 18 month follow-up between the SAD and BD groups, but not with the MDP group. This suggests that the course of symptoms only may not be relevant to

identify differences between groups, and thus to develop adapted early intervention strategies. It therefore seems important to develop other stratification strategies based on criteria other than symptoms and their evolution to subtype patients that would require specific early intervention strategies.

In sum, study 1, 2, and 3 highlight the relevance of using the conceptual grouping of affective psychoses in early intervention. First, our findings in the narrative review (Study 1) show that first-episode affective psychoses remain largely neglected in the literature despite specific clinical features and challenging issues. Second, clinical features of first-episode affective psychoses and their early course diverge when examining the non-affective ones, which may require pharmacological and psychosocial adjustment of interventions (Study 2). Third, the diagnostic categories gathered under the concept of affective psychoses show several important similarities regarding the early course of illness and outcomes that could be used to develop shared clinical guidelines for affective psychoses (Study 3). However, some degree of clinical heterogeneity observed within affective psychoses could not be explained and identified based on differences regarding the course of symptomatology. This points out the importance of developing other stratification strategies (not only the diagnoses or a larger conceptual dichotomy between affective and non-affective) to subtype patients with specific needs that may require adapted early intervention strategies. Nevertheless, in our view the advantages outweigh the drawbacks of adopting this conceptual grouping because it is mostly supported by empirical data and it could be used clinically to improve early intervention. Using other clinical elements would thus be a complement to a primarily global stratification based on the concept of affective psychoses.

3.2. The usefulness of the concept of affective psychoses in developing stratification strategies to adapt early intervention

This thesis provides evidence for the usefulness of identifying premorbid profiles within the conceptual grouping of affective psychoses. In the review (Study 1), we report that diagnostic process is a major issue of early intervention in affective psychoses (Berk et al., 2007; Malhi et al., 2008). Indeed, the overlap between mood and schizophrenia spectrum disorders makes such process especially complex for patients presenting psychotic symptoms but no manic, or only hypomanic symptomatology (Arrasate et al., 2014). Strategies to stratify patients based on other clinical cues seem essential to subtype patients that may require adapted early intervention strategies, rather than only relying on long diagnostic process. Study 2 provides evidence that the use of a categorical approach, based on clinical presentation in addition to dimensional measures of symptoms, may be useful for the practical purpose of stratifying and accurately characterizing groups of patients and their evolution. The categorical approach is often criticized in the literature, it is considered as a limited view compared to the dimensional perspective defining psychiatric disorders as a continuum on which each patients' position is determined by their expression of multiple symptom dimensions (Borsboom, 2008). However, our findings show that such a categorical approach, combined with the accuracy of a dimensional follow-up of symptoms, enable to subtype patients with specific needs that may require adapted intervention strategies, which is in line with previous studies recommending to combine categorical and dimensional perspectives (Arrasate et al., 2014; Craddock & Owen, 2007; Keshavan et al., 2011). This kind of approach may thus address a clinical stratification issue on a scientific basis that is complementary to the complex pure dimensional perspective, and that also identifies specific therapeutic targets to adapt interventions.

Furthermore, our results suggest that clinical features of SAD, BD, and MDP were homogeneous enough to use the large conceptual grouping of affective

psychoses despite some differences (Study 3). In addition, our findings reveal that symptom-based differentiation might be limited to identifying patients with specific needs within affective psychoses (Study 3). Moreover, our mixed results in study 2 suggest that complementing the dichotomy approach based on symptoms by including other patient dimensions (e.g. life story) would be important as previously suggested (Kenneth S. Kendler & Eric J. Engstrom, 2018). Stratifying patients with an affective psychosis based on premorbid factors and previous life events could therefore offer an opportunity to accurately subtype patients with specific needs based on elements that are accessible to clinicians at the beginning of intervention programmes.

We used study 4 to explore premorbid-based subtypes within affective psychoses to identify patients at a very early stage that would benefit from specific early intervention strategies. Based on latent class analysis, we were able to identify three groups of patients within affective psychoses with distinct early course of mood symptoms and functional outcomes, who were independent of the diagnostic categories. These distinct premorbid profiles may thus require adjustment of pharmacological treatment and psychosocial intervention. Therefore, our results suggest that using premorbid characteristics may be relevant for clinicians to adapt intervention strategies very early on for specific groups of first-episode psychosis patients with a mood disorder.

However, our exploration throughout the whole cohort, including the non-affective group, confirmed that such premorbid-based subtyping strategy was relevant within the conceptual grouping of affective psychoses, but it was not considering the whole cohort. The use of the affective psychoses concept has practical purposes, as well as for research, and may therefore be a first-step to classify patients with first-episode psychosis and a mood disorder that may require specific early intervention strategies. As a second step, it seems necessary to develop stratification strategies within the conceptual grouping of affective psychoses based on clinical elements other than symptoms like premorbid characteristics. Our results (Studies 1, 2, 3,

4), show that the affective psychosis large grouping may be relevant for rapid and easy classification of first-episode psychosis patients with a mood disorder (either depressive, manic or mixed) that may require adapted intervention strategies. Study 4 also supports the usefulness of other clinical elements of patients, including life story (Kenneth S. Kendler & Eric J. Engstrom, 2018), to better cope with the heterogeneity within affective psychoses. Indeed, it may enable to identify groups of patients that may require adapted early intervention strategies. Combining the use of the affective psychosis umbrella with premorbid-based subtypes may be particularly pertinent to dealing with the diagnosis issues of first-episode affective psychoses patients without a full-blown manic syndrome (Arrasate et al., 2014).

In sum, studies 1, 2, 3, and 4 highlight the relevance of using stratification strategies based on premorbid characteristics within the conceptual grouping of affective psychoses to identify groups of patients that may require adapted early intervention strategies. First, study 1 reveals several diagnoses and stratification issues within first-episode affective psychoses. Second, our results in study 2 and 3 confirm that dealing with the heterogeneity of patients included within the affective psychoses group would require stratifying patients based on other elements than the course of symptoms only. Finally, study 4 shows that premorbid characteristics may be used to stratify first-episode affective psychosis patients with specific needs in the early phase of intervention. Combining the use of the conceptual grouping of affective psychoses with premorbid-based subtyping profiles may therefore be relevant to deal with stratification issues, and to develop adapted early intervention strategies.

3.3. Strengths and limitations

This thesis project has several strengths. First, the cohort of patients studied in studies 2, 3, and 4 is rare considering the large sample of patients, the breadth of assessments available and the three-year duration

of the follow-up. This naturalistic and representative sample may likely allow the generalization of results to other patients with a first-episode affective psychosis. We were also able to include SAD, BD as well as MDP. The latter is often neglected, but more and more evidence show the importance of including MDP to study the psychosis spectrum (Study 4; Keshavan et al., 2011; Waddington & Buckley, 2013). In addition, the three-year follow-up allows us to provide robust results, substantiated by long-term change dynamics of symptoms. Second, the combination of frequentist and Bayesian statistics allowed us to provide strong evidence for differences between psychotic disorders but also to provide evidence of support for similarities within affective psychoses. The Bayesian approach was also a good way to partly circumvent the Type I and Type II error trade-off in a moderate-size sample of affective psychoses (Study 3). Third, our analyses were based on clinical data that were collected as a clinical routine, and thus directly accessible to clinicians. This project may thus provide clues to adapt intervention strategies that can be easily implemented in clinical practice.

Our findings must however be taken with caution while considering several limitations. First, most of the studies had a prospective design which does not allow to control for all possible confounding variables which might have influenced our results. Second, the exhaustive search strategy used in study 1, although exploring five different data bases, may fail to scope all the studies of the literature as a proper scoping review would have maybe achieved. Third, the latent class analyses in study 4 were used in a relatively small sample, leaving the categories identified subject to change in a larger or different sample. Our results would thus require replication. Fourth, symptom differences between groups might have been hidden by the fact that we were not able to assess patients during the acute phase at entry, and also by the 6-month interval assessment of the longitudinal follow-up that may fail to catch the complex short term temporal dynamic of symptoms, which would ideally require even shorter assessment intervals. Fifth, the sample studied was recruited in one specialized early intervention

programme. It would therefore be important to reproduce the studies in other early intervention centers or other clinical settings including first-episode psychosis patients. Finally, it would be important to consider, not only the onset, but the whole early development period of illness, including the prodromal period, to improve our understanding of the early course of illness and to face the identification and detection issues.

3.4. Future perspectives

This thesis project highlights the relevance of developing research on early intervention using the affective psychosis concept. Study 1 revealed that suicidal behaviour, substance abuse, adherence to treatment and multiple relapses despite remission phases represent major issues of early intervention in affective psychoses (Berk et al., 2007; Conus, 2010; Conus & McGorry, 2002). However, most studies on these topics in early intervention have not focused on affective psychoses. For example, while investigating suicidality, some studies examined first-episode psychosis (Björkenstam, Björkenstam, Hjern, Bodén, & Reutfors, 2014; Dutta et al., 2010; Pompili et al., 2011; Robinson et al., 2010), or others focused on first-episode non-affective psychosis (Ayesa-Arriola et al., 2015; Canal-Rivero et al., 2018; Canal-Rivero et al., 2020). Nevertheless to our knowledge, none of them investigated suicidality specifically in first-episode affective psychoses, including SAD, BP and MDP. Developing research focusing on such major issues in first-episode affective psychoses may thus offer an opportunity to improve our understanding of mechanisms underlying clinical issues to point out therapeutic targets, and to develop adapted early intervention strategies for this sensitive population. We therefore started to investigate these specific issues in early affective psychoses. A study on suicidality is currently under review.

Otherwise, this thesis project shows the importance of studying dimensionally over the course of affective symptoms, both depressive and manic, to differentiate affective from non-affective psychoses groups (Study 2), as well as sub-groups within affective psychoses (Study 4). This is in

line with previous literature showing the major role of affective dimensions (Ciompi, 2015; Salazar de Pablo et al., 2021; Sanchez-Gistau et al., 2015; Waddington & Buckley, 2013). We thus started to investigate the longitudinal co-occurrence of depressive and manic dimensions to identify profiles of patients and their evolution based on depressive and manic dimensions.

Furthermore, this thesis project points out specific clinical challenges of affective psychoses and stratification strategies that enable to identify patients that may require adapted early intervention strategies (Studies 1, 2, 3, 4). Because our work did not test any intervention strategies, further studies are required to investigate the impact of specific early intervention adjustment for affective psychoses. However, developing adapted intervention strategies for first episode affective psychoses that could be tested in a proper randomized-control trial would also require more studies to specify therapeutic targets of early affective psychoses. Such studies should also not be limited to one early intervention service, but should be reproduced in other early intervention programmes, or should be part of multicentric projects. We thus started a collaboration to develop a shared data base with another early intervention center in Australia. This PhD project is therefore a first step to pave the way toward the development and implementation of specific early intervention strategies for affective psychoses.

Moreover, this PhD thesis highlights several stratification issues in early affective psychoses (Studies 1, 2, 3, 4; Berk et al., 2007; Keshavan et al., 2011; Waddington & Buckley, 2013). All the prospective studies included in this thesis investigated the early course of illness in patients followed in an ambulatory programme for three years after their first-episode psychosis. However, the clinical data did not allow us to explore the acute clinical profiles of patients. It would thus be interesting to further explore the clinical profiles of affective psychoses patients during the acute first-episode phase, their specificities and evolution, to improve our ability to differentiate

affective from non-affective psychosis patients at first hospitalization. In our clinical setting, this kind of study would require the collection of retrospective data based on patients' files of their first hospitalization before entry.

Finally, this thesis project was limited to the first three years after the onset of psychosis. However, our findings reveal the importance of studying the course of symptoms dimensionally, and not only the full-blown syndromes. In order to develop our understanding of the early course of affective psychoses and respective identification tools, it would be important to develop studies investigating the course of manic, depressive and psychotic symptom dimensions in patients before the onset of psychosis. For example, studying the prodromal phase in young people with a risk of psychotic transition may enable us to improve our ability to identify atypical manic syndrome (Berk et al., 2007) or to distinguish affective from non-affective psychosis earlier (Fusar-Poli et al., 2017). However, previous studies suggested that discriminant components within mood or psychotic symptoms would be important to consider such as activation (Arrasate et al., 2014), aggressive impulsivity, somatic delusion or imperative auditory hallucination (Salvatore, Baldessarini, Khalsa, & Tohen, 2021).

4. Conclusion

This PhD thesis aimed to address the relevance of the concept of affective psychosis in early intervention and its usefulness in developing stratification strategies. Study 1 shows that first-episode affective psychoses have specific clinical features, and that major issues of early intervention in affective psychoses need to be addressed. Studies 2 and 3 highlight the clinical relevance of the conceptual grouping of affective psychoses considering differences with the non-affective, but also similarities between the diagnostic categories within the affective psychoses. Study 4 shows that, based on this conceptual grouping, premorbid-based profiles can be identified to develop adapted early intervention strategies. Therefore, our results show that the use of the concept of affective psychosis is clinically relevant, and suggests that complementing such a conceptual grouping with premorbid-based subtyping enabled us to identify groups of patients that may benefit from specific early intervention strategies. Further studies on early affective psychoses are however required to develop such adapted early intervention strategies.

5. References

1. Aas, M., Dazzan, P., Fisher, H. L., Morgan, C., Morgan, K., Reichenberg, A., . . . Pariante, C. M. (2011). Childhood trauma and cognitive function in first-episode affective and non-affective psychosis. *Schizophr Res, 129*(1), 12-19. doi:https://doi.org/10.1016/j.schres.2011.03.017
2. Arrasate, M., Gonzalez-Ortega, I., Alberich, S., Gutierrez, M., Martinez-Cengotitabengoa, M., Mosquera, F., . . . Gonzalez-Pinto, A. (2014). Affective dimensions as a diagnostic tool for bipolar disorder in first psychotic episodes. *Eur Psychiatry, 29*(7), 424-430. doi:10.1016/j.eurpsy.2013.07.005
3. Ayesa-Arriola, R., Alcaraz, E. G., Hernández, B. V., Pérez-Iglesias, R., López Moríñigo, J. D., Duta, R., . . . Crespo-Facorro, B. (2015). Suicidal behaviour in first-episode non-affective psychosis: Specific risk periods and stage-related factors. *Eur Neuropsychopharmacol, 25*(12), 2278-2288. doi:10.1016/j.euroneuro.2015.09.008
4. Baethge, C., Smolka, M. N., Gruschka, P., Berghöfer, A., Schlattmann, P., Bauer, M., . . . Müller-Oerlinghausen, B. (2003). Does prophylaxis-delay in bipolar disorder influence outcome? Results from a long-term study of 147 patients. *Acta Psychiatr Scand, 107*(4), 260-267. doi:10.1034/j.1600-0447.2003.02057.x
5. Bauer, M. S., Simon, G. E., Ludman, E., & Unützer, J. (2005). 'Bipolarity' in bipolar disorder: Distribution of manic and depressive symptoms in a treated population. *British Journal of Psychiatry, 187*(1), 87-88. doi:10.1192/bjp.187.1.87
6. Baumann, P. S., Crespi, S., Marion-Veyron, R., Solida, A., Thonney, J., Favrod, J., . . . Conus, P. (2013). Treatment and early intervention in psychosis program (TIPP-Lausanne): Implementation of an early intervention programme for psychosis in Switzerland. *Early Interv Psychiatry, 7*(3), 322-328. doi:10.1111/eip.12037
7. Bergé, D., Mané, A., Salgado, P., Cortizo, R., Garnier, C., Gomez, L., . . . Pérez, V. (2016). Predictors of Relapse and Functioning in First-Episode Psychosis: A Two-Year Follow-Up Study. *Psychiatr Serv, 67*(2), 227-233. doi:10.1176/appi.ps.201400316
8. Berk, M., Hallam, K., Lucas, N., Hasty, M., McNeil, C. A., Conus, P., . . . McGorry, P. D. (2007). Early intervention in bipolar disorders: opportunities and pitfalls. *Med J Aust, 187*(S7), S11-14.
9. Birchwood, M., Todd, P., & Jackson, C. (1998). Early intervention in psychosis: The critical period hypothesis. *British Journal of Psychiatry, 172*(S33), 53-59. doi:10.1192/S0007125000297663
10. Björkenstam, C., Björkenstam, E., Hjern, A., Bodén, R., & Reutfors, J. (2014). Suicide in first episode psychosis: A nationwide cohort study. *Schizophr Res, 157*(1), 1-7. doi:https://doi.org/10.1016/j.schres.2014.05.010

11. Borsboom, D. (2008). Psychometric perspectives on diagnostic systems. *J Clin Psychol, 64*(9), 1089-1108. doi:10.1002/jclp.20503

12. Bowtell, M., Eaton, S., Thien, K., Bardell-Williams, M., Downey, L., Ratheesh, A., . . . O'Donoghue, B. (2018). Rates and predictors of relapse following discontinuation of antipsychotic medication after a first episode of psychosis. *Schizophr Res, 195*, 231-236. doi:https://doi.org/10.1016/j.schres.2017.10.030

13. Brockington, I. F., Kendell, R. E., & Leff, J. P. (1978). Definitions of schizophrenia: concordance and prediction of outcome. *Psychol Med, 8*(3), 387-398. doi:10.1017/s0033291700016068

14. Brockington, I. F., Kendell, R. E., Wainwright, S., Hillier, V. F., & Walker, J. (1979). The distinction between the affective psychoses and schizophrenia. *Br J Psychiatry, 135*, 243-248. doi:10.1192/bjp.135.3.243

15. Buck, G., Lavigne, K. M., Makowski, C., Joober, R., Malla, A., & Lepage, M. (2020). Sex Differences in Verbal Memory Predict Functioning Through Negative Symptoms in Early Psychosis. *Schizophr Bull*. doi:10.1093/schbul/sbaa054

16. Canal-Rivero, M., López-Moríñigo, J. D., Setién-Suero, E., Ruiz-Veguilla, M., Ayuso-Mateos, J. L., Ayesa-Arriola, R., & Crespo-Facorro, B. (2018). Predicting suicidal behaviour after first episode of non-affective psychosis: The role of neurocognitive functioning. *Eur Psychiatry, 53*, 52-57. doi:10.1016/j.eurpsy.2018.06.001

17. Canal-Rivero, M., Tordesillas-Gutiérrez, D., Ruiz-Veguilla, M., Ortiz-García de la Foz, V., Cuevas-Esteban, J., Marco de Lucas, E., . . . Crespo-Facorro, B. (2020). Brain grey matter abnormalities in first episode non-affective psychosis patients with suicidal behaviours: The role of neurocognitive functioning. *Prog Neuropsychopharmacol Biol Psychiatry, 102*, 109948. doi:10.1016/j.pnpbp.2020.109948

18. Chang, W. C., Lau, E. S. K., Chiu, S. S., Hui, C. L. M., Chan, S. K. W., Lee, E. H. M., & Chen, E. Y. H. (2016). Three-year clinical and functional outcome comparison between first-episode mania with psychotic features and first-episode schizophrenia. *Journal of Affective Disorders, 200*, 1-5. doi:10.1016/j.jad.2016.01.050

19. Cheniaux, E., Landeira-Fernandez, J., Lessa Telles, L., Lessa, J. L. M., Dias, A., Duncan, T., & Versiani, M. (2008). Does schizoaffective disorder really exist? A systematic review of the studies that compared schizoaffective disorder with schizophrenia or mood disorders. *J Affect Disord, 106*(3), 209-217. doi:https://doi.org/10.1016/j.jad.2007.07.009

20. Chia, M. F., Cotton, S., Filia, K., Phelan, M., Conus, P., Jauhar, S., . . . Ratheesh, A. (2019). Early intervention for bipolar disorder - Do current treatment guidelines provide recommendations for the early stages of

the disorder? *J Affect Disord, 257*, 669-677. doi:10.1016/j.jad.2019.07.062

21. Ciompi, L. (2015). The key role of emotions in the schizophrenia puzzle. *Schizophr Bull, 41*(2), 318-322. doi:10.1093/schbul/sbu158

22. Coentre, R., Fonseca, A., Mendes, T., Rebelo, A., Fernandes, E., Levy, P., . . . Figueira, M. L. (2021). Suicidal behaviour after first-episode psychosis: results from a 1-year longitudinal study in Portugal. *Annals of General Psychiatry, 20*(1), 35. doi:10.1186/s12991-021-00356-0

23. Conus, P. (2010). First episode of mood disorders: an opportunity for early intervention in bipolar disorders. *L'Encephale, 36*, S71-76.

24. Conus, P., & Bonsack, C. (2004). [Early intervention for the initial phase of psychotic disorders in Lausanne: what problems and what solutions?]. *Rev Med Suisse Romande, 124*(4), 221-224.

25. Conus, P., Cotton, S., Abdel-Baki, A., Lambert, M., Berk, M., & McGorry, P. D. (2006). Symptomatic and functional outcome 12 months after a first episode of psychotic mania: barriers to recovery in a catchment area sample. *Bipolar Disord, 8*(3), 221-231. doi:10.1111/j.1399-5618.2006.00315.x

26. Conus, P., & McGorry, P. D. (2002). First-episode mania: a neglected priority for early intervention. *Aust N Z J Psychiatry, 36*(2), 158-172. doi:10.1046/j.1440-1614.2002.00994.x

27. Correll, C. U., Galling, B., Pawar, A., Krivko, A., Bonetto, C., Ruggeri, M., . . . Kane, J. M. (2018). Comparison of Early Intervention Services vs Treatment as Usual for Early-Phase Psychosis: A Systematic Review, Meta-analysis, and Meta-regression. *JAMA Psychiatry, 75*(6), 555-565. doi:10.1001/jamapsychiatry.2018.0623

28. Craddock, N., O'Donovan, M. C., & Owen, M. J. (2009). Psychosis genetics: modeling the relationship between schizophrenia, bipolar disorder, and mixed (or "schizoaffective") psychoses. *Schizophr Bull, 35*(3), 482-490. doi:10.1093/schbul/sbp020

29. Craddock, N., & Owen, M. J. (2007). Rethinking psychosis: the disadvantages of a dichotomous classification now outweigh the advantages. *World Psychiatry, 6*(2), 84-91.

30. Craig, T. K. J., Garety, P., Power, P., Rahaman, N., Colbert, S., Fornells-Ambrojo, M., & Dunn, G. (2004). The Lambeth Early Onset (LEO) Team: randomised controlled trial of the effectiveness of specialised care for early psychosis. *BMJ, 329*(7474), 1067. doi:10.1136/bmj.38246.594873.7C

31. Daglas, R., Allott, K., Yücel, M., Henry, L. P., Macneil, C. A., Hasty, M. K., . . . Cotton, S. M. (2017). Cognitive functioning following stabilisation from first episode mania. *International Journal of Bipolar Disorders, 5*(1). doi:10.1186/s40345-017-0108-2

32. Daglas, R., Conus, P., Cotton, S. M., Macneil, C. A., Hasty, M. K., Kader, L., . . . Hallam, K. T. (2014). The impact of past direct-personal traumatic events on 12-month outcome in first episode psychotic mania: Trauma and early psychotic mania. *Australian and New Zealand Journal of Psychiatry, 48*(11), 1017-1024. doi:10.1177/0004867414545672

33. Driessen, G., Gunther, N., Bak, M., van Sambeek, M., & van Os, J. (1998). Characteristics of early- and late-diagnosed schizophrenia: implications for first-episode studies. *Schizophr Res, 33*(1), 27-34. doi:https://doi.org/10.1016/S0920-9964(98)00059-0

34. Dutta, R., Murray, R. M., Hotopf, M., Allardyce, J., Jones, P. B., & Boydell, J. (2010). Reassessing the Long-term Risk of Suicide After a First Episode of Psychosis. *Arch Gen Psychiatry, 67*(12), 1230-1237. doi:10.1001/archgenpsychiatry.2010.157

35. Eaton, W. W., Badawi, M., & Melton, B. (1995). Prodromes and precursors: epidemiologic data for primary prevention of disorders with slow onset. *The American journal of psychiatry, 152*(7), 967-972. doi:10.1176/ajp.152.7.967

36. Egeland, J. A., Blumenthal, R. L., Nee, J., Sharpe, L., & Endicott, J. (1987). Reliability and relationship of various ages of onset criteria for major affective disorder. *J Affect Disord, 12*(2), 159-165. doi:10.1016/0165-0327(87)90009-7

37. Fusar-Poli, P., McGorry, P. D., & Kane, J. M. (2017). Improving outcomes of first-episode psychosis: an overview. *World Psychiatry, 16*(3), 251-265. doi:10.1002/wps.20446

38. Garety, P. A., & Rigg, A. (2001). Early psychosis in the inner city: a survey to inform service planning. *Soc Psychiatry Psychiatr Epidemiol, 36*(11), 537-544. doi:10.1007/s001270170004

39. Ivleva, E. I., Morris, D. W., Moates, A. F., Suppes, T., Thaker, G. K., & Tamminga, C. A. (2010). Genetics and intermediate phenotypes of the schizophrenia--bipolar disorder boundary. *Neurosci Biobehav Rev, 34*(6), 897-921. doi:10.1016/j.neubiorev.2009.11.022

40. Kendell, R. E., & Gourlay, J. (1970). The clinical distinction between the affective psychoses and schizophrenia. *Br J Psychiatry, 117*(538), 261-266.

41. Kendler, K. S. (2020). The Development of Kraepelin's Concept of Dementia Praecox: A Close Reading of Relevant Texts. *JAMA Psychiatry, 77*(11), 1181-1187. doi:10.1001/jamapsychiatry.2020.1266

42. Kenneth S. Kendler, M.D. ,, & Eric J. Engstrom, Ph.D. (2018). Criticisms of Kraepelin's Psychiatric Nosology: 1896–1927. *American Journal of Psychiatry, 175*(4), 316-326. doi:10.1176/appi.ajp.2017.17070730

43. Keshavan, M. S., Morris, D. W., Sweeney, J. A., Pearlson, G., Thaker, G., Seidman, L. J., . . . Tamminga, C. (2011). A dimensional approach

to the psychosis spectrum between bipolar disorder and schizophrenia: the Schizo-Bipolar Scale. *Schizophr Res, 133*(1-3), 250-254. doi:10.1016/j.schres.2011.09.005

44. Kovasznay, B., Fleischer, J., Tanenberg-Karant, M., Jandorf, L., Miller, A. D., & Bromet, E. (1997). Substance Use Disorder and the Early Course of Illness in Schizophrenia and Affective Psychosis. *Schizophr Bull, 23*(2), 195-201. doi:10.1093/schbul/23.2.195

45. Kraepelin, E. (1903). *Psychiatrie : ein Lehrbuch für Studierende und Aerzte*. Leipzig: J.A. Barth.

46. Krebs, M. O., Magaud, E., Willard, D., Elkhazen, C., Chauchot, F., Gut, A., . . . Kazes, M. (2014). Évaluation des états mentaux à risque de transition psychotique : validation de la version française de la CAARMS. *L'Encéphale, 40*(6), 447-456. doi:https://doi.org/10.1016/j.encep.2013.12.003

47. Lambert, M., Conus, P., Lambert, T., & McGorry, P. D. (2003). Pharmacotherapy of first-episode psychosis. *Expert Opin Pharmacother, 4*(5), 717-750. doi:10.1517/14656566.4.5.717

48. Lee, R. S. C., Hermens, D. F., Scott, J., Redoblado-Hodge, M. A., Naismith, S. L., Lagopoulos, J., . . . Hickie, I. B. (2014). A meta-analysis of neuropsychological functioning in first-episode bipolar disorders. *Journal of Psychiatric Research, 57*(1), 1-11. doi:10.1016/j.jpsychires.2014.06.019

49. Malhi, G. S., Green, M., Fagiolini, A., Peselow, E. D., & Kumari, V. (2008). Schizoaffective disorder: diagnostic issues and future recommendations. *Bipolar Disord, 10*(1 Pt 2), 215-230. doi:10.1111/j.1399-5618.2007.00564.x

50. McGorry, P. D. (1994). The Influence of Illness Duration on Syndrome Clarity and Stability in Functional Psychosis: Does the Diagnosis Emerge and Stabilise with Time? *Australian & New Zealand Journal of Psychiatry, 28*(4), 607-619. doi:10.1080/00048679409080784

51. McGorry, P. D. (2002). The recognition and optimal management of early psychosis: an evidence-based reform. *World Psychiatry, 1*(2), 76-83.

52. McGorry, P. D., Killackey, E., & Yung, A. R. (2007). Early intervention in psychotic disorders: detection and treatment of the first episode and the critical early stages. *Med J Aust, 187*(S7), S8-S10. doi:https://doi.org/10.5694/j.1326-5377.2007.tb01327.x

53. McGorry, P. D., Mihalopoulos, C., Henry, L., Dakis, J., Jackson, H. J., Flaum, M., . . . Karoly, R. (1995). Spurious precision: procedural validity of diagnostic assessment in psychotic disorders. *The American journal of psychiatry, 152*(2), 220-223. doi:10.1176/ajp.152.2.220

54. Moller, H. J. (2003). Bipolar disorder and schizophrenia: distinct illnesses or a continuum? *J Clin Psychiatry, 64 Suppl 6*, 23-27; discussion 28.

55. Olvet, D. M., Burdick, K. E., & Cornblatt, B. A. (2013). Assessing the potential to use neurocognition to predict who is at risk for developing bipolar disorder: A review of the literature. *Cognitive Neuropsychiatry, 18*(1-2), 129-145. doi:10.1080/13546805.2012.724193

56. Petersen, L., Jeppesen, P., Thorup, A., Abel, M.-B., Øhlenschlæger, J., Christensen, T. Ø., . . . Nordentoft, M. (2005). A randomised multicentre trial of integrated versus standard treatment for patients with a first episode of psychotic illness. *BMJ, 331*(7517), 602. doi:10.1136/bmj.38565.415000.E01

57. Pompili, M., Serafini, G., Innamorati, M., Lester, D., Shrivastava, A., Girardi, P., & Nordentoft, M. (2011). Suicide risk in first episode psychosis: A selective review of the current literature. *Schizophr Res, 129*(1), 1-11. doi:https://doi.org/10.1016/j.schres.2011.03.008

58. Post, R. M., Leverich, G. S., Altshuler, L. L., Frye, M. A., Suppes, T. M., Keck, P. E., Jr., . . . Walden, J. (2003). An overview of recent findings of the Stanley Foundation Bipolar Network (Part I). *Bipolar Disord, 5*(5), 310-319. doi:10.1034/j.1399-5618.2003.00051.x

59. Proctor, S. E., Mitford, E., & Paxton, R. (2004). First episode psychosis: a novel methodology reveals higher than expected incidence; a reality-based population profile in Northumberland, UK. *J Eval Clin Pract, 10*(4), 539-547. doi:https://doi.org/10.1111/j.1365-2753.2003.00474.x

60. Ratheesh, A., Davey, C. G., Daglas, R., Macneil, C., Hasty, M., Filia, K., . . . Cotton, S. (2017). Social and academic premorbid adjustment domains predict different functional outcomes among youth with first episode mania. *Journal of Affective Disorders, 219*, 133-140. doi:10.1016/j.jad.2017.05.030

61. Reddy, M. S. (2012). The bipolar spectrum. *Indian journal of psychological medicine, 34*(1), 1-4. doi:10.4103/0253-7176.96146

62. Robinson, J., Harris, M. G., Harrigan, S. M., Henry, L. P., Farrelly, S., Prosser, A., . . . McGorry, P. D. (2010). Suicide attempt in first-episode psychosis: A 7.4year follow-up study. *Schizophr Res, 116*(1), 1-8. doi:https://doi.org/10.1016/j.schres.2009.10.009

63. Salazar de Pablo, G., Moreno, D., Gonzalez-Pinto, A., Paya, B., Castro-Fonieles, J., Baeza, I., . . . Moreno, C. (2021). Affective symptom dimensions in early-onset psychosis over time: a principal component factor analysis of the Young Mania Rating Scale and the Hamilton Depression Rating Scale. *Eur Child Adolesc Psychiatry*. doi:10.1007/s00787-021-01815-5

64. Salvadore, G., Drevets, W. C., Henter, I. D., Zarate, C. A., & Manji, H. K. (2008). Early intervention in bipolar disorder, part I: Clinical and imaging findings. *Early Intervention in Psychiatry, 2*(3), 122-135. doi:10.1111/j.1751-7893.2008.00071.x

65. Salvatore, P., Baldessarini, R. J., Khalsa, H. K., & Tohen, M. (2021). Prodromal features in first-psychotic episodes of major affective and schizoaffective disorders. *J Affect Disord, 295*, 1251-1258. doi:https://doi.org/10.1016/j.jad.2021.08.099

66. Sanchez-Gistau, V., Baeza, I., Arango, C., González-Pinto, A., de la Serna, E., Parellada, M., . . . Castro-Fornieles, J. (2015). The affective dimension of early-onset psychosis and its relationship with suicide. *Journal of Child Psychology and Psychiatry, 56*(7), 747-755. doi:https://doi.org/10.1111/jcpp.12332

67. Strakowski, S. M., Keck, P. E., Jr., McElroy, S. L., West, S. A., Sax, K. W., Hawkins, J. M., . . . Bourne, M. L. (1998). Twelve-month outcome after a first hospitalization for affective psychosis. *Arch Gen Psychiatry, 55*(1), 49-55. doi:10.1001/archpsyc.55.1.49

68. Strakowski, S. M., McElroy, S. L., Keck, P. E., & West, S. A. (1996). The effects of antecedent substance abuse on the development of first-episode psychotic mania. *Journal of Psychiatric Research, 30*(1), 59-68. doi:https://doi.org/10.1016/0022-3956(95)00044-5

69. Taylor, M., Bressan, R. A., Pan, P. M., & Brietzke, E. (2011). Early intervention for bipolar disorder: current imperatives, future directions. *Brazilian Journal of Psychiatry, 33*, s197-s212.

70. Thaker, G. K. (2008). Neurophysiological endophenotypes across bipolar and schizophrenia psychosis. *Schizophr Bull, 34*(4), 760-773. doi:10.1093/schbul/sbn049

71. Tohen, M., Hennen, J., Zarate, C. M., Jr., Baldessarini, R. J., Strakowski, S. M., Stoll, A. L., . . . Cohen, B. M. (2000). Two-year syndromal and functional recovery in 219 cases of first-episode major affective disorder with psychotic features. *Am J Psychiatry, 157*(2), 220-228. doi:10.1176/appi.ajp.157.2.220

72. Tohen, M., Strakowski, S. M., Zarate, C., Jr., Hennen, J., Stoll, A. L., Suppes, T., . . . Baldessarini, R. J. (2000). The McLean-Harvard first-episode project: 6-month symptomatic and functional outcome in affective and nonaffective psychosis. *Biol Psychiatry, 48*(6), 467-476. doi:10.1016/s0006-3223(00)00915-x

73. Torrent, C., Reinares, M., Martinez-Aran, A., Cabrera, B., Amoretti, S., Corripio, I., . . . Vieta, E. (2018). Affective versus non-affective first episode psychoses: A longitudinal study. *J Affect Disord, 238*, 297-304. doi:10.1016/j.jad.2018.06.005

74. Waddington, J. L., & Buckley, P. F. (2013). Psychotic depression: an underappreciated window to explore the dimensionality and pathobiology of psychosis. *Schizophr Bull, 39*(4), 754-755. doi:10.1093/schbul/sbt083

75. Yung, A. R., Yuen, H. P., McGorry, P. D., Phillips, L. J., Kelly, D., Dell'Olio, M., . . . Buckby, J. (2005). Mapping the onset of psychosis: the Comprehensive Assessment of At-Risk Mental States. *Aust N Z J Psychiatry, 39*(11-12), 964-971. doi:10.1080/j.1440-1614.2005.01714.x

6. Appendices

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A narrative review of intervention in first-episode affective psychoses

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ABSTRACT

While first-episode schizophrenia has received extensive attention in the literature, few studies have focused on the first episode of affective psychoses. Considering the lack of structured data regarding this diagnostic grouping commonly used in clinical settings, our aim was to scope the literature on first-episode affective psychoses to consolidate current knowledge and to identify areas to be targeted in future studies. We also planned to investigate the relevance of the "affective psychosis" concept regarding diagnostic categories and specific needs of intervention. We conducted a search on the Embase, Medline, PubMed, PsycINFO and Web Of Science databases until October 2020. We selected studies and synthesized the key findings into a narrative review regarding major topics of early intervention research: diagnostic categorization, premorbid factors, intervention, duration of untreated illness, neurobiology and neurocognition. After screening 961 titles and abstracts and 193 full-text papers, we selected 77 studies for inclusion. Our results showed heterogeneity in diagnosis-related grouping under the concept of affective psychoses, especially variability regarding the inclusion of schizoaffective disorder. Nonetheless, this concept still encompasses patients with different psychopathological and neurocognitive profiles from the non-affective patients requiring specialized intervention. This study thus provided support for the relevance of this concept as well as a need for further investigation.

1. Introduction

Early intervention in psychosis offers opportunities to improve care during the critical phase of the first few years of illness to prevent a chronic course of the disorder (Conus and McGorry, 2002). While schizophrenia spectrum disorders have received extensive attention, affective psychoses remain a neglected area of research (Berk, 2007; Chia et al., 2019; Conus et al., 2010; Conus and McGorry, 2002). Affective psychoses encompass patients who, in addition to psychotic symptoms, have a mood syndrome. This group of psychoses includes two forms of the affective disorders DSM-5 diagnostic category (major depression with psychotic symptoms and bipolar disorder with psychotic symptoms), and depending on authors also includes schizoaffective disorder, which is a mixed form between schizophrenia and bipolar disorder (Lambert et al., 2003; Malhi et al., 2008; Proctor et al., 2004; Strakowski et al., 1998), which is classified in the schizophrenia spectrum and other psychotic disorders category (American Psychiatric Association, 2013). Indeed, the large spectrum of psychotic and affective disorders overlaps when affective psychoses are concerned reflecting the dimensional nature of the disorders rather than innate and distinct diagnostic categories (Lambert et al., 2003; Malhi et al., 2008; Proctor et al., 2004; Strakowski et al., 1998). First-episode affective psychosis thus includes patients who in addition to the onset of psychosis revealed manic, depressive, or mixed form of mood disturbance. While largely neglected in the literature, affective psychoses represent an important proportion (~30%) of the diagnoses in first-episode psychosis programs (Proctor et al., 2004), and there is a considerable risk of relapse and poor outcome if not treated adequately (Berk, 2007; Conus and McGorry, 2002; Strakowski et al., 1998).

Early intervention in affective psychoses is especially challenging considering that despite a good syndromic recovery, symptomatic and functional recoveries remain poor (Conus et al., 2006b; Strakowski et al., 1998). Furthermore, previous literature reported that patients combining mood disturbance with psychosis are at high risk of suicidal behaviour, non-adherence to treatment as well as substance abuse and may also have comorbidity leading to poor prognosis without adapted treatment (Berk, 2007; Conus et al., 2006a,b; Conus and McGorry, 2002; Smith et al., 2014; Strakowski et al., 2000; Zarate and Tohen, 2000). The common overlap between mood and psychotic symptoms in schizophrenia spectrum disorders (~30% depression; Majadas et al., 2012),

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bipolar disorder (~58% experience at least one psychotic symptom; Goodwin and Jamison, 2007), and major depressive disorder (~15% psychotic features; Johnson et al., 1991) should also urge the development of early intervention for such sensitive population. Despite these challenging issues, the early phase of affective psychoses remains understudied (Chia et al., 2019; Conus and McGorry, 2002). Moreover, affective psychoses are often included in larger studies on first-episode, failing to provide guidelines and intervention packages adapted to the specific needs of these patients (Chia et al., 2019; Marwaha et al., 2018). In addition, much of the available data on this sub-group of disorders has often focused on specific symptomatic phases, mainly first-episode mania (Chang et al., 2016; Conus and McGorry, 2002; Strakowski et al., 1996; Tohen et al., 2000a,b), and very few studies have explored the larger domain of First-Episode Affective Psychoses (FEAP).

A review of early intervention in FEAP would enable to synthesize our current scientific knowledge on this topic to fill an important research gap. Moreover, it would enable to point out the potential specific treatment needs and challenges of intervention in first-episode affective psychosis to better inform clinical practice but also to highlight issues that has to be investigated in further studies. Thus, it may be a useful study to ultimately improve outcomes for people with FEAP. In light of this, we conducted a narrative review of the literature on early intervention in FEAP. In this narrative review, we selected and synthesized the main findings of the literature on early intervention in FEAP regarding what we consider as major topics of early intervention research: 1) diagnostic categorization, 2) premorbid factors, 3) intervention, outcomes, 4) duration of untreated illness, 5) neurobiology and neurocognition.

2. Method

2.1. Data sources and search strategy

A literature search based on an exhaustive search strategy (Bramer et al., 2018) was performed in five bibliographic databases (June 2019, updated in October 2020): Embase.com, Medline Ovid SP, PubMed (not Medline), PsycINFO Ovid SP and Web Of Science. This search strategy was developed to screen most of the studies available to provide a representative review of the literature on early intervention in FEAP. The search strategies were developed in collaboration with a librarian. They were adapted to the syntax and subject headings of each database and performed without date restrictions. For the full search strategy, see appendix 1.

2.2. Study selection

We screened all studies on FEAP based on predefined inclusion criteria: (1)"Affective psychoses" including schizoaffective disorder, bipolar disorder with psychosis and major depressive disorder with psychosis; (2) first-episode psychosis including patients who met the psychosis threshold criteria for the first time; (3) early intervention including any kind of psychiatric or psychological intervention. Exclusion criteria were (1) non-affective psychosis including schizophrenia, schizophreniform disorders (2) intoxication or organic brain disease psychotic disorder (3) first-episode affective disorders without psychotic features (4) early intervention for other disorders. In the first screening on abstracts, key words, and titles, we selected studies mentioning the first episode or early intervention without specification and at least one of the affective psychoses previously mentioned. Studies on schizotypy, high-risk populations, or prodromal periods were excluded, as were studies on first-episode schizophrenia. Then, the full texts of all potentially eligible studies were reviewed. In the selection based on the full text, we removed conference abstracts and book sections to ensure that the content was a direct source of study and had been reviewed by experts. We also removed the remaining studies not mentioning results regarding affective psychoses and the first episode. One expert reviewer in the field performed every step in the selection process and handpicked additional papers that were relevant to the subject. We only included studies in English and French.

3. Results

The screening of the electronic databases identified 961 eligible papers. Thirteen additional papers from other sources were added. Of these, 77 articles met the final criteria for inclusion after the screening and selection process (Fig. 1). We organized the results by themes that emerged from the selected papers.

3.1. Justifications for specific early intervention and challenges (Table 1)

Early intervention in FEAP seems particularly important since the delay until the introduction of an appropriate treatment after the onset and the number of manic episodes are associated with greater risk of relapse, severe cognitive deficits, and worse general outcome (Conus and McGorry, 2002). However, although some clinical cues of the very early phase of mania have been identified, the challenge in establishing early intervention strategies remains complex since no clear consensus has been established to identify the actual onset of illness (Conus, 2010). Furthermore, the identification of affective psychoses is difficult, especially bipolar disorder with insidious or depressive onset. In addition, the high prevalence of atypical features of mania during adolescence or early adulthood (with a higher prevalence of irritability rather than euphoria, for example) leads to a broad differential diagnosis with schizophrenia, personality disorders or behavioural disorders (Berk, 2007; Conus et al., 2010).

Once identified, the treatment itself is challenging as well, considering difficulties in engaging patients and the high prevalence of suicidal behaviour, comorbid substance misuse and relapses (Berk, 2007), as well as potential difficulty in parenting (Craig and Bromet, 2004).

3.2. Diagnostic categorization (Table 2)

3.2.1. Diagnostic issues

In 1997 in the UK, clinicians developed an observational database of an unselected population with first-episode psychosis (Proctor et al., 2004). They found an annual incidence for affective psychoses of 8.43 per 100 000 population per year, psychotic depression (19%) being the most common of these diagnoses (Proctor et al., 2004). These results highlighted the importance of affective psychoses within a cohort of first-episode psychosis. However, diagnosis is difficult to establish in first-episode patients (Radmanović, 2012) and may change within the first years (Pedrós et al., 2009) due to the emergence of mood episodes. For example, in this latter study, an initial diagnosis of schizophreniform and not otherwise specified psychotic disorders could evolve towards schizophrenia or affective psychoses over time, and none of the socio-demographic and clinical variables were significantly predictive of this evolution. Arrasate et al. (2014) suggested that affective dimensions play an important role in these diagnostic issues. Indeed, while activation dimensions predicted a diagnosis of bipolar disorder, early misdiagnosis was predicted by the presence of a depressive dimension but not by a manic dimension. To accurately differentiate psychotic disorders, Salvatore et al. (2007) suggested using psychopathological features at onset. They found four subtypes of patients including mania with psychosis (I), mixed depressive-agitated state (II), excited-hallucinatory-delusional state (III), and disorganized-catatonic-autistic state (IV). Subtypes I and III were associated with mania, II with major depression or bipolar mixed state, and IV with major depression but negatively associated with mania.

Despite these diagnostic issues, Subramaniam et al. (2007) found that schizophrenia and affective psychoses were the most stable diagnoses. This result is in line with Coentre et al. (2011), who reported no cross-diagnosis between bipolar disorder and schizophrenia or schizophreniform disorder (schizophrenia criteria for more than a month but

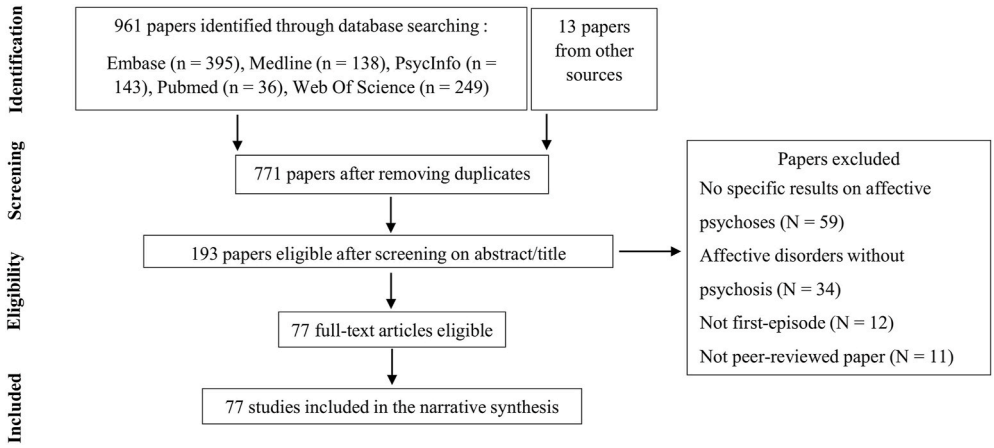

Fig. 1. Flow diagram of the process of study selection for the review.

Table 1
Summary of results on justifications for specific early intervention and challenges in first-episode affective psychoses.

Study	Method	Country	Population (N; age)	Follow-up	Key findings
Berk (2007)	Review		Bipolar disorder		• specific challenges AP: psychotic symptoms, poor insight and rapid relapses associated with non-adherence to medication, high comorbidity with substance misuse, high risk of suicide and the impact of illness on the family • the bipolar disorder onset is often insidious starting with depression
Conus et al. (2010)	Review		Bipolar disorder		• atypical features of mania during adolescence or early adulthood • clinical cues of mania: irritability, increase of energy, flight of thoughts, euphoria • no consensus to identify the onset of illness • 60% of adolescents with a first episode of mania would also have psychotic symptoms • positive symptoms (self-recognition disorder), supposed to be specific to schizophrenia, can also be present in bipolar disorder • anomalous self-experience specific to schizophrenia • key manic features in first episode psychosis (irritability and increase of energy) have to be carefully differentiated from elements of behavioral disorders
Conus and McGorry (2002)	Review		First-episode mania		• symptomatic recovery AP > NAP • 40% of patients with first manic episode experience functional recovery at 24 months • worse outcomes in patients with mixed episode • the delay until the introduction of an appropriate treatment after the onset and the number of manic episodes associated with greater risk of disruptive effects such as relapse, severe cognitive deficits and worse general outcome • earlier onset of bipolar disorder associated with greater risk of psychotic features and greater severity of symptoms, worse outcomes and more comorbidities
Craig and Bromet (2004)	Descriptive study	USA	First-admission psychosis (N = 453; 15–60 years)	24 months	• at the entry, nearly half of females with mood disorders were parents and 29.1% of females with schizophrenia/schizoaffective • the highest lifetime substance use disorder rates for mothers in the bipolar disorder group (41.9%), 37% in the major depression group • 75% of fathers with bipolar disorders, and 50% with major depressive disorder lived with children at the entrance, only 5–15% of parents lived with their children at 6 months follow-up • postpartum psychosis is not more frequent AP than in NAP • frequent thoughts of harm regarding child requiring close attention after childbirth

Note. *AP = Affective psychoses; NAP = Non-Affective psychoses.

less than 6 months) in classifications, suggesting a good practical use of classifications in the diagnostic process. It is important to note that while assessment by a specialized professional team may ensure high diagnostic stability, a differential diagnosis between bipolar and schizoaffective disorders requires longitudinal follow-up (Schimmelmann et al., 2005; Schottle et al., 2012).

3.2.2. *Differentiation between affective and non-affective psychoses*

In general, presenting an affective psychosis rather than schizophrenia predicts better clinical and functional outcomes, and patients with first-episode mania may be more likely to achieve functional remission than first-episode with schizophrenia (Chang et al., 2016; Henry et al., 2010). However, contact with care usually occurs later in adolescents with affective psychoses than those with schizophrenia (Emck et al., 2001). Other inter-group differences were reported, for example, adolescents with affective psychoses were more likely to be females and to have manic symptoms (Emck et al., 2001). They reported no differences regarding premorbid functioning and depressive symptoms. In another prospective study including both adolescents and young adults, Harris et al. (2005) found that the affective psychosis group was younger, included more females and had better psychosocial functioning than the non-affective psychosis group. Although patients with affective psychosis may recover more rapidly, they were significantly impaired overall.

Furthermore, some studies specifically differentiated subgroups of affective psychoses from other psychotic disorders. Macmillan et al.

Table 2
Summary of results on diagnostic categorization in first-episode affective psychoses.

Study	Method	Country	Population (N; age)	Follow-up	Key findings
Diagnostic issues					
Arrasate et al. (2014)	Prospective study	Spain	First-episode psychosis (N = 112; Mean age = 28.8)	5 years	• mood dimensions, a good diagnostic tool to differentiate affective from non-affective psychoses • patients with bipolar disorder scored higher on manic symptoms both at baseline and at follow-up • activation dimension predicted a bipolar disorder at follow-up • absence of manic and presence of depressive symptoms predicted early misdiagnosis
Coentre et al. (2011)	Restrospective study	England	First-episode psychosis (N = 148; 25.5)	24 months	• no cross-diagnosis between bipolar disorders and schizophrenia/schizophreniform disorders confirming the existence of two distinct entities • the highest agreement between classifications in affective disorders, namely in major depressive disorders with psychotic features • no difference between classifications for rating psychotic depression, mania/bipolar disorder with psychosis
Schimmelmann et al. (2005)	Prospective study	Australia	First-episode psychosis (N = 492; Mean age = 22.0)	18 months	• Schizophrenia, schizoaffective disorder, bipolar disorder were the most stable diagnoses, schizophreniform disorder were the least stable • High diagnostic stability with assessment of patient and family by a specialized team • Longitudinal follow-up necessary especially for diagnoses such as schizophreniform disorder and bipolar disorder
Subramaniam et al. (2007)	Prospective study	Singapore	First-episode psychosis (N = 154; 18–41 years)	24 months	• schizophrenia and affective psychoses were the most stable diagnosis • a shorter DUP predicted a diagnostic change at follow-up
Pedrós et al. (2009)	Prospective study	Spain	First-admission with acute psychosis (N = 48; Mean age = 28.1)	24 months	• diagnosis difficult to establish in first episode patients, may change within the first years • a diagnosis of schizophreniform and not otherwise specified psychotic disorders predicted an evolution toward schizophrenia and affective psychoses • none of the sociodemographic and clinical variables predicted the diagnostic evolution
Proctor et al. (2004)	Epidemiological study	England	First-episode psychosis (N = 227; ≥15 years)		• the commonest diagnoses were psychotic depression (19%) paranoid schizophrenia (11%), persistent delusional disorder (7%) and bipolar affective disorder (7.5%) • annual incidence for affective psychoses of 8.43 per 100 000 population per year
Radmanović (2012)	Review		First-episode psychosis (children & adolescents)		• distinguishing schizophrenia and bipolar disorder in psychotic adolescents is a key diagnostic issue
Schottle et al. (2012)	Epidemiological study	Australia	First-episode psychotic mania (N = 134; Mean age = 22.3)	18 months	• schizoaffective disorder associated with longer DUP, higher illness severity and non-adherence rate at baseline, more traumatic events than bipolar disorder • at follow-up, patients with bipolar disorder had better social functioning, less illness severity, more likely to achieve remission in positive symptoms, and to be employed than those with schizoaffective disorder
Affective and non-affective distinctions					
Chang et al. (2016)	Prospective study	China	First-episode mania with psychotic features and schizophrenia (N = 420; 15–25 years)	3 years	• patients with first episode mania were younger, more likely to be hospitalized, had shorter DUP, had more severe positive symptoms and lower functioning at baseline compared to first episode schizophrenia • at follow-up, patients with first episode mania, had milder positive symptom severity, higher rates of sustained employment, better functioning and functional remission than patients with first episode schizophrenia • first episode of psychotic mania rather than schizophrenia predicted better clinical and functional outcomes
Emck et al. (2001)	Retrospective study	Netherlands	Early psychosis (N = 129; 12–18 years)		• shorter DUP in adolescents with affective vs non-affective psychoses • adolescents with schizophrenia have treatment contact 2 months before the onset of prodromal symptoms whereas it takes place 8 months after in affective psychoses • adolescents with non-affective psychoses were more likely to be boys, had more adjustment problems at school, had more frequently drug use, as well as positive and negative symptoms • no difference between groups regarding depressive symptoms but manic symptoms were more frequent in affective psychoses • adolescents with affective psychoses were more likely to be girls • no difference between groups on premorbid functioning
Harris et al. (2005)	Restrospective study	Australia	First-episode psychosis (N = 94; 13–25 years)		• "mood disorder" psychosis group was younger, included more females, had a better psychosocial functioning than "schizophrenia" and "mixed" psychosis

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Table 2 (*continued*)

Study	Method	Country	Population (N; age)	Follow-up	Key findings
Kapila et al. (2019)	Prospective study	England	First-episode psychosis (N = 1014; 18–35 years)	12 months	• atypical antipsychotics were similarly used across groups but the "mood disorder" group more likely to be prescribed mood stabilizers and to be polymedicated • patients with "mood disorder" psychosis may recover more rapidly but significantly impaired overall • patients with manic psychosis were younger, had shorter DUP, higher level of education, compared to both depressive and schizophrenia-spectrum psychoses • patients with manic psychosis had more manic symptoms, lower positive and negative symptoms at presentation than both depressive and schizophrenia-spectrum psychoses • patients with depressive psychosis were older, had lower positive symptoms at baseline and were more likely to be white
Macmillan et al. (2007)	Prospective study	England	First-episode bipolar psychoses (N = 78; 14–35 years)	12 months	• bipolar psychoses had lower level of negative symptoms, better quality of life and functioning at 3–6 months and at follow-up than other psychoses
Selvendra et al. (2014)	Descriptive study	Australia	First-episode psychosis (N = 164; 16–65 years)		• higher proportion of depression with psychotic features in older onset patients (over 40 years), higher rates of metabolic issues (diabetes, cholesterol, lipids, weight gain) and longer DUP than other psychoses • a majority of females in patients with depression with psychotic features
Sim et al. (2007)	Prospective study	Singapore	First-episode schizophrenia and schizoaffective disorder (N = 278; 18–40 years)	24 months	• schizoaffective disorder was associated with a higher level of education, a better employment status, a shorter DUP, higher scores on general psychopathology than schizophrenia • a shorter DUP was associated with better subjective quality of life.

Note. *DUP = Duration of Untreated Psychosis.

(2007) indicated that bipolar psychoses can be distinguished from other psychotic disorders based on a lower level of negative symptoms at the one-year follow-up. Kapila et al. (2019) reported that patients with manic psychosis were younger and had shorter Duration of Untreated Psychosis (DUP) compared to both depressive and schizophrenia-spectrum psychoses. They also found that they had a higher level of education and more manic symptoms but fewer positive and negative symptoms at presentation. Additionally, patients with schizoaffective disorder differed from those with schizophrenia by higher levels of education, better employment status, and shorter DUP but higher scores on general psychopathology (Sim et al., 2007). Finally, patients with depression with psychotic features were more likely to have metabolic issues and a longer DUP than those with other psychotic disorders (Selvendra et al., 2014). Depression with psychotic features may be more frequent in older-onset patients and females (Macmillan et al., 2007). Kapila et al. (2019) also reported that these patients, compared to those with manic and schizophrenia-spectrum psychosis, were older, had lower positive symptoms at baseline and were more likely to be white.

3.3. Premorbid factors (*Table 3*)

Regarding socio-demographic information, premorbid characteristics seem to differ between affective and non-affective psychoses. While non-affective psychosis occurred more often in economically deprived, isolated places with less racial/ethnic diversity, affective psychoses were more likely to occur in neighbourhoods with lower intragroup racial/ethnic density and higher intragroup racial/ethnic fragmentation (Richardson et al., 2018). Otherwise, affective psychoses were associated with more stable social support (DeVylder and Gearing, 2013) and with shorter help-seeking delays than non-affective psychoses (O'Callaghan et al., 2010). Among those with affective psychoses, premorbid characteristics may also depend on gender. Indeed, Cotton et al. (2013) reported that females were more likely to have experienced sexual abuse, while men were more likely to have experienced forensic issues, as well as antecedents of drug abuse (Strakowski et al., 1996).

Certain issues are highly prevalent in the history of patients with affective psychoses and may affect the course of illness. Firstly, the prevalence of past traumatic events experienced directly and personally was very high (48%) in first-episode psychotic mania (Daglas et al., 2014). Most patients had been exposed to stressful life events during childhood or adolescence (Conus et al., 2010). A history of direct personal trauma was associated with poorer social and occupational functioning, as well as higher levels of manic, depressive and general symptoms at follow-up (Daglas et al., 2014). Although the experience of psychosis in itself can be an opportunity for growth, it is another important traumatic issue (Dunkley et al., 2007). Secondly, past substance abuse is widespread in first-episode affective psychoses and may influence the onset of illness and the time to hospitalisation (Strakowski et al., 1996). Indeed, antecedents of both alcohol and drug abuse, relative to their absence, were associated with more manic symptoms and more rapid hospitalisation in bipolar disorder (Strakowski et al., 1996). Patients with a history of alcohol abuse had a later onset than those without any past drug abuse.

3.4. Intervention (*Table 4*)

3.4.1. Pharmacological treatment

There are few guidelines for the treatment of first-episode mania (Power, 2015). Treatment in first-episode mania leads to full remission of the manic syndrome in most cases, but it may take longer for males, younger patients or those with psychotic features or a longer duration of untreated mania (Power, 2015). Available recommendations for the treatment of first-episode mania are similar in children and adults according to Power (2015) but with poor response rates in children. There is a stronger evidence base for the use of atypical antipsychotics than lithium in children and adolescents. Furthermore, combination therapies are more effective for severe presentations (Power, 2015). Pharmacological treatment in first-episode affective psychoses also depends on the type of episode (Douki et al., 1999). Lambert, Conus, Lambert, and McGorry (2003) recommended treating psychotic and affective syndromes as two dimensions using an accurate assessment of both. However, antipsychotics can be used as adjunctive treatment for FEAP regardless of manic or depressive aspects. Benzodiazepines can help

Table 3
Summary of results on premorbid factors in first-episode affective psychoses.

Study	Method	Country	Population (N; age)	Follow-up	Key findings
Socio-economic factors					
Cotton et al. (2013)	Prospective study	Australia	First-episode psychotic mania (N = 118; Mean age = 22.4)	18 months	• males were more likely to have past history of substance use and forensic issues • females were more likely to have experienced sexual abuse • at service entry, males had more substance use issues (cannabis) but were more likely to stop substance use during treatment than females. Males had also a more severe form of illness and poorer functioning • at follow-up, men were more likely to live with their families and there were no gender differences regarding psychopathology or functioning
DeVylder and Gearing (2013)	Retrospective study	Canada	First-episode psychosis adolescents (N = 84; Mean age = 14.7)		• bipolar disorder and manic symptoms associated with more stable social support
O'Callaghan et al. (2010)	Retrospective study	Ireland	First-episode psychosis (N = 142; 16–65 years)	18 months	• AP associated with shorter help-seeking delays both in the prodromal and psychotic phases than NAP
Richardson et al. (2018)	Epidemiological study	England	First-episode psychosis (N = 631; Mean age = 23.8)		• reduced risk of AP associated with higher intragroup racial/ethnic density and lower intragroup racial/ethnic fragmentation.
Trauma					
Conus et al. (2010)	Prospective study	Australia	First-episode psychotic mania (N = 118; Mean age = 22.4)	18 months	• 80% first-episode psychotic mania experienced stressful life events during childhood or adolescence • 24.9% of sexual or physical abuse history, and 29.8% of females sexually abused • Patients sexually or physical abused had poorer functioning and higher rates of forensic history, more likely to disengage from treatment and less likely to live with their family • history of sexual or physical history was not associated with poorer symptomatic or functional outcome
Daglas et al. (2014)	Prospective study	Australia	First-episode psychotic mania (N = 65; Mean age = 21.60)	12 months	• very high prevalence (48%) of past traumatic events experienced directly and personally • no difference on global functioning at discharge • patients with past history of direct-personal trauma had poorer social and occupational functioning, higher levels of manic, depressive and general symptoms at follow-up
Dunkley et al. (2007)	Qualitative study	Australia	First-episode psychosis (Bipolar I disorder) (N = 2; 22 and 25 years)		• the experience of psychosis, treatment, symptoms, loss of control, powerlessness, the impact on relationships and insight on illness are traumatic • the experience of psychosis can be an opportunity of growth regarding appreciation of life, deeper relating to others, enhanced perceptions of personal strength, and creation of new opportunities
Substance abuse					
Strakowski et al. (1996)	Retrospective study	USA	First-episode psychotic mania (N = 59; Mean age = 25)		• past alcohol abuse was associated with later onset than those without any drug abuse • both antecedent of alcohol and drug abuse were associated with more manic symptoms and more rapid hospitalization than those without any substance abuse antecedents • men were more likely than females to have an antecedent of drug abuse

Note. *AP = Affective psychoses; NAP = Non-Affective psychoses.

with behavioural disturbances, agitation and insomnia. If psychotic symptoms persist, it is recommended to first switch to another atypical antipsychotic and continue with the mood stabilizer.

Furthermore, Conus, Berk, and McGorry (2006) concluded that mood stabilizers, in contrast to antipsychotics, were often not prescribed in first-episode mania with psychotic features. They also highlighted poor treatment adherence in first-episode mania. Moreover, although atypical antipsychotics constitute a promising alternative to typical neuroleptics in acute mania, their prescription requires high awareness regarding side effects. Salvadore, Drevets, Henter, Zarate, and Manji (2008b) reported that both valproate and olanzapine are efficient pharmacological strategies in FEAP. Finally, Conus et al. (2015) showed that olanzapine and combined chlorpromazine and lithium had similar safety profiles, although olanzapine showed a higher rate and earlier occurrence of mania remission.

Recently, Chia and colleagues' (2019) manuscript, in addition to mentioning a lack of specific guidelines for first-episode mania patients, summarized current knowledge. It put forward that (a) a combination of mood stabilizers and atypical antipsychotics should be used, (b) past occurrences of manic or hypomanic episodes should always be investigated in first-episode depression patients, (c) lithium acts as a first-line mood stabilizer, followed by valproate as second-line treatment, and (d) risperidone, quetiapine, ziprasidone, and aripiprazole are the recommended atypical antipsychotic medications. They also mentioned the absence of recommendations regarding the duration of maintenance treatment. As maintenance treatment in first-episode mania, Jauhar et al. (2019) recommended lithium but raised concerns regarding tolerability and adherence.

3.4.2. *Psychosocial interventions*

Psychosocial interventions are essential to reduce residual symptoms, prevent recurrence of mood episodes, improve psychosocial functioning, and to sustain remission in first-episode mania (McMurrich et al., 2012; Power, 2015). The development of a clear care package of early intervention and further professional training on the identification and management of FEAP are required (Marwaha et al., 2018). It is also necessary to develop psychoeducation and psychological interventions targeting engagement, the development of insight, adherence to treatment, comorbidities such as substance abuse, social phobia, self-esteem, and vocational recovery strategies that take into account the effect of illness on age-appropriate developmental tasks (Douki et al., 1999). Therefore, previous studies explored the implementation of psychosocial interventions.

Macneil et al. (2012) tested a manualized psychological

Table 4
Summary of results on intervention in first-episode affective psychoses.

Study	Method	Country	Population (N; age)	Follow-up	Key findings
Pharmacological treatment					
Chia et al. (2019)	Review		Bipolar disorder		• A lack of differentiation first vs multiple episodes in guidelines • For a first episode psychotic mania or depression, a combination of mood stabilizers and atypical antipsychotics is the first-line treatment • Past manic or hypomanic episodes should be explored in case of a first episode depression • The first-line mood stabilizer is lithium carbonate, sodium valproate the second-line • Second generation antipsychotics recommended are risperidone, quetiapine, ziprasidone, and aripiprazole • In case of inadequate response, switching to another second-generation anti-psychotic and optimizing psychosocial intervention • A lack of guidelines regarding the duration and dose of maintenance treatment
Conus et al. (2006a)	Review		Bipolar disorder		• mood stabilizers often not prescribed in first-episode mania with psychotic features contrary to antipsychotics • treatment with mood stabilizers is stopped very early and treatment adherence is poor in first-episode mania • characterizing mania and depression leading to bipolar disorders to reduce delay before introducing appropriate treatment atypical antipsychotics, a promising alternative to typical neuroleptics in acute mania, but their prescription requires awareness regarding side effects (extra-pyramidal syndromes, tardive dyskinesia)
Conus et al. (2015)	RCT	Australia	First-episode psychotic mania (N = 74; Mean age = 21.5)	8 weeks	• similar safety profile of olanzapine and chlorpromazine plus lithium • higher rate and earlier occurrence of mania remission with olanzapine
Daglas et al. (2016)	RCT	Australia	First-episode mania (N = 34; Mean age = 21.41)	12 months	• for most cognitive domains, similar effects of treatment with lithium vs quetiapine • better improvement in phonemic fluency when participants were treated with lithium vs quetiapine
Douki et al. (1999)	Review		First-episode psychosis		• a manic episode can be treated with both mood stabilizers and antipsychotics or with antipsychotics • a depressive episode can be treated with both antidepressants and antipsychotics
Jauhar et al. (2019)	Review		First-episode mania		• pharmacological treatment for acute mania should consider recommendations for established illness • lithium may be the gold standard treatment for maintenance treatment • for individuals with concerns regarding adherence and tolerability with lithium, low-dose antipsychotics may be more tolerable with less propensity for weight gain • maintenance treatment should be based on natural course of illness considering previous mood symptoms, and taking into account variability in efficacy of antipsychotic medication as maintenance treatment
Lambert et al. (2003)	Review		First-episode psychosis		• treating psychotic and affective syndromes as two dimensions with accurate assessment of both, subtyping regarding the course and psychosocial features • antipsychotics the most commonly prescribed adjunctive treatment in FEAP which can be introduced regardless of manic or depressive aspect • Benzodiazepines added for behavioral disturbances, agitation and insomnia • for long-term treatment, antipsychotic treatment should be discontinued for 6–8 weeks until the full remission of the affective syndrome in bipolar disorder, a schizoaffective disorder should be treated with a combination of mood stabilizer and atypical antipsychotic • if psychotic symptoms persist, first switch to another atypical antipsychotic and continue with the mood stabilizer
Power (2015)	Review		Bipolar disorder		• treatment in first-episode mania lead to full remission in 6 weeks in 50% of cases, take longer for males, younger patients or those with psychotic features or a longer duration of untreated mania • patients with adult onset will achieved remission by 1 year in 90% of cases, adolescents in 85% of cases • lithium, valproate or atypical antipsychotic remain the first line of treatment • phase-specific pharmacological treatment would be useful • combination therapy is more efficacious for severe presentation • similar treatment in children and adults, but poor response rates in children • in children and adolescents, atypical antipsychotics have a stronger evidence base than lithium. Lamotrogine is not recommended (risk of fatal skin rashes), little evidence in favor of valproate or carbamazepine, risperidone is approved for a brief use with greater safety concerns
Salvadore et al. (2008b)	Review		Bipolar disorder		• Valproate (mood stabilizer) and olanzapine (atypical antipsychotic) efficient pharmacological strategy and commonly used in first-episode AP
Zarate and Tohen (2000)	Prospective study	USA	First-episode psychosis (N = 158; Mean age = 30.6)	6 months	• Lower antipsychotic medication exposure in manic patients than in nonaffective psychotic patients at follow-up • Manic patients more likely to be treated with mood stabilizer than nonaffective psychotic patients • Manic patients more likely to receive lower doses of antipsychotics at discharge, at follow-up than the nonaffective group, and if recovered

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Table 4 (*continued*)

Study	Method	Country	Population (N; age)	Follow-up	Key findings
					• No difference between groups regarding the frequency of antipsychotic medication use
Psychosocial interventions					
Douki et al. (1999)	Review		First-episode psychosis		• necessary to develop psycho-education and psychological interventions targeting engagement, development of insight, adherence to treatment, comorbidities (substance abuse), social phobia, self-esteem, vocational recovery strategies and that would consider the effect of illness on age-appropriate developmental tasks
Macneil et al. (2012)	RCT	Australia	First-episode mania (N = 40; Mean age = 21.5)	18 months	• the manualized psychological intervention for bipolar disorder had a significant effect on depressive and general symptoms but not on manic symptoms, improved significantly social and occupational functioning after 18 months, no significant effect regarding number or type of relapses
Marwaha et al. (2018)	Qualitative study	England	Staff of an intervention service		• sufficient knowledge about AP • the development of clear package in early intervention of AP and more training required
Maurel et al. (2010)	Review		First-episode mania		• Important to establish a good therapeutic alliance for treatment adherence and psychoeducation for patients and their relatives • observance is one main challenge considering the severity of a first episode requiring biotherapy, and the young addict population affected
McMurrich et al. (2012)	Review		First-episode mania		• psychosocial interventions reduce residual symptoms, prevent recurrence from mood episodes, improve psychosocial functioning • pharmacotherapy showed good results for acute episodes but not for sustained remission
Perlini et al. (2020)	Review		Early psychosis		• mindfulness-based intervention may improve symptomatology, functioning, emotion regulation, and reduced the psychological distress of the onset of mania and/or psychosis • it may be a feasible, well-tolerated, and effective approach
Power (2015)	Review		Bipolar disorder		• psychological interventions promote recovery, reduce risk of relapses and secondary morbidity in first-episode mania • psychoeducation, cognitive behavioral therapy (CBT) have shown good results in bipolar disorder, especially early in the course of illness, and with young people • In young people, adding CBT to medication reduces risk of relapse and is cost saving • family interventions reduce rates of mania and depression at 12 months follow-up for young people with a bipolar disorder • psychotherapy, self-help resources (books) provide useful support • young first-episode people need practical advice to re-establish a daily routine, long term-recommendations should include information about drugs, alcohol, stimulants, steroids, childbirth and reducing risk for one's children
Vallarino et al. (2015)	Review		Bipolar disorder		• the Internet is an effective way of delivering individualized intervention, improves social connectedness, reduces depressive symptoms and showed high uptake to the program • better clinical and functional outcomes in bipolar disorder than schizoaffective disorder to integrated and individualized case management intervention

Note. *AP = Affective psychoses; NAP = Non-Affective psychoses.

intervention. They found that this intervention improved depressive and general symptoms but not manic symptoms. It also improved social and occupational functioning after 18 months. Perlini et al. (2020) reported that mindfulness-based intervention may also be effective, especially to reduce distress associated with the onset of mania and/or psychosis. Furthermore, psychoeducation, Cognitive Behavioural Therapy (CBT), and family interventions have shown good results in bipolar disorder, especially in the early course of illness, and with young people (Power, 2015). Otherwise, Vallarino et al. (2015) suggested the Internet as a suitable way of delivering individualized interventions.

In addition to psychotherapy, self-help resources, practical advice to re-establish a daily routine, and long-term recommendations may be crucial in FEAP (Power, 2015). Not only does psychosocial intervention requires several therapeutic tools, but also a good therapeutic alliance for treatment adherence combined with psychoeducation for patients and their relatives (Maurel et al., 2010). However, some differences between bipolar and schizoaffective disorders in therapeutic response, especially to integrated and individualized case management intervention, suggests the necessity of more intense care for schizoaffective disorder (Vallarino et al., 2015).

3.5. Outcomes (Table 5)

3.5.1. Symptoms

Some studies investigated symptomatic differences within affective psychoses. In a study on first-episode mania, Azorin et al. (2012) pointed out that people with a unique episode can be distinguished from those experiencing multiple episodes by more psychotic and fewer depressive symptoms but not by temperament and anxiety. In contrast, higher level of anxiety, and especially social anxiety, distinguished patients with unipolar depression from those with bipolar disorder (Scott et al., 2013). Sub-groups differences within bipolar I manic patients on mood symptoms (depressive, manic, mixed) expressed at onset were also observed (Azorin et al., 2011).

Otherwise, symptomatic recovery seems challenging in affective psychoses. Although a majority of adolescents or adults with affective psychoses achieved syndromal recovery (8 weeks without a depressive or manic episode), they did not achieve symptomatic recovery (8 contiguous weeks with minimal affective symptoms) within 2 years after a first episode (Salvadore, Drevets, Henter, Zarate and Manji, 2008a). A more frequent and rapid syndromic recovery was associated with full compliance (Strakowski et al., 1998). However, although the development of insight has a large impact on hospital admission (Ramu et al., 2019), it may partially improve the course of symptoms in FEAP (Smith

Table 5
Summary of results on outcomes in first-episode affective psychoses.

Study	Method	Country	Population (N; age)	Follow-up	Key findings
Symptoms					
Azorin et al. (2011)	Retrospective study	France	First-episode bipolar I disorder (N = 1008; Mean age = 42.9)		• patients with manic onset had a hyperthymic temperamental predisposition, had a first episode triggered by substance abuse, an illness course with pure, severe and psychotic mania. • patients with depressive onset had a first episode triggered by stress and alcohol, had an illness course with more episodes, cyclicity, suicide attempts, anxious comorbidity and residual symptoms • patients with mixed episode at onset shared characteristics with both manic and depressive onset but had more mixed episodes and cyclothymic temperament
Azorin et al. (2012)	Retrospective study	France	First- and multiple-episode mania (N = 1090; 18–65 years)		• people with first episode mania had more psychotic and fewer depressive symptoms but were comparable to multiple episode patients regarding temperament and anxiety • the prodromal phase of first episode mania was characterized by a shorter delay before correct diagnosis, greater substance use, being not divorced, greater stressors before current mania, a prior diagnosis of an anxiety disorder, lower levels of depression during index manic episode, more suicide attempts in the past year
Ramu et al. (2019)	Prospective study	England	First-episode psychosis (N = 2026; both children and adults)	from 12 to 60 months	• poor insight was positively associated with age 16–35, bipolar disorder, history of cannabis use, and negatively associated with white ethnicity and depression • poor insight was significantly associated for higher levels of outcomes (number of psychiatric hospital admission, legally enforced admission, number of unique antipsychotics prescribed, number of inpatient days) at follow-up
Salvatore et al. (2007)	Prospective study	USA	First-episode psychosis (N = 377; Mean age = 30.8)	24 months	• Psychopathological features gathered into four factors: mania with psychosis (I), mixed depressive-agitated state (II), excited-hallucinatory-delusional state (III), disorganized-catatonic-autistic state (IV) • Factors I and III were associated with mania, II with major-depression or bipolar mixed-state, IV with major depression and negatively with mania
Salvadore et al. (2008a)	Review		Bipolar disorder		• A majority of adolescents or adults with affective psychoses achieve syndromal recovery (8 weeks without a depressive or manic episode) but not symptomatic recovery (8 contiguous weeks with minimal affective symptoms) within 2 years after a first episode
Scott et al. (2013)	Retrospective study	Australia	Bipolar disorder and unipolar depression (N = 308; Mean age = 19.4)		• comparable psychological distress, depressive symptoms, current role impairment, neuropsychological dysfunction, and alcohol or substance misuse between both groups • the unipolar depression group showed higher level of social anxiety reported • bipolar patients were more likely to have a family history of bipolar or psychotic disorder as well as substance misuse but not depressive disorders
Smith et al. (2014)	Prospective study		First-episode psychotic mania (N = 83; Mean age = 21.5)	18 months	• poor functioning, great severity of manic and overall symptoms were associated with poor insight at baseline • level of insight at baseline did not predict symptomatology or functioning at follow-up
Strakowski et al. (1998)	Prospective study	USA	First-episode affective psychosis (N = 109; Mean age = 26)	12 months	• full compliance was associated with more frequent and rapid syndromic recovery, and was more common in white patients, and in patients without substance abuse • delayed symptomatic recovery in patients with substance abuse • higher socio-economic status was associated with both symptomatic and functional recovery • good premorbid function was associated with functional recovery • only 35% of patients achieved functional recovery
Strakowski et al. (2000)	Prospective study	USA	First episode mania (N = 42; 16–45 years)	8 months	• Mood-incongruent psychosis was associated with longer time exhibiting psychotic symptoms, poorer overall functioning than mood-congruent psychosis • The two sub-groups had similar percent of weeks with affective symptoms or syndromes
Functioning					
Abdel-Baki et al. (2013)	Descriptive study	Canada	First-episode psychosis (N = 97; 18–30 years)	Over 60 months	• AP vs NAP were more likely to have a productive occupation at follow-up • prior employment predicted better occupation at follow-up
Berge et al. (2016)	Prospective study	Spain	First-episode psychosis (N = 140; Mean age = 25.4)	24 months	• affective psychoses and non-affective psychoses did not differ in terms of days until the first relapse and global functioning at follow-up
Conus et al. (2006b)	Prospective study	Australia	First-episode psychotic mania (N = 87; Mean age = 22.1)	12 months	• 90% of syndromic and 60% of symptomatic recovery at 6 and 12 months • A majority of patients both at 6 months (66%) and at 12 months (61%) fail to get back to their premorbid functioning

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Table 5 (*continued*)

Study	Method	Country	Population (N; age)	Follow-up	Key findings
					• Age at intake, family history of affective disorder, illicit drug use, functional recovery at 6 months predicted functional recovery at 12 months
Henry et al. (2010)	Prospective study	Australia	First-episode psychosis (N = 651; Mean age = 28.7)	7 years	• better global and psychosocial functioning and quality of life in affective psychoses than in schizophrenia at follow-up, no difference regarding vocation (time living independently, work status)
Ratheesh et al. (2017)	Prospective study	Australia	First-episode mania (N = 117; Mean age = 21.4)	18 months	• premorbid social adjustment predicted short to medium term interpersonal functioning • premorbid adjustment was not associated with illness severity at follow-up • premorbid academic adjustment correlated with vocational functioning
Shinn et al. (2017)	Descriptive study	USA	First-episode psychosis (N = 92; Mean age = 21.4)	30 months	• patients with affective psychoses had better premorbid functioning, baseline indices of severity between groups were similar, the retention rate was lower in the not otherwise specified (NOS) group than in affective psychoses • primary psychosis groups and affective psychoses or NOS groups had a majority of individuals who dropped out of treatment early
Tohen et al. (2000a)	Prospective study	USA	First episode major affective disorders with psychotic features (N = 219; Mean age = 34.1)	24 months	• While most patients attained syndromal recovery, only one third of them recovered functionally • Low initial depression severity, functional recovery by 6 months, short length of stay, and age of onset of 30 years or older were associated with syndromal recovery • Age of onset of 30 years or older, and short length of stay were associated with functional recovery
Tohen et al. (2000b)	Prospective study	USA	First-episode psychosis (N = 296; Mean age = 31.9)	6 months	• Syndromal recovery rates were the highest in the major affective disorder sub-group (81%), followed by non affective acute psychoses (74%), schizoaffective disorders (70%), and the lowest were for schizophrenia (36%) • Functional recovery was associated with syndromal recovery, shorter hospitalization normalized to year, and older age at onset • Two third of patients who had attained syndromal recovery did not achieved functional recovery at follow-up
Physical health					
Archie et al. (2015)	Retrospective study	Canada	First-episode affective psychoses (N = 53; Mean age = 23.8)		• a probability of 75% to develop an abnormal lipid test within the first 18 months after receiving antipsychotic medications • the median time to develop an abnormal lipid test was 8 months for men and 12 months for females
Strassnig et al. (2017)	Prospective study	USA	First-episode bipolar disorder and schizophrenia (N = 233; 15–60 years)	20 years	• early overweight was a predictor of eventual obesity • around 50% of patients with bipolar disorder were obese at follow-up but greater prevalence of obesity in schizophrenia • bipolar patients experience a later development of obesity than in schizophrenia, probably due to their lower initial BMI, suggesting more time to intervene to prevent weight gain

Note. *AP = Affective psychoses; NAP = Non-Affective psychoses.

et al., 2014). Finally, symptomatic recovery was correlated with higher socioeconomic status (Strakowski et al., 1998) and may be more difficult in patients with mood incongruent symptoms (Strakowski et al., 2000) and substance abuse.

3.5.2. Functioning

While most patients with a first-episode mania achieve syndromic recovery, most of them fail to recover at the functional level (Conus et al., 2006b; Tohen et al., 2000a,b). Previous literature thus identified some factors that may affect functional recovery, among those an age of onset over 30 years and a short length of stay (Tohen et al., 2000). At 12 months, it was predicted by age at intake, familial antecedents of affective disorder, illicit drug use and functional recovery at 6 months (Conus et al., 2006b). However, although premorbid social adjustment predicted short-to medium-term interpersonal functioning in first-episode mania, functioning at the 18-month follow-up was not predicted by premorbid adjustment (Ratheesh et al., 2017).

Elsewhere, previous literature compared affective and non-affective psychoses in terms of functional adjustment. In a first-episode psychosis cohort, Shinn et al. (2017) found that patients with affective psychoses had better premorbid functioning than those with other psychotic disorders. Moreover, Abdel-Baki et al. (2013) found a higher rate of productive occupation at the 5-year follow-up in the affective than the non-affective psychosis sub-group. Although Henry et al. (2010) reported a better global and psychosocial functioning in those with affective than those with non-affective psychoses at 7-year follow-up, they found no difference regarding vocation. Berge et al. (2016) also did not find any inter-group differences on global functioning after 2 years.

3.5.3. Physical health

Very few studies have reported results regarding physical health in FEAP. Early overweight was a predictor of obesity (Strassnig et al., 2017). At a 20-year follow-up, approximately 50% of patients with bipolar disorder were obese, but the prevalence of obesity was greater in patients with schizophrenia, and those with bipolar disorder experienced a later development of obesity. Furthermore, Archie et al. (2015) highlighted that there was a 75% probability of developing an abnormal lipid test result within the first 18 months after receiving antipsychotic medication, with men showing a shorter median time to develop this than females.

3.6. Duration of untreated illness (DUI) (*Table 6*)

In general, diagnoses of affective psychoses and psychotic mania, but not of psychotic depression, have been associated with a shorter DUP in comparison to schizophrenia (Basu et al., 2015; Bhui et al., 2014; Large et al., 2008). The Nottingham Onset Schedule was reported to be an easy and reliable standardized tool to measure DUP (Singh et al., 2005).

Table 6
Summary of results on DUI (Duration of Untreated Illness) in first-episode affective psychoses.

Study	Method	Country	Population (N; age)	Follow-up	Key findings
Basu et al. (2015)	Retrospective study	Singapore	First-episode psychosis (N = 794; Mean age = 27.1)	24 months	• affective psychoses was associated with shorter DUP than schizophrenia spectrum and delusional disorders
Bhui et al. (2014)	Retrospective study	England	First-episode psychosis (N = 480; 18–64 years)	24 months	• affective psychoses and psychotic mania but not psychotic depression associated with a shorter DUP in comparison to schizophrenia
Dagani et al. (2017)	Meta-analysis		Bipolar disorder (N = 9415)		• the delay between the onset and management of bipolar disorder was 5.8 years but there was high heterogeneity between samples • a longer interval in studies defining the onset as the first episode and management as age at diagnosis
Large et al. (2008)	Meta-analysis		Psychosis (N = 9870)		• affective psychoses associated with a shorter DUP than schizophrenia • necessary to examine DUP separately affective (DUP proportion of less than a week) and non-affective (length of DUP) psychosis
Malik et al. (2010)	Experimental study	Pakistan	First-episode psychosis (N = 60; Mean age = 26)		• no significant differences in emotion recognition between diagnostic categories • longer DUP was associated with more difficulties in facial emotion recognition and patients with schizoaffective disorders had longer DUP than those with substance-induced psychosis • patients with longer DUP more likely to have more severe positive symptoms
Malla et al. (2014)	Quasi-experimental study	Canada	First-episode psychosis (N = 295; 14–30 years)		• Test of a targeted intervention (intensive training and education regarding early signs of FEP and benefits of early intervention) to reduce DUP. Results showed an increase in the proportion of patients referred to the early intervention service especially for those with affective psychoses
Singh et al. (2005)	Psychometric study	England	First-episode psychosis (N = 20; Mean age = 25)		• The Nottingham Onset Schedule, a reliable and easy to use scale to measure onset in psychosis • shorter DUP in AP than in schizophrenia • longer onset in schizophrenia than in AP

Note. *DUP = Duration of Untreated Psychosis; AP = Affective psychoses; FEP = First-Episode Psychosis.

However, the definition of the DUI or DUP may vary across studies, which affects the results. Indeed, in a meta-analysis including studies on bipolar disorders with or without psychosis, the delay between the onset and management of illness was 5.8 years, but there was a high degree of heterogeneity between samples (Dagani et al., 2017). Studies defining the onset as the first episode and management of illness as the age at diagnosis found longer intervals.

Reducing DUI is a major challenge in early intervention, and some studies have explored its impact and possible specific interventions. Considering the central role of emotional disturbances in patients with psychosis associated with interpersonal problems, Malik et al. (2010) investigated the impact of DUP on emotion recognition. They found that a longer DUP was associated with more difficulties in facial emotion recognition. Moreover, Malla et al. (2014) implemented a targeted intervention to reduce DUP. Interestingly, the impact on DUP was significant. Indeed, they showed an increase in the proportion of patients referred to early intervention services, especially for those with affective psychoses.

3.7. Neurobiology and neurocognition (Table 7)

3.7.1. Neurocognitive and neurostructural abnormalities

Previous literature has suggested important neurocognitive impairments associated with affective psychoses. In line with this, patients with FEAP show impaired psychomotor speed, attention, working memory, verbal learning, visual and verbal memory, and cognitive flexibility (Daglas et al., 2016; Lee et al., 2014; Olvet et al., 2013). While Lee et al. (2014) suggested that these deficits were not mood-state dependent, Sax et al. (1998) found that attentional impairments were associated with mania and did not persist after 2 months. Furthermore, these neurocognitive deficits, especially those regarding attentional performance, did not differ between diagnostic categories within affective psychoses (Sax et al., 1998). Nonetheless, although this is non-specific to affective psychoses, verbal memory deficits at baseline predicted more negative symptoms which in turn predicted poorer functioning at one year follow-up (Buck et al., 2020).

Regarding neurostructural abnormalities, Kozicky et al. (2016) showed that changes in grey matter loss did not differ between patients and healthy controls after a year. However, patients with recurrent manic episodes had greater grey matter loss than healthy controls, especially in left frontal and bilateral temporal regions that are important for emotion regulation. They also had greater loss of grey matter volume in bilateral frontal, temporal and left parietal regions than those with sustained remission. Moreover, Hirayasu et al. (1998) mentioned that patients with affective psychosis, similarly to those with schizophrenia, presented significantly less left than right asymmetry in the posterior amygdala-hippocampal complex. Finally, Salvadore et al. (2008a) mentioned an abnormal decrease in grey matter volume in the cingulate gyrus in first-episode affective psychoses. Additionally, those with a family history of mood disorders showed a reduction in left subgenual anterior cingulate cortex volume.

3.7.2. Differences in neurocognition between affective and non-affective psychoses

Some studies have compared the neuropsychological aspects of affective and non-affective psychoses. Amoretti et al. (2018) examined cognitive reserve in FEP patients to compare inter-group differences in brain capacity for dealing with pathology to minimize symptoms. Patients with affective psychoses had higher cognitive reserve than those with non-affective psychoses.

Elsewhere neuropsychological functioning differences have been investigated, showing a tendency for patients with schizophrenia to have more severe neurocognitive deficits than patients with bipolar disorder (Olvet et al., 2013). However, bipolar disorder associated with psychosis may lead to a greater frequency and severity of cognitive impairment, similar to schizophrenia syndrome. In line with the above review suggesting neurocognitive similarities between schizophrenia and affective psychoses, Torrent et al. (2018) did not find any neuropsychological differences between those with affective and non-affective psychoses at 2-year follow-up. Finally, Lee et al. (2015) also did not find inter-group differences in neuropsychological changes.

4. Discussion

Our aim was to synthesize current knowledge and to identify specificities of FEAP regarding what we consider important topics of FEP early intervention research such as diagnostic categorization, premorbid factors, intervention, outcomes, duration of untreated illness,

Table 7
Summary of results on neurobiology and neurocognition in first-episode affective psychoses.

Study	Method	Country	Population (N; age)	Follow-up	Key findings
Amoretti et al. (2018)	Prospective study	Spain	First-episode psychosis (N = 247 patients vs 205 healthy controls; Mean age = 25.2)	24 months	• people with affective psychoses had higher cognitive reserve (including premorbid IQ, education-occupation, leisure activities) than those with non-affective psychoses • in the affective psychosis subgroup, people with low cognitive reserve were more likely to have a lower socio-economic level as well as a lower level of education than those with high cognitive reserve. People with high cognitive reserve had also better functioning and global cognition at follow-up, a better verbal memory both at baseline and at follow-up.
Buck et al. (2020)	Prospective study	Canada	First-episode psychosis (N = 435 patients, vs 138 controls; Mean age = 23.9)	12 months	• verbal memory deficits in first-episode psychosis vs healthy controls • verbal memory was worst in males than females in both affective and non-affective psychosis at baseline • better baseline verbal memory predicted better functioning at follow-up, mediated through fewer negative symptoms at baseline
Daglas et al. (2017)	RCT	Australia	First-episode mania (N = 40 first-episode mania vs 21 healthy controls; Mean age = 21.32)		• patients with first-episode mania had significantly a lower full-scale IQ score, more difficulties in processing speed, verbal learning and memory, working memory and cognitive flexibility than healthy controls
Hirayasu et al. (1998)	Prospective study	USA	First-episode psychosis (N = 33 first-episode vs 18 healthy controls; Mean age = 24.8)		• both the patients with schizophrenia and those with affective psychosis had significantly less left than right asymmetry of the posterior amygdala-hippocampal complex
Kozicky et al. (2016)	Prospective study	Canada	First-episode mania (N = 41 first-episode mania vs 25 healthy controls; Mean age = 22.9)	12 months	• the grey matter loss change did not differ between patients and healthy controls at follow-up • patients with recurrence of manic episode had greater grey matter loss than healthy controls, especially in left frontal and bilateral temporal regions that are important for emotion regulation • patients with recurrence had also greater loss of grey matter volume in bilateral frontal, temporal and left parietal regions than those with sustained remission • there was no significant difference in grey matter volume between sustained-remission patients and healthy controls • symptoms severity associated with poor performance in executive functions predicted lower functioning at follow-up
Lee et al. (2014)	Meta-analysis		First-episode bipolar disorder		• medium to large deficits in psychomotor speed, attention and working memory, and cognitive flexibility • smaller deficits in verbal learning and memory, attentional switching, and verbal fluency • no difference on visual learning and memory functioning compared to controls • cognitive deficits are not mood-state dependent
Lee et al. (2015)	RCT	Australia	First-episode psychosis (N = 311; 12–35 years)	Between 12 and 36 months	• neuropsychological changes did not differ between diagnostic categories • neuropsychological functioning remained stable excepting verbal memory improved at follow-up • verbal memory improvement associated with a decrease of positive and negative residual symptoms
Olvet et al. (2013)	Review		Bipolar disorder		• visual, verbal, and working memory deficits were consistently higher in first episode mania than in healthy controls. Both groups were comparable regarding premorbid and current IQ • patients with schizophrenia tend to have more severe neurocognitive deficits as well as lower premorbid and current IQ than patients with bipolar disorder • bipolar disorder with psychotic symptoms associated with more severe and frequent cognitive deficits.
Torrent et al. (2018)	Prospective study	Spain	First-episode psychosis (N = 192; 7–35 years)	24 months	• less perseverative errors in affective than in non-affective psychoses at baseline • no neuropsychological differences between groups at follow-up
Salvadore et al. (2008a)	Review		Bipolar disorder		• an abnormal decrease in grey matter volume in the cingulate gyrus for fist-episode affective psychoses • First-episode affective psychoses with family history of mood disorders had reduction in left subgenual anterior cingulate cortex volume
Sax et al. (1998)	Prospective study	USA	First-episode affective psychosis (N = 27 FEAP vs N = 31 healthy controls; Mean age = 25.5)	2 months	• No difference on attentional performance between diagnostic categories (depression with psychotic features, schizoaffective disorder, bipolar disorder) • Worse attentional performance at baseline but no difference at follow-up in FEAP vs healthy controls • Attentional performance correlated with manic state

neurobiology and neurocognition. Our findings showed psychopathological and neurocognitive differences between affective and non-affective psychosis suggesting the need for developing specific intervention strategies for FEAP. However, most studies did not include schizoaffective disorder in the affective group considering its schizophrenic appearance or only included it in first-episode mania studies. Considering its affective dimension, either depressive or manic, which requires mood treatment strategies, it would be important to include such diagnostic category to further investigate FEAP and to develop clinical guidelines. Finally, the literature on early intervention

in FEAP remains sparse suggesting the need for further studies to better understand the challenges of such clinical entity and to explore whether specific intervention strategies would improve outcomes.

Our review of the literature on FEAP highlighted differences between affective and non-affective psychoses. Especially, although symptomatic recovery in affective psychosis may be more frequent than in non-affective psychosis (Conus and McGorry, 2002), the development of specific interventions is required. Indeed, the previous literature has highlighted major challenges associated with affective psychoses such as suicidal risk, non-adherence to treatment, and substance abuse (Berk, 2007; Strakowski et al., 1996). The results also pointed out that early intervention in FEAP is particularly important because most people with delayed treatment will experience multiple relapses, increasing the risk of damaging effects (Conus and McGorry, 2002). However, identifying affective psychoses at onset is particularly difficult because of overlapping symptomatology with both depression and schizophrenia (Berk, 2007; Conus, 2010). It is especially complex with psychotic patients presenting depressive but no manic or only hypomanic symptoms (Arrasate et al., 2014). There are thus many challenges with current diagnostic practice and difficulties related to differential diagnosis. A useful way of differentiating affective from non-affective psychoses may be activation (Arrasate et al., 2014). Psychopathological features at onset may also enable subtyping (Salvatore et al., 2007). However, further investigation on affective psychoses is required to address identification issues associated with the presence of a depressive dimension without mania. Finally, due to the highlighted challenges specific to FEAP, it is important to focus interventions on the development of insight, comorbidities, therapeutic engagement, educational and vocational counselling, and follow-up through age-appropriate developmental tasks (Berk, 2007; Douki et al., 1999; Ramu et al., 2019). In order to cope with such specific challenges, further studies are however required to investigate potential internal differences within affective psychoses to develop more adaptive intervention strategies.

Despite the few guidelines for intervention in FEAP, the previous literature provided some recommendations. Namely, pharmacological treatment first requires accurate assessments of both psychotic and affective dimensions (Douki et al., 1999; Lambert et al., 2003). Moreover, combining mood stabilizers with atypical antipsychotics remains the most effective strategy to deal with FEAP. Benzodiazepines can also be included in cases of behavioural disturbances, agitation or insomnia. While mood stabilizers like lithium are recommended during the maintenance phase (Jauhar et al., 2019), antidepressants should only be cautiously introduced due to the risk of manic relapse. To avoid relapses during the maintenance phase, psychosocial intervention is essential. Psychoeducation and psychotherapy, especially CBT and mindfulness-based intervention, have been reported to be effective (Douki et al., 1999; Maurel et al., 2010; Perlini et al., 2020; Power, 2015). Finally, self-help resources and daily routine recommendations may be helpful tools for young people (Power, 2015).

The consulted literature also provides some interesting potential targets for early interventions in FEAP, namely premorbid history and socio-demographic factors. Indeed, although premorbid history is mainly characterized by good socio-professional adaptation and functioning, there is a high prevalence of past traumatic events linked to poor outcomes (Conus et al., 2010; Daglas et al., 2014). It is therefore crucial to accurately explore past personal trauma (potential or acknowledged) and to develop psychotherapeutic tools to focus early intervention on traumatic experience. Otherwise, considering the high rate of parenthood among those with FEAP, there is a clear need to develop family interventions and psychoeducation to protect children from the adverse effects of their parents' illness (Abdel-Baki et al., 2013).

Furthermore, despite a lack of literature on remission that would require further investigation, some studies have highlighted key findings on outcomes, which may provide opportunities to accurately monitor care in FEAP. While FEAP is often associated with shorter DUP and better socio-professional and global functioning recovery than non-affective psychoses (Shinn et al., 2017; Sim et al., 2007), it can induce severe deficits, especially in cases of multiple episodes (Conus, 2010). It is especially important to consider that relapses are frequent and that symptomatic recovery (8 contiguous weeks with minimal affective symptoms) and functional recovery remain challenging (Conus et al., 2006b; Salvadore et al., 2008a; Tohen et al., 2000a,b). Preventing relapses requires both psychosocial and pharmacological intervention with a good therapeutic alliance to prevent non-adherence to treatment (Maurel et al., 2010). Finally, subtyping affective psychoses patients using affective symptoms may improve intervention monitoring (Azorin et al., 2011, 2012; Scott et al., 2013; Selvendra et al., 2014).

Considering neurocognition, the previous literature has consistently reported deficits in psychomotor speed, verbal and working memory in those with FEAP compared to healthy controls (Buck et al., 2020; Daglas et al., 2017; Lee et al., 2014; Olvet et al., 2013; Torrent et al., 2018). Verbal memory should be carefully assessed, especially in males (Buck et al., 2020), because of its impact on negative symptoms, and thus on functional recovery which remains challenging in FEAP (Conus et al., 2006b). Furthermore, the impact of illness on cognition may depend on cognitive reserve; thus, it may be useful to subtype patients regarding their cognitive reserve (Amoretti et al., 2018). It should be noted that the studied samples did not include the whole spectrum of affective psychoses. It is therefore important to confirm these results in a cohort that includes every FEAP diagnostic category. While these cognitive deficits were independent of mood-state (Olvet et al., 2013), grey matter loss was more prominent in patients with recurrent manic episodes (Kozicky et al., 2016). It remains unclear how neurocognitive deficits and grey matter loss are linked, as well as how relapse impacts neurocognition and grey matter loss. These questions require further investigation.

While this narrative review adequately presents current knowledge on FEAP, it has limitations. First, the literature on FEAP remaining scarce, this review included studies on various topics which did not enable us to provide clear and straightforward guidelines for early intervention in FEAP. Secondly, the selection process was conducted by one person alone, and it may therefore lack the reliability of multiple ratings. Third, despite a rational selection process, as a narrative review, we selectively reviewed data/papers that is less likely to be both transparent and reproducible as a systematic review would be. Fourth, we were not able to peer-review our search strategy, we might thus fail to screen all the existing studies in the literature as a proper scoping review search strategy would do.

5. Conclusion

Affective psychoses require specific treatment to prevent adverse development of illness. Despite few clear guidelines emerging, our synthesis identified some recommendations for early intervention in FEAP. Our review also highlighted the lack of accurate tools to characterize the early course of affective psychoses. Through this review, we identified the specific needs of FEAP patients, but research remains sparse in this field, suggesting that further investigation is required, especially in cohort including every FEAP diagnostic category.

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Declaration of competing interest

The authors declare that they have no conflict of interest.

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Appendix A. Supplementary data

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References

Abdel-Baki, A., Létourneau, G., Morin, C., Ng, A., 2013. Resumption of work or studies after first-episode psychosis: the impact of vocational case management. Early Intervention in Psychiatry 7 (4), 391–398. https://doi.org/10.1111/eip.12021.

American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders (DSM-5). American Psychiatric Association, p. 70.

Amoretti, S., Cabrera, B., Torrent, C., Mezquida, G., Lobo, A., Gonzalez-Pinto, A., 2018. Cognitive reserve as an outcome predictor: first-episode affective versus non-affective psychosis. Acta Psychiatrica Scandinavica 138 (5), 441–455. https://doi.org/10.1111/acps.12949. PepsGrp.

Archie, S., Zangeneh-Kazemi, A., Akhtar-Danesh, N., 2015. First-episode affective psychosis and lipid monitoring: survival analysis of the first abnormal lipid test. Early Intervention in Psychiatry 9 (6), 507–511. https://doi.org/10.1111/eip.12180.

Arrasate, M., Gonzalez-Ortega, I., Alberich, S., Gutierrez, M., Martinez-Cengotitabengoa, M., Mosquera, F., Gonzalez-Pinto, A., 2014. Affective dimensions as a diagnostic tool for bipolar disorder in first psychotic episodes. Eur Psychiatry 29 (7), 424–430. https://doi.org/10.1016/j.eurpsy.2013.07.005.

Azorin, J.M., Kaladjian, A., Adida, M., Fakra, E., Hantouche, E., Lancrenon, S., 2011. Correlates of first-episode polarity in a French cohort of 1089 bipolar i disorder patients: role of temperaments and triggering events. Journal of Affective Disorders 129 (1–3), 39–46. https://doi.org/10.1016/j.jad.2010.08.020.

Azorin, J.M., Kaladjian, A., Adida, M., Fakra, E., Hantouche, E., Lancrenon, S., 2012. Baseline and prodromal characteristics of first- versus multiple-episode mania in a French cohort of bipolar patients. European Psychiatry 27 (8), 557–562. https://doi.org/10.1016/j.eurpsy.2010.11.001.

Basu, S., Subramaniam, M., Abdin, E., Poon, L.Y., Verma, S., 2015. Does ethnicity have an impact on duration of untreated psychoses: a retrospective study in Singapore. The International journal of social psychiatry 61 (7), 623–630. https://doi.org/10.1177/0020764014568128.

Berge, D., Mane, A., Salgado, P., Cortizo, R., Garnier, C., Gomez, L., Perez, V., 2016. Predictors of relapse and functioning in first-episode psychosis: a two-year follow-up study. Psychiatric Services 67 (2), 227–233. https://doi.org/10.1176/appi.ps.201400316.

Berk, M., 2007. Early intervention in bipolar disorders: opportunities and pitfalls. Acta Neuropsychiatrica 19 (1), 68–69.

Bramer, W.M., de Jonge, G.B., Rethlefsen, M.L., Mast, F., Kleijnen, J., 2018. A systematic approach to searching: an efficient and complete method to develop literature searches. Journal of the Medical Library Association : JMLA 106 (4), 531–541. https://doi.org/10.5195/jmla.2018.283.

Bhui, K., Ullrich, S., Coid, J.W., 2014. Which pathways to psychiatric care lead to earlier treatment and a shorter duration of first-episode psychosis? BMC Psychiatry 14 (1). https://doi.org/10.1186/1471-244X-14-72.

Buck, G., Lavigne, K.M., Makowski, C., Joober, R., Malla, A., Lepage, M., 2020. Sex differences in verbal memory predict functioning through negative symptoms in early psychosis. Schizophr Bull. https://doi.org/10.1093/schbul/sbaa054.

Chang, W.C., Lau, E.S.K., Chiu, S.S., Hui, C.L.M., Chan, S.K.W., Lee, E.H.M., Chen, E.Y.H., 2016. Three-year clinical and functional outcome comparison between first-episode mania with psychotic features and first-episode schizophrenia. Journal of Affective Disorders 200, 1–5. https://doi.org/10.1016/j.jad.2016.01.050.

Chia, M.F., Cotton, S., Filia, K., Phelan, M., Conus, P., Jauhar, S., Ratheesh, A., 2019. Early intervention for bipolar disorder-Do current treatment guidelines provide recommendations for the early stages of the disorder? Journal of Affective Disorders 257, 669–677. https://doi.org/10.1016/j.jad.2019.07.062.

Coentre, R., Blanco, P., Fontes, S., Power, P., 2011. Initial diagnosis and treatment in first-episode psychosis: can an operationalized diagnostic classification system enhance treating clinicians' diagnosis and the treatment chosen? Early Intervention in Psychiatry 5 (2), 132–139. https://doi.org/10.1111/j.1751-7893.2010.00247.x.

Conus, P., 2010. First episode of mood disorders: an opportunity for early intervention in bipolar disorders. Encephale 36 (Suppl. 3), S71–S76. https://doi.org/10.1016/S0013-7006(10)70034-8.

Conus, P., Berk, M., Cotton, S.M., Kader, L., Macneil, C., Hasty, M.K., McGorry, P.D., 2015. Olanzapine or chlorpromazine plus lithium in first episode psychotic mania: an 8-week randomised controlled trial. Eur Psychiatry 30 (8), 975–982. https://doi.org/10.1016/j.eurpsy.2015.09.009.

Conus, P., Berk, M., McGorry, P.D., 2006a. Pharmacological treatment in the early phase of bipolar disorders: what stage are we at? Australian and New Zealand Journal of Psychiatry 40 (3), 199–207. https://doi.org/10.1080/j.1440-1614.2006.01775.x.

Conus, P., Cotton, S., Abdel-Baki, A., Lambert, M., Berk, M., McGorry, P.D., 2006b. Symptomatic and functional outcome 12 months after a first episode of psychotic mania: barriers to recovery in a catchment area sample. Bipolar Disorders 8 (3), 221–231. https://doi.org/10.1111/j.1399-5618.2006.00315.x.

Conus, P., Cotton, S., Schimmelmann, B.G., Berk, M., Daglas, R., McGorry, P.D., Lambert, M., 2010. Pretreatment and outcome correlates of past sexual and physical trauma in 118 bipolar I disorder patients with a first episode of psychotic mania. Bipolar Disorders 12 (3), 244–252. https://doi.org/10.1111/j.1399-5618.2010.00813.x.

Conus, P., McGorry, P.D., 2002. First-episode mania: a neglected priority for early intervention. Australian and New Zealand Journal of Psychiatry 36 (2), 158–172. https://doi.org/10.1046/j.1440-1614.2002.00994.x.

Cotton, S.M., Lambert, M., Berk, M., Schimmelmann, B.G., Butselaar, F.J., McGorry, P.D., Conus, P., 2013. Gender differences in first episode psychotic mania. BMC Psychiatry 13. https://doi.org/10.1186/1471-244x-13-82.

Craig, T., Bromet, E.J., 2004. Parents with psychosis. Annals of Clinical Psychiatry 16 (1), 35–39. https://doi.org/10.1080/10401230490281384.

Dagani, J., Signorini, G., Nielssen, O., Bani, M., Pastore, A., de Girolamo, G., Large, M., 2017. Meta-analysis of the interval between the onset and management of bipolar disorder. Canadian Journal of Psychiatry-Revue Canadienne De Psychiatrie 62 (4), 247–258. https://doi.org/10.1177/0706743716656607.

Daglas, R., Allott, K., Yücel, M., Henry, L.P., Macneil, C.A., Hasty, M.K., Cotton, S.M., 2017. Cognitive functioning following stabilisation from first episode mania. International Journal of Bipolar Disorders 5 (1). https://doi.org/10.1186/s40345-017-0108-2.

Daglas, R., Conus, P., Cotton, S.M., Macneil, C.A., Hasty, M.K., Kader, L., Hallam, K.T., 2014. The impact of past direct-personal traumatic events on 12-month outcome in first episode psychotic mania: trauma and early psychotic mania. Australian and New Zealand Journal of Psychiatry 48 (11), 1017–1024. https://doi.org/10.1177/0004867414545672.

Daglas, R., Cotton, S.M., Allott, K., Yücel, M., Macneil, C.A., Hasty, M.K., Berk, M., 2016. A single-blind, randomised controlled trial on the effects of lithium and quetiapine monotherapy on the trajectory of cognitive functioning in first episode mania: a 12-month follow-up study. European Psychiatry 31, 20–28. https://doi.org/10.1016/j.eurpsy.2015.09.460.

DeVylder, J.E., Gearing, R.E., 2013. Declining social support in adolescents prior to first episode psychosis: associations with negative and affective symptoms. Psychiatry Research 210 (1), 50–54. https://doi.org/10.1016/j.psychres.2013.02.004.

Douki, S., Taktak, M.J., Ben Zineb, S., Cheour, M., 1999. Management strategies in first psychotic episode. Encephale-Revue De Psychiatrie Clinique Biologique Et Therapeutique 25, 44–51.

Dunkley, J.E., Bates, G.W., Foulds, M., Fitzgerald, P., 2007. Understanding adaptation to first-episode psychosis: the relevance of trauma and posttraumatic growth. Australasian Journal of Disaster and Trauma Studies *2007* (1) (No Pagination Specified).

Emck, C., Schothorst, P.F., Van Engeland, H., 2001. Early onset psychosis. Tijdschrift voor Psychiatrie 43 (11), 757–765.

Goodwin, F.K., Jamison, K.R., 2007. Manic-depressive Illness: Bipolar Disorders and Recurrent Depression, vol. 2. Oxford University Press.

Harris, A., Brennan, J., Anderson, J., Taylor, A., Sanbrook, M., Fitzgerald, D., Gordon, E., 2005. Clinical profiles, scope and general findings of the western sydney first episode psychosis project. Australian and New Zealand Journal of Psychiatry 39 (1–2), 36–43. https://doi.org/10.1111/j.1440-1614.2005.01517.x.

Henry, L.P., Amminger, G.P., Harris, M.G., Yuen, H.P., Harrigan, S.M., Prosser, A.L., McGorry, P.D., 2010. The EPPIC follow-up study of first-episode psychosis: longer-term clinical and functional outcome 7 Years after index admission. Journal of Clinical Psychiatry 71 (6), 716–728. https://doi.org/10.4088/JCP.08m04846yel.

Hirayasu, Y., Shenton, M.E., Salisbury, D.F., Dickey, C.C., Fischer, I.A., Mazzoni, P., McCarley, R.W., 1998. Lower left temporal lobe MRI volumes in patients with first-episode schizophrenia compared with psychotic patients with first-episode affective disorder and normal subjects. Am J Psychiatry 155 (10), 1384–1391. https://doi.org/10.1176/ajp.155.10.1384.

Jauhar, S., Ratheesh, A., Davey, C., Yatham, L.N., McGorry, P.D., McGuire, P., Young, A.H., 2019. The case for improved care and provision of treatment for people with first-episode mania. The Lancet Psychiatry 6 (10), 869–876. https://doi.org/10.1016/S2215-0366%2819%2930082-3.

Johnson, J., Horwath, E., Weissman, M.M., 1991. The validity of major depression with psychotic features based on a community study. Archives of general psychiatry 48 (12), 1075–1081.

Kapila, A., Fisher, H.L., Johnson, S., Major, B., Rahaman, N., Joyce, J., Stone, J.M., 2019. Clinical and demographic differences between patients with manic, depressive and schizophrenia-spectrum psychoses presenting to Early Intervention Services in London. Early Intervention in Psychiatry 13 (3), 509–516. https://doi.org/10.1111/eip.12511.

Kozicky, J.M., McGirr, A., Bond, D.J., Gonzalez, M., Silveira, L.E., Keramatian, K., Yatham, L.N., 2016. Neuroprogression and episode recurrence in bipolar I disorder: a study of gray matter volume changes in first-episode mania and association with clinical outcome. Bipolar Disorders 18 (6), 511–519. https://doi.org/10.1111/bdi.12437.

Lambert, M., Conus, P., Lambert, T., McGorry, P.D., 2003. Pharmacotherapy of first-episode psychosis. Expert Opinion on Pharmacotherapy 4 (5), 717–750. https://doi.org/10.1517/14656566.4.5.717.

Large, M., Nielssen, O., Slade, T., Harris, A., 2008. Measurement and reporting of the duration of untreated psychosis. Early Intervention in Psychiatry 2 (4), 201–211. https://doi.org/10.1111/j.1751-7893.2008.00080.x.

Lee, R.S.C., Hermens, D.F., Naismith, S.L., Lagopoulos, J., Jones, A., Scott, J., Hickie, I.B., 2015. Neuropsychological and functional outcomes in recent-onset major depression, bipolar disorder and schizophrenia-spectrum disorders: a longitudinal cohort study. Translational Psychiatry 5. https://doi.org/10.1038/tp.2015.50.

Lee, R.S.C., Hermens, D.F., Scott, J., Redoblado-Hodge, M.A., Naismith, S.L., Lagopoulos, J., Hickie, I.B., 2014. A meta-analysis of neuropsychological functioning in first-episode bipolar disorders. Journal of Psychiatric Research 57 (1), 1–11. https://doi.org/10.1016/j.jpsychires.2014.06.019.

Macmillan, I., Howells, L., Kale, K., Hackmann, C., Taylor, G., Hill, K., Fowler, D., 2007. Social and symptomatic outcomes of first-episode bipolar psychoses in an early intervention service. Early Intervention in Psychiatry 1 (1), 79–87. https://doi.org/10.1111/j.1751-7893.2007.00014.x.

Macneil, C.A., Hasty, M., Cotton, S., Berk, M., Hallam, K., Kader, L., Conus, P., 2012. Can a targeted psychological intervention be effective for young people following a first manic episode? Results from an 18-month pilot study. Early Intervention in Psychiatry 6 (4), 380–388. https://doi.org/10.1111/j.1751-7893.2011.00336.x.

Majadas, S., Olivares, J., Galan, J., Diez, T., 2012. Prevalence of depression and its relationship with other clinical characteristics in a sample of patients with stable schizophrenia. Comprehensive Psychiatry 53 (2), 145–151. https://doi.org/10.1016/j.comppsych.2011.03.009.

Malhi, G.S., Green, M., Fagiolini, A., Peselow, E.D., Kumari, V., 2008. Schizoaffective disorder: diagnostic issues and future recommendations. Bipolar Disorders 10 (1p2), 215–230. https://doi.org/10.1111/j.1399-5618.2007.00564.x.

Malik, F., Khawar, R., Chaudhry, H.R., Humphreys, G.W., 2010. Emotion recognition and duration of untreated first-episode psychosis among patients in Pakistan. East Asian Archives of Psychiatry 20 (1), 31–38.

Malla, A., Jordan, G., Joober, R., Schmitz, N., Norman, R., Brown, T., Rochford, J., 2014. A controlled evaluation of a targeted early case detection intervention for reducing delay in treatment of first episode psychosis. Social Psychiatry and Psychiatric Epidemiology 49 (11), 1711–1718. https://doi.org/10.1007/s00127-014-0893-1.

Marwaha, S., Beirne, T., Broome, M., Upthegrove, R., Rowland, T., Thompson, A., 2018. The views of early intervention service staff on the treatment of first episode bipolar disorder. International Journal of Psychiatry in Clinical Practice 22 (3), 225–231. https://doi.org/10.1080/13651501.2017.1401640.

Maurel, M., Kaladjian, A., Fakra, E., Besnier, N., Adida, M., Azorin, J.M., 2010. Treatment of a first manic episode. Encephale-Revue De Psychiatrie Clinique Biologique Et Therapeutique 36, S23–S26.

McMurrich, S., Sylvia, L.G., Dupuy, J.M., Peckham, A.D., Peters, A.T., Deckersbach, T., Perlis, R.H., 2012. Course, outcomes, and psychosocial interventions for first-episode mania. Bipolar Disorders 14 (8), 797–808. https://doi.org/10.1111/bdi.12001.

O'Callaghan, E., Turner, N., Renwick, L., Jackson, D., Sutton, M., Foley, S.D., Kinsella, A., 2010. First episode psychosis and the trail to secondary care: help-seeking and health-system delays. Social Psychiatry and Psychiatric Epidemiology 45 (3), 381–391. https://doi.org/10.1007/s00127-009-0081-x.

Olvet, D.M., Burdick, K.E., Cornblatt, B.A., 2013. Assessing the potential to use neurocognition to predict who is at risk for developing bipolar disorder: a review of the literature. Cognitive Neuropsychiatry 18 (1–2), 129–145. https://doi.org/10.1080/13546805.2012.724193.

Pedrós, A., Martí, J., Gutiérrez, G., Tenías, J.M., Ruescas, S., 2009. Two-year diagnostic stability and prognosis in acute psychotic episodes. Actas Espanolas de Psiquiatria 37 (5), 245–251.

Perlini, C., Bellani, M., Rossetti, M.G., Rossin, G., Zovetti, N., Rossi, A., Brambilla, P., 2020. Mindfulness-based interventions in the early phase of affective and non-affective psychoses: special section on "translational and neuroscience studies in affective disorders". In: Nobile, Maria (Ed.), Journal of Affective Disorders, 263, pp. 747–753. https://doi.org/10.1016/j.jad.2019.10.011.

Power, P., 2015. Intervening early in bipolar disorder in young people: a review of the clinical staging model. Irish Journal of Psychological Medicine 32 (1), 31–43. https://doi.org/10.1017/ipm.2014.72.

Proctor, S.E., Mitford, E., Paxton, R., 2004. First episode psychosis: a novel methodology reveals higher than expected incidence; a reality-based population profile in Northumberland, UK. Journal of Evaluation in Clinical Practice 10 (4), 539–547. https://doi.org/10.1111/j.1365-2753.2003.00474.x.

Radmanović, M.B., 2012. First-psychotic episode in childhood and adolescence. Psychiatria Danubina 24 (Suppl. 3), 388–391.

Ramu, N., Kolliakou, A., Sanyal, J., Patel, R., Stewart, R., 2019. Recorded poor insight as a predictor of service use outcomes: cohort study of patients with first-episode psychosis in a large mental healthcare database. BMJ Open 9 (6). https://doi.org/10.1136/bmjopen-2019-028929.

Ratheesh, A., Davey, C.G., Daglas, R., Macneil, C., Hasty, M., Filia, K., Cotton, S., 2017. Social and academic premorbid adjustment domains predict different functional outcomes among youth with first episode mania. Journal of Affective Disorders 219, 133–140. https://doi.org/10.1016/j.jad.2017.05.030.

Richardson, L., Hameed, Y., Perez, J., Jones, P.B., Kirkbride, J.B., 2018. Association of environment with the risk of developing psychotic disorders in rural populations: findings from the social epidemiology of psychoses in east anglia study. JAMA Psychiatry 75 (1), 75–83. https://doi.org/10.1001/jamapsychiatry.2017.3582.

Salvadore, G., Drevets, W.C., Henter, I.D., Zarate, C.A., Manji, H.K., 2008a. Early intervention in bipolar disorder, part I: clinical and imaging findings. Early Intervention in Psychiatry 2 (3), 122–135. https://doi.org/10.1111/j.1751-7893.2008.00071.x.

Salvadore, G., Drevets, W.C., Henter, I.D., Zarate, C.A., Manji, H.K., 2008b. Early intervention in bipolar disorder, part II: Therapeutics. Early Intervention in Psychiatry 2 (3), 136–146. https://doi.org/10.1111/j.1751-7893.2008.00072.x.

Salvatore, P., Khalsa, H.M., Hennen, J., Tohen, M., Yurgelun-Todd, D., Casolari, F., Baldessarini, R.J., 2007. Psychopathology factors in first-episode affective and non-affective psychotic disorders. J Psychiatr Res 41 (9), 724–736. https://doi.org/10.1016/j.jpsychires.2006.04.008.

Sax, K.W., Strakowski, S.M., Keck Jr., P.E., McElroy, S.L., West, S.A., Stanton, S.P., 1998. Symptom correlates of attentional improvement following hospitalization for a first episode of affective psychosis. Biol Psychiatry 44 (8), 784–786. https://doi.org/10.1016/s0006-3223(97)00528-3.

Schimmelmann, B.G., Conus, P., Edwards, J., McGorry, P.D., Lambert, M., 2005. Diagnostic stability 18 months after treatment initiation for first-episode psychosis. J Clin Psychiatry 66 (10), 1239–1246. https://doi.org/10.4088/jcp.v66n1006.

Schottle, D., Schimmelmann, B.G., Conus, P., Cotton, S.M., Michel, C., McGorry, P.D., Lambert, M., 2012. Differentiating schizoaffective and bipolar I disorder in first-episode psychotic mania. Schizophr Res 140 (1–3), 31–36. https://doi.org/10.1016/j.schres.2012.07.010.

Scott, E.M., Hermens, D.F., Naismith, S.L., Guastella, A.J., De Regt, T., White, D., Hickie, I.B., 2013. Distinguishing young people with emerging bipolar disorders from those with unipolar depression. Journal of Affective Disorders 144 (3), 208–215. https://doi.org/10.1016/j.jad.2012.06.031.

Selvendra, A., Baetens, D., Trauer, T., Petrakis, M., Castle, D., 2014. First episode psychosis in an adult area mental health service-a closer look at early and late-onset first episode psychosis. Australasian Psychiatry 22 (3), 235–241. https://doi.org/10.1177/1039856214532558.

Shinn, A.K., Bolton, K.W., Karmacharya, R., Lewandowski, K.E., Yuksel, C., Baker, J.T., Öngür, D., 2017. McLean OnTrack: a transdiagnostic program for early intervention in first-episode psychosis. Early Intervention in Psychiatry 11 (1), 83–90. https://doi.org/10.1111/eip.12299.

Sim, K., Yiong, H.C., Siow, A.C., Siris, S.G., 2007. A 24-month prospective outcome study of first-episode schizophrenia and schizoaffective disorder within an early psychosis intervention program. Journal of Clinical Psychiatry 68 (9), 1368–1376. https://doi.org/10.4088/JCP.v68n0907.

Singh, S.P., Cooper, J.E., Fisher, H.L., Tarrant, C.J., Lloyd, T., Banjo, J., Jones, P., 2005. Determining the chronology and components of psychosis onset: the Nottingham Onset Schedule (NOS). Schizophrenia Research 80 (1), 117–130. https://doi.org/10.1016/j.schres.2005.04.018.

Smith, L.T., Shelton, C.L., Berk, M., Hasty, M.K., Cotton, S.M., Henry, L., Conus, P., 2014. The impact of insight in a first-episode mania with psychosis population on outcome at 18 months. Journal of Affective Disorders 167, 74–79. https://doi.org/10.1016/j.jad.2014.05.055.

Strakowski, S.M., Keck Jr., P.E., McElroy, S.L., West, S.A., Sax, K.W., Hawkins, J.M., Bourne, M.L., 1998. Twelve-month outcome after a first hospitalization for affective psychosis. Arch Gen Psychiatry 55 (1), 49–55. https://doi.org/10.1001/archpsyc.55.1.49.

Strakowski, S.M., McElroy, S.L., Keck, P.E., West, S.A., 1996. The effects of antecedent substance abuse on the development of first-episode psychotic mania. Journal of Psychiatric Research 30 (1), 59–68. https://doi.org/10.1016/0022-3956(95)00044-5.

Strakowski, S.M., Williams, J.R., Sax, K.W., Fleck, D.E., DelBello, M.P., Bourne, M.L., 2000. Is impaired outcome following a first manic episode due to mood-incongruent psychosis? J Affect Disord 61 (1–2), 87–94. https://doi.org/10.1016/s0165-0327(99)00192-5.

Strassnig, M., Kotov, R., Cornaccio, D., Fochtmann, L., Harvey, P.D., Bromet, E.J., 2017. Twenty-year progression of body mass index in a county-wide cohort of people with schizophrenia and bipolar disorder identified at their first episode of psychosis. Bipolar Disorders 19 (5), 336–343. https://doi.org/10.1111/bdi.12505.

Subramaniam, M., Pek, E., Verma, S., Chong, S.A., Chan, Y.H., 2007. Diagnostic stability 2 years after treatment initiation in the early psychosis intervention programme in Singapore. Australian and New Zealand Journal of Psychiatry 41 (6), 495–500. https://doi.org/10.1080/00048670701332276.

Tohen, M., Hennen, J., Zarate Jr., C.M., Baldessarini, R.J., Strakowski, S.M., Stoll, A.L., Cohen, B.M., 2000a. Two-year syndromal and functional recovery in 219 cases of first-episode major affective disorder with psychotic features. Am J Psychiatry 157 (2), 220–228. https://doi.org/10.1176/appi.ajp.157.2.220.

Tohen, M., Strakowski, S.M., Zarate Jr., C., Hennen, J., Stoll, A.L., Suppes, T., Baldessarini, R.J., 2000b. The McLean-Harvard first-episode project: 6-month symptomatic and functional outcome in affective and nonaffective psychosis. Biol Psychiatry 48 (6), 467–476. https://doi.org/10.1016/s0006-3223(00)00915-x.

Torrent, C., Reinares, M., Martinez-Aran, A., Cabrera, B., Amoretti, S., Corripio, I., Vieta, E., 2018. Affective versus non-affective first episode psychoses: a longitudinal study. J Affect Disord 238, 297–304. https://doi.org/10.1016/j.jad.2018.06.005.

Vallarino, M., Henry, C., Etain, B., Gehue, L.J., Macneil, C., Scott, E.M., Scott, J., 2015. An evidence map of psychosocial interventions for the earliest stages of bipolar disorder. The Lancet Psychiatry 2 (6), 548–563.

Zarate Jr., C.A., Tohen, M., 2000. Antipsychotic drug treatment in first-episode mania: a 6-month longitudinal study. J Clin Psychiatry 61 (1), 33–38. https://doi.org/10.4088/jcp.v61n0109.

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ORIGINAL ARTICLE

WILEY

Exploring the clinical relevance of a dichotomy between affective and non-affective psychosis: Results from a first-episode psychosis cohort study

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Abstract

Aim: Defining diagnosis is complex in early psychosis, which may delay the introduction of an appropriate treatment. The dichotomy of affective and non-affective psychosis is used in clinical setting but remains questioned on a scientific basis. In this study, we explore the clinical relevance of this dichotomy on the basis of clinical variables in a sample of first-episode psychosis patients.

Method: We conducted a prospective study in a sample of 330 first-episode psychosis treated at an early intervention program. Affective and non-affective psychosis patients were compared on premorbid history, baseline data, outcomes and course of symptoms over the 3 years of treatment.

Results: Affective psychosis patients (22.42%) were more likely to be female, and had a shorter duration of untreated psychosis. The longitudinal analyses revealed that positive symptoms remained higher over the entire follow-up in the non-affective sub-group. A higher degree of variability of manic symptoms and a significantly better insight after 6 months were observed in the affective sub-group. No difference was observed regarding depressive and negative symptoms. At discharge, only the environmental quality of life and insight recovery were better in affective psychosis.

Conclusions: Our study suggests that despite marginal differences at baseline presentation, these sub-groups differ regarding outcome, which may require differentiation of treatment and supports the utility of this dichotomy.

KEYWORDS
early medical intervention, mood disorders, patient outcome assessment, psychotic disorders, symptom assessment

1 | INTRODUCTION

Affective and non-affective psychoses are nosological entities derived from Kraepelin's dichotomy (Kraepelin, 1992) between schizophrenia (dementia preacox) and psychotic mood disorders (manic-depressive insanity). Although understudied (Chia et al., 2019; Conus & McGorry, 2002), affective psychosis is a concept applied in clinical settings referring to forms of psychoses marked by a severe disturbance of mood (Kraepelin, 1992; Lambert et al., 2003). It has emerged as a way to stratify patients on the basis of clinical presentation, grouping bipolar disorder with psychotic features, major depression with psychotic features and schizoaffective disorder as "affective psychoses", schizophrenia and schizophreniform disorders as non-affective psychoses (Lambert et al., 2003). In order to provide early intervention adjusted to the specificities of psychotic disorders, this dichotomy is nowadays used in treatment guidelines (Lambert

et al., 2003). Indeed, the co-occurrence of mood episodes and psychotic features in affective psychosis may require pharmacotherapy considering both dimensions. Differences in the illness course between affective and non-affective psychosis have been well documented. However, this dichotomy is mainly based on clinical observations. Recently, the classic concept of categories has been challenged and the idea of a continuum between the non-affective psychoses and affective psychoses has been emphasized, suggesting the need to further investigate their psychopathological differences.

Although schizophrenia and bipolar disorder have been identified as distinct entities through dichotomous classifications, more and more papers point towards a continuum between both entities with prototypic forms of each disorder at the extremes but a majority of people expressing mixed forms (Keshavan et al., 2011; Thaker, 2008). Such studies highlight the limitations of a categorical classification of mental disorders and the need for a more dimensional concept based on clinico-pathological factors, and especially including longitudinal follow-up (Craddock & Owen, 2007; Keshavan et al., 2011; Thaker, 2008). This way of thinking boundaries between disorders would not only provide a distinction of clinical utility but, would also enable to cluster individuals sharing similar features that do not correspond to the prototypical forms of these disorders (Craddock & Owen, 2007). This point is especially crucial in first-sis as studies highlighted a spectrum of disorders rather than discrete diagnostic entities, making diagnostic categorisation and treatment intervention even trickier due to both blurred boundaries and instability of diagnosis in this phase of illness (Conus et al., 2010; McGorry, 1994; Schimmelmann et al., 2005; Shinn et al., 2017). Indeed, diagnostic classifications are usually based on studies conducted in chronic samples, and therefore are not well adapted to early phases of disorders (McGorry, 1994; McGorry et al., 1995). Dimensional and longitudinal symptom assessment may thus provide a helpful way of identifying differences between diagnostic groups in the early phase of illness (Arrasate et al., 2014).

Although limited, there is some research data suggesting the existence of factors differing between affective and non-affective psychosis, and that the study of this dichotomy may provide elements to improve early diagnosis accuracy, and thus treatment management (Kapila et al., 2019; Schothorst et al., 2006). First, some authors suggested that distinctive characteristics can be observed at baseline within first episode cohorts. Indeed, previous studies suggest that patients with affective psychosis were more likely to be women, had a higher level of education, were less likely to be single, had a shorter duration of untreated psychosis (DUP), an older age at onset, were less likely to attempt suicide, were more likely to have a past history of psychiatric disorder and substance use, and had a better premorbid functioning and adjustment (Conus et al., 2007; Kapila et al., 2019; Schothorst et al., 2006). Second, regarding psychopathological features, Kapila et al. (2019) pointed out fewer psychotic symptoms, but more manic symptoms in first episode manic psychosis than in schizophrenia spectrum psychosis at baseline. Another naturalistic longitudinal prospective study showed that the affective psychosis sub-group had less negative but more manic symptoms at baseline than the non-affective one (Torrent et al., 2018). At two-year follow-up, these differences had decreased but the affective psychosis sub-group displayed less positive, negative and general symptoms as well as less depressive symptoms. Similarly, Henry et al. (2010) found lower general psychopathology scores and fewer psychotic symptoms after two-year follow-up in affective psychosis. They also highlighted differences in psychotic illness course (episodic vs. continuous) which may require specific intervention. Considering recovery, although Banayan et al. (2007) reported better functioning, symptomatic remission and quality of life at follow-up in the affective psychosis sub-group, they found no difference between sub-groups regarding employment and time living independently.

Considering both the paucity of data and the clinical relevance of the dichotomy between affective and non-affective psychoses in order to guide treatment in the early phase of psychosis, and following the suggestion by Craddock and Owen (2007) we investigated this topic with a longitudinal approach using different symptom dimensions with the following aims: (1) to consolidate previous results regarding baseline characteristics and outcomes differences between affective and non-affective psychoses; (2) to investigate differences between both groups regarding the course of symptoms in the early phase of psychosis.

2 | METHOD

2.1 | Sample and procedure

This is a prospective study on a cohort of first-episode psychosis patients treated at a specialized early psychosis intervention program, Treatment and Early Intervention in Psychosis Program (TIPP), implemented in Lausanne (Switzerland) since 2004 at the CHUV's Department of Psychiatry (Baumann et al., 2013; P. Conus & Bonsack, 2004). Patients entering the program are aged between 18 and 35, reside in the catchment area of Lausanne and have crossed the psychosis threshold according to the "*Psychosis threshold*" subscale of the Comprehensive Assessment of At Risk Mental States scale (CAARMS; Yung et al., 2005). Patients are directed to other programs if they have been on antipsychotic medication for more than 6 months, an intoxication or an organic brain disease induced psychosis, or if their intelligence quotient is lower than 70. In this program, every patient is followed for 3 years by a psychiatrist and a case manager. The TIPP program favours a bio-psycho-social perspective, and as such provides treatment that includes psychotherapy, psycho-education, family support and therapy, cognitive assessment and remediation, social support, supported employment, psychological interventions for cannabis use, and pharmacological treatment. In line with international guidelines, atypical antipsychotics are first-line pharmacological treatment with a prospective monitoring of any side-effects (Baumann et al., 2013). Case managers fill out for every patient a questionnaire specifically designed for the TIPP. This questionnaire gathers information about demographic characteristics, past medical history, exposure to life events, symptomatology and functioning. Follow-up assessments are carried out at 2, 6, 12, 18, 24, 30 and 36 months by a research psychologist and case managers, exploring

various aspects of treatment, evolution of psychopathology and functional level, as well as co-morbidities (e.g., level of insight; treatment adherence; presence or absence of forensic history and substance use; intermittent exposure to trauma; suicide attempts and forensic events). This study was approved by the Human Research Ethics Committee of the Canton Vaud (protocol #2020-00272). The data generated by the follow-up of all patients were used in the study if they provided consent. All of them agreed for their clinical data to be used for research.

2.2 | Diagnostic assessment

Diagnosis results from an expert consensus discussed at 18 and 36 months, based on the DSM-IV criteria using the information from medical or hospitalization reports from treating psychiatrists, as well as from the TIPP-assigned psychiatrist and case manager. We used the latest consensus diagnostic available. Considering potential diagnostic instability in first-episode psychosis cohorts (Gale-Grant et al., 2020), we also examined the diagnostic stability between the first and the latest diagnosis. Patients diagnosed with bipolar disorder, major depression with psychotic features and schizoaffective disorder were included in the affective psychosis group, while those with schizophrenia or other schizophreniform disorders were included in the non-affective psychosis group. Considering the instability of the diagnosis of unspecified psychosis (Cawkwell et al., 2020; Taş et al., 2019) and its unclear status between affective and non-affective psychoses, these patients were excluded.

2.3 | Socio-demographic and premorbid characteristics

According to the CAARMS criteria, DUP was defined as the time elapsed from the onset of psychosis until admission to TIPP. Socio-economic status (SES) was subdivided into three categories: low, intermediate and high (Chandola & Jenkinson, 2000). Independent living refers to patients living in independent households, living alone or with friends or family without supervision. The employment situation was subdivided into student or traineeship, active employment, which was defined as partial or full-time job, or other. The premorbid functional level was assessed with the Premorbid Adjustment Scale (PAS; Cannon-Spoor et al., 1982) using the childhood and early adolescence sub-scores (MacBeth & Gumley, 2008), and the total score. We considered that patients had a history of trauma if they had experienced at least one instance of sexual or physical abuse before the onset of psychosis (Alameda et al., 2015; Alameda et al., 2016). We defined migration in adversity as migration occurring in adverse contexts (e.g., seeking protection for political reasons, threat of death, exposure to war or extreme poverty). Past psychiatric and substance abuse or dependence diagnoses were evaluated with DSM-IV criteria (American Psychiatric Association, 1994), and past suicide attempts with the ICD-10 classification (Dilling & Dittmann, 1990). Forensic history included all types of offences. Insight was rated by the case manager as being absent, partial, or full regarding awareness of illness and necessity of treatment.

2.4 | Symptomatic and functioning data

The functional level at baseline was assessed with the Social and Occupational Functioning Assessment Scale (SOFAS; American Psychiatric Association, 1994) and the Global Assessment of Functioning (GAF; American Psychiatric Association, 1994). While the SOFAS focuses on social and occupational levels, the GAF also includes the impact of symptomatology. Psychotic, depressive, manic symptoms and insight were assessed at 2, 6, 12, 18, 24, 30, 36 months follow-up. Insight was also measured at baseline. Psychotic symptoms were assessed using the positive and negative symptom subscales of the Positive and Negative Psychotic Syndrome Scale (PANSS; Kay et al., 1987). We measured the severity of depressive symptoms using the Montgomery-Asberg Depression Rating Scale (MADRS; Montgomery & Asberg, 1979), and manic symptoms with the Young Mania Rating scale (YMRS; Young et al., 1978). As the YMRS, MADRS and PANSS scores were not available at baseline in our data, we used the assessment at 2 months as a measure of the level of symptoms at the beginning of the program. Adherence to treatment was repeatedly assessed on a 3-point scale with 1 corresponding to nonF adherence (0–25% of prescribed medication taken), 2 to partial adherence (25–75% of prescribed medication taken) and 3 to full adherence (75–100% of prescribed medication taken).

2.5 | Outcomes at discharge

We assessed quality of life at discharge with the World Health Organization Quality Of Life scale ("The World Health Organization Quality of Life assessment (WHOQOL): position paper from the World Health Organization," 1995). It measures satisfaction with life and self-esteem through 26 self-rated items with 5-point Likert scales ranging from 1 (low satisfaction) to 5 (high satisfaction). We used eight items of the PANSS (delusion, unusual thought content, hallucinatory behaviour, conceptual disorganization, mannerisms, blunted affect, social withdrawal, lack of spontaneity; Andreasen et al., 2005) following Andreasen's Criteria (score ≤ 3) to determine symptomatic recovery. A PAS score equal or lower to the premorbid rating on four of the five PAS general scale's items defined functional recovery (Strakowski et al., 1998). The assessment of independent living recovery (head of household/living alone, with partner, or with peers/living with family with minimal supervision) was carried out using the Modified Vocational Status Index (MVSI) and working recovery (paid or unpaid full- or part-time employment/being an active student in school or university/head of household with employed partner [homemaker]/full or part-time volunteer) using the Modified Location Code Index Independent living (MLCI; Tohen et al., 2000). Insight recovery was defined as full insight at discharge.

2.6 | Statistical analysis

A series of exploratory logistic regression analyses were conducted with the sub-group affective psychosis (Yes/No) as the dependent variable, and the individual premorbid and baseline variables as predictors (one at a time for each model). We first conducted logistic regression analysis on the main socio-demographic measures (age, gender, SES, DUP) to explore statistical differences between affective and non-affective psychosis and identify control variables. Because the affective and non-affective psychosis differed for gender and DUP, these two variables were also included in the models. The course of symptoms (positive, negative, depressive, manic) and insight over time were compared between sub-groups using exploratory mixed effects models repeated measures analysis of variance (MMRM). In these models, the "within-group" factor was time and the "between-groups" factor was the sub-group. From the model, the main effects of affective psychosis and time can be examined as well as their interaction. Main effects were examined only if the interaction term was not significant. We selected the optimal within-subject covariance matrix in each MMRM with the Akaike Information Criterion (AIC) coefficient. We tested for any effect of adherence to treatment during follow-up with chi-square tests at each time point. Finally, to assess outcome differences between affective and non-affective sub-groups, we performed logistic regression. All the analyses were performed with IBM SPSS statistics 25.

3 | RESULTS

3.1 | Patient sample

Our final sample consisted of 330 patients, composed of 74 patients (22.42%) who met diagnostic criteria for affective psychosis (24 with bipolar disorder, 17 with major depression with psychotic features, 33 with schizoaffective disorder) and 256 (77.58%) who met diagnostic criteria for non-affective psychosis (209 with schizophrenia, 47 with schizophreniform disorder). We examined the diagnostic stability over the program, we found that only 2.3% of the patients diagnosed with a non-affective psychosis at 18 months changed to a diagnosis of affective psychosis at 36 months, and none of those diagnosed with an affective psychosis at 18 months changed to a diagnosis of non-affective psychosis at 36 months.

3.2 | Socio-demographic and premorbid characteristics

Socio-demographic and premorbid characteristics are reported in Table 1. There was significantly more females in the affective psychosis group (p = .008). Patients with affective psychosis displayed a significantly shorter DUP than non-affective psychosis patients (p = .002). No other differences were observed.

3.3 | Symptomatic and functional characteristics at the beginning of the program

There was no significant difference between sub-groups regarding symptoms and functioning at entry (Table 2).

3.4 | Clinical course of psychotic, depressive, manic symptoms and insight over time

The course of symptoms over time differed between affective and non-affective psychosis. The level of positive symptoms over the 3 years was significantly higher in the non-affective sub-group (mean difference = 1.502, df = 262.048, p = .006; Figure 1(a)). Negative symptoms did not differ significantly (mean difference = 1.339, df = 234.047, p = .068, Figure 1(b)).

The variability of manic symptoms over the course of the program was high in the affective psychosis group whereas this dimension remained stable in non-affective psychosis (Figure 2(a)). As a result, affective and non-affective psychosis differed both at 6 months (mean difference = 1.887, df = 150.161, p = .037) and at 18 months (mean difference = 2.425, df = 153.553, p = .031) in this regard. The course and level of depressive symptoms (Figure 2(b)) did not differ significantly between the sub-groups (mean difference = −1.379, df = 258.234, p = .223). While the level of insight was similar between affective and non-affective psychosis at the beginning of the program, it differed significantly after 6 months (mean difference = −.206, df = .087, p = .019; Figure 2(c)), the affective sub-group displaying a higher level of insight. This difference was maintained all along the follow-up but was not significant at 30 months. We did not find any significant differences between affective and non-affective psychosis on adherence to treatment at any time point of the follow-up.

3.5 | Outcome differences at discharge

Results regarding outcome at discharge are reported in Table 3. Patients in the affective psychosis sub-group perceived the quality of their environment as better than in the non-affective sub-group (p = .006). Furthermore, patients with affective psychosis had developed a higher level of insight towards the end of the treatment period than those with non-affective psychosis (p = .021). No other significant differences were observed.

4 | DISCUSSION

Our study aimed at exploring the clinical relevance of the dichotomy between affective and non-affective psychosis in a first-episode psychosis sample. Based on our data, and despite many commonalities both at baseline and over the follow-up, in addition to gender and DUP previously reported (Conus et al., 2007; Kapila

et al., 2019; Schothorst et al., 2006), these two sub-groups differed significantly regarding the course of positive, manic symptoms and insight, elements which might justify the development of distinct therapeutic approaches.

First, our results revealed important differences between affective and non-affective psychosis regarding the course of symptoms. Despite a similar trajectory, the level of positive psychotic symptoms remained higher in the non-affective sub-group. However, we did not

TABLE 1 Sociodemographic and premorbid characteristics of affective and non-affective psychosis

	Total	Affective	Non-affective		95% CI of OR_a		
	N = 330	*N* = 74 (22.42%)	*N* = 256 (77.58%)	OR_a	LCI	UCI	*p*-value
Gender, male % (*N*)	64.2 (212)	50.0 (37)	68.4 (175)	2.053	1.202	3.506	.008*
Age in year, M (SD)	24.54 (4.687)	25.16 (4.932)	24.32 (4.566)	1.032	0.975	1.093	.281
Age of onset, M (SD)	23.12 (5.016)	24.19 (5.090)	22.75 (4.964)	1.030	0.974	1.088	.299
Duration of untreated psychosis (days), Mdn (IQR)[a]	93.50 (477.25)	50.00 (181.50)	121.50 (617.25)	0.597	0.429	.831	.002*
Socio-economical level, % (*N*)				1.073	0.744	1.548	.706
Low	37.3 (123)	37.8 (28)	31.7 (95)				
Intermediate	43.6 (144)	41.9 (31)	44.1 (113)				
High	19.1 (63)	20.3 (15)	48.8 (18)				
Living situation, % (*N*)				1.196	0.670	2.135	.544
Independent	67.8 (217)	67.1 (49)	68.0 (168)				
Others	32.2 (103)	32.9 (24)	32.0 (79)				
Employment situation, % (*N*)							
Active	14.4 (47)	18.1 (13)	13.4 (34)	Ref. cat	–	–	–
Student/Traineeship	17.8 (58)	26.4 (19)	15.4 (39)	1.293	0.543	3.078	.562
Others	67.8 (221)	55.6 (40)	71.3 (181)	0.678	0.321	1.429	.307
Education in year, M (SD)	10.02 (2.766)	10.48 (2.566)	9.96 (2.804)	1.071	0.958	1.198	.228
Marital status, % (*N*)							
Single	84.0 (272)	78.1 (57)	85.7 (215)	Ref. cat	–	–	–
Married	9.0 (29)	12.3 (9)	8.0 (20)	1.568	0.642	3.826	.323
Divorced	3.4 (11)	6.8 (5)	2.4 (6)	2.660	0.736	9.609	.136
Cohabitation	3.7 (12)	2.7 (2)	4.0 (10)	0.623	0.129	3.013	.556
Premorbid adjustment, M (SD)							
Childhood	0.299 (0.187)	0.271 (0.201)	0.306 (0.184)	0.426	0.078	2.337	.326
Early adolescence	0.319 (0.177)	0.303 (0.183)	0.323 (0.176)	0.658	0.116	3.734	.637
Total	0.309 (0.171)	0.295 (0.188)	0.313 (0.169)	0.668	0.102	4.355	.673
Past suicide attempt, % (*N*)	13.6 (43)	16.4 (12)	12.7 (31)	1.311	0.615	2.792	.483
History of trauma[b], % (*N*)	27.8 (91)	26.8 (19)	28.1 (72)	0.847	0.456	1.571	.598
Migration in adversity, % (*N*)	30.9(102)	37.8(28)	28.9(74)	1.481	0.845	2.593	.170
Psychiatric history, % (*N*)	59.9 (194)	50.7 (37)	62.5 (157)	0.656	0.376	1.143	.137
Familial psychiatric history, % (*N*)	57.5 (176)	62.9 (44)	55.9 (132)	1.152	0.801	1.658	.445
Lifetime substance abuse (DSM-IV), % (*N*)	53.2 (174)	46.6 (34)	55.1 (140)	0.824	0.475	1.427	.490
Forensic history, % (*N*)	13.5 (39)	11.3 (7)	14.1 (32)	0.995	0.395	2.504	.991

Note: All models were adjusted for gender and duration of untreated psychosis. Quantitative variables were treated as continuous variables. We used affective psychosis as the reference category of the dependent variable.

Abbreviations: CI, confidence interval; IQR, interquartile range; M, mean; Mdn, median; *N*, total number; OR_a, adjusted odds ratio; Ref.cat, reference category.

[a]Raw data are presented, however the test statistics were based on log10 (+constant) transformed data because of extreme positive skewness.

[b]Physical or sexual abuse.

*$p < .05$.

TABLE 2 Symptomatic and functional characteristics of affective or non-affective psychosis at the beginning of the program

	Total	Affective	Non-affective		95% CI of OR_a		
	N = 330	*N* = 74 (22.42%)	*N* = 256 (77.58%)	OR_a	LCI	UCI	*p*-value
SOFAS at baseline, M (SD)	42.66 (16.171)	42.10 (16.750)	42.30 (16.450)	0.998	0.982	1.015	.834
GAF at baseline, M (SD)	41.29 (17.159)	41.67 (18.177)	40.74 (17.301)	1.001	0.985	1.017	.920
YMRS at the beginning, M (SD)	6.58 (5.805)	6.03 (5.398)	6.83 (6.137)	0.973	0.904	1.048	.474
MADRS at the beginning, M (SD)	15.91 (9.770)	17.47 (11.404)	15.19 (9.219)	1.029	0.985	1.074	.198
PANSS at the beginning, M (SD)							
Positive	13.67 (4.862)	12.77 (4.240)	13.99 (5.158)	0.953	0.873	1.041	.283
Negative	15.95 (6.070)	15.23 (5.271)	16.54 (6.299)	0.966	0.899	1.037	.333
General	34.52 (8.162)	34.39 (6.859)	34.61 (8.621)	0.994	0.945	1.045	.812
Insight at baseline, % (*N*)				0.996	0.687	1.443	.983
Full	20.4 (65)	22.5 (16)	19.8 (49)				
Partial	45.8 (146)	42.3 (30)	46.8 (116)				
Null	33.9 (108)	35.2 (25)	33.5 (83)				

Note: All models were adjusted for gender and duration of untreated psychosis. Quantitative variables were treated as continuous variables. We used affective psychosis as the reference category of the dependent variable.
Abbreviations: CI, confidence interval; GAF, Global Assessment of Functioning scale; M, mean; MADRS, Montgomery-Asberg Depression Rating Scale; *N*, total number; OR_a, adjusted odds ratio; PANSS, Positive and Negative Syndrome Scale; SOFAS, Social and Occupational Functioning Scale; YMRS, Young Mania Rating Scale.
$^*p < .05$.

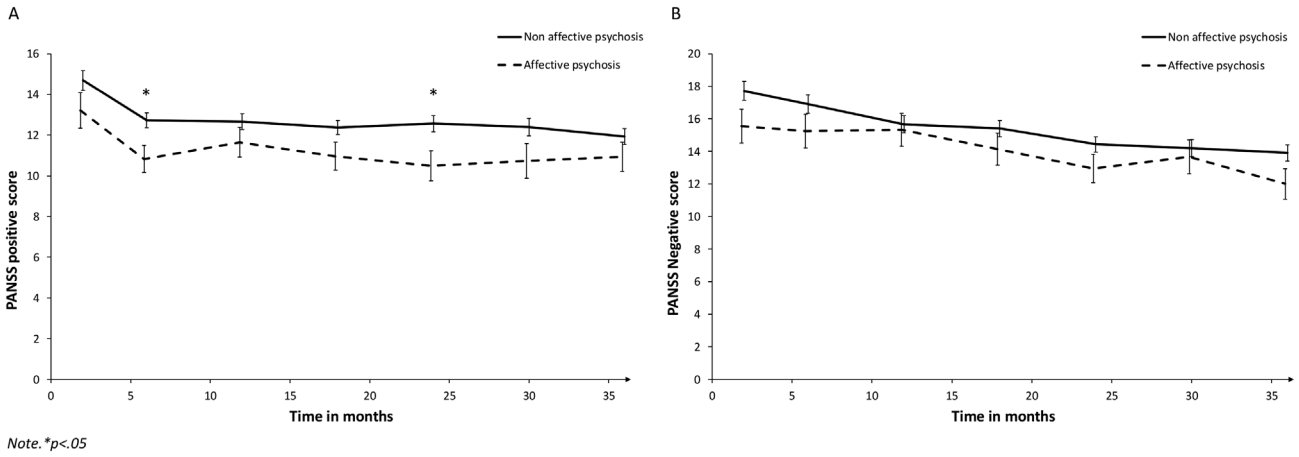

FIGURE 1 Course of positive (a) and negative (b) symptoms of affective (*N* = 74) and non-affective psychosis (*N* = 256) across the 36 months follow-up

find any differences between sub-groups regarding negative symptoms. These results are partially in line with previous studies comparing affective and non-affective groups, and reporting higher levels of both negative and positive symptoms at follow-up for the non-affective one (Henry et al., 2010; Kapila et al., 2019; Torrent et al., 2018). However, contrary to these previous studies, our study observed the course of psychotic symptoms over a three-year follow-up. Considering the crucial role of negative symptoms in long-term recovery (Austin et al., 2013), the absence of difference between affective and non-affective psychosis highlights the risk of poor long-term outcome in both disorders, confirming a challenging recovery previously reported in affective psychosis as well (Conus et al., 2006; Conus et al., 2010; Conus & McGorry, 2002). Our results suggest that positive symptoms remain the main distinctive symptomatic feature of non-affective psychosis. However, we did not investigate symptomatic trajectories within affective and non-affective psychosis to identify different patterns like previously found (Austin et al., 2015), it would thus be interesting to further explore the heterogeneity in the course of positive symptoms to develop targeted intervention. Moreover, considering mood symptoms, we found no difference in the course of depressive symptoms between affective and non-affective psychosis, and found that only the variability of manic symptoms was more important in affective psychosis. Previous literature on schizoaffective disorder reported similarities regarding treatment

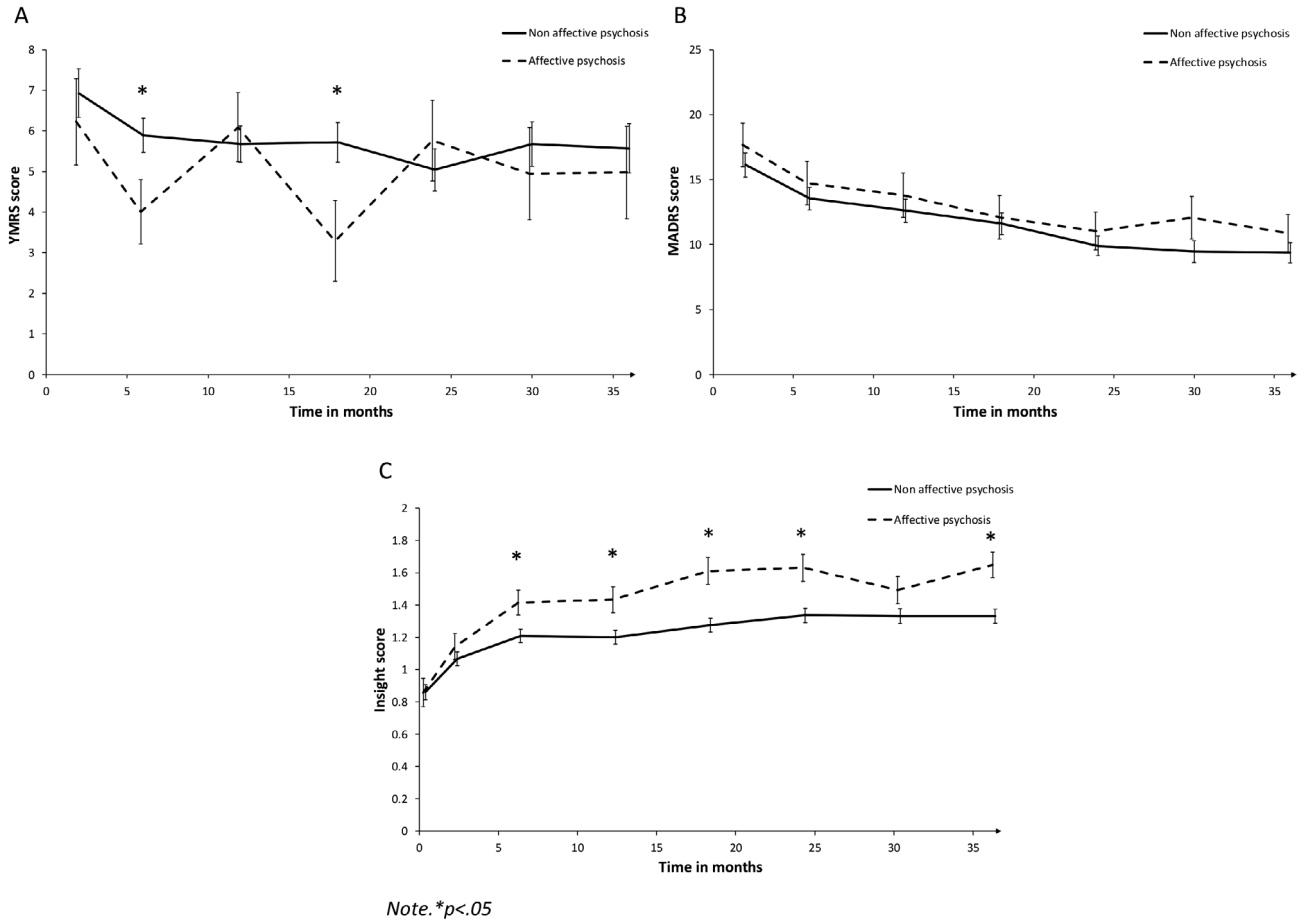

FIGURE 2 Course of manic (a), depressive (b) symptoms and insight (c) of affective (*N* = 74) and nonaffective psychosis (*N* = 256) across the 36 months follow-up

TABLE 3 Outcome differences between affective and non-affective psychosis at discharge

				95% CI of OR_a		
	Affective	**Non-affective**	**OR_a**	**LCI**	**UCI**	***p*-value**
Quality of life						
Quality of physical health, M (SD)	25.90 (5.05)	25.08 (4.38)	0.997	0.885	1.124	.962
Quality of psychological aspects, M (SD)	21.88 (4.43)	21.66 (3.44)	1.011	0.879	1.162	.881
Quality of social relationships, M (SD)	11.13 (2.03)	10.36 (2.16)	1.179	0.893	1.557	.246
Quality of environment, M (SD)	32.59 (5.75)	27.91 (5.91)	1.172	1.047	1.311	.006*
Symptomatic recovery, % (N)	51.9 (14)	44.2 (46)	1.024	0.405	2.586	.960
General functional recovery, % (*N*)	53.4 (31)	40.7 (83)	1.433	0.779	2.636	.247
Premorbid adjustment recovery, % (*N*)	52.5 (21)	43.4 (62)	1.228	0.591	2.550	.582
Working recovery, % (*N*)	27.6 (16)	27.4 (52)	0.745	0.370	1.499	.409
Independent living recovery, % (N)	74.1 (43)	55.3 (105)	1.940	0.987	3.813	.055
Insight recovery, % (N)	71.4 (40)	49.7 (88)	2.200	1.125	4.302	.021*

Note. All models were adjusted for gender and duration of untreated psychosis. Quantitative variables were treated as continuous variables. We used affective psychosis as the reference category of the dependent variable, all the results come from a bivariate analysis.

Abbreviations: CI, confidence interval; LCI, lower limit of the confidence interval; M, mean; *N*, total number; OR_a, adjusted odds ratio; OR, odds ratio; UCI, upper limit of the confidence interval.

*$p < .05$.

between schizophrenia and schizoaffective disorders, especially depressed type (Keck Jr et al., 1996), as well as similar outcome between schizoaffective disorder, major depression, and schizophrenia (Coryell et al., 1987). These results, therefore, suggest that the manic dimension may play an important role to differentiate affective from non-affective psychosis rather than the depressive one. Further investigation of such specificities within affective psychoses are however required to identify those not displaying the full blown mania syndrome considering that they are at risk of delayed identification (Arrasate et al., 2014; Conus, 2010) despite requiring specific treatment (Strakowski et al., 1998).

Second, we observed that patients with affective psychosis were more likely to develop insight over the treatment period than those with non-affective psychosis. Indeed, we found an early improvement of insight in the affective psychosis sub-group, which was significantly better after 6-month follow-up. This might be linked to the trait like condition of insight in non-affective psychosis contrasting with a state-dependent insight (Ghaemi & Rosenquist, 2004) associated with greater fluctuations of manic symptoms in affective psychosis, allowing for phases of full symptom recovery. Development of insight remains challenging in early psychosis, especially among patients with non-affective psychosis (Keshavan et al., 2004).

Third, regarding clinical data at entry, and as already reported previous publications (Conus et al., 2007; Kapila et al., 2019; Schothorst et al., 2006), gender and DUP differed significantly between affective and non-affective psychosis with a higher rate of women and a shorter DUP in the affective psychosis sub-group. However, contrary to these studies, we did not find any difference between groups regarding suicide attempts, past history of psychiatric disorder or substance use, premorbid functioning or adjustment, or psychotic and manic symptoms at baseline. Our results therefore suggest that premorbid and socio-demographic information may not provide clues to identify patients who will develop affective or non-affective psychosis contrary to previous findings regarding diagnosis identification (Kapila et al., 2019).

Fourth, while previous studies reported a better functioning and symptomatic recovery in affective than in non-affective psychosis (Kapila et al., 2019), our study did not reveal such differences. Nevertheless, this is in line with other studies suggesting that outcome in affective psychoses is not as good as previously thought, especially regarding functioning (Conus et al., 2006). However, despite the absence of differences between sub-groups regarding clinical recovery, we found that the sub-group with affective psychosis had a better quality of environment at discharge. This may be linked to the fact that this subgroup had also a shorter DUP previously reported to be associated with a better quality of life (Marshall et al., 2005).

Fifth, our findings suggest overall that affective and non-affective psychosis might benefit from specific intervention strategies like previously reported (Berk et al., 2017; Lambert et al., 2003). For example, a previous study on first-episode bipolar disorder reported that these patients benefit more of a mood stabilizer like lithium as maintenance treatment rather than an antipsychotic like quetiapine (Berk et al., 2017). In addition to treatment, Kessing et al. (2013) reported that patients in the early course of bipolar disorder may benefit from a specialized out-patients mood disorder clinic rather than standard care. However, further studies including schizoaffective disorder, major depression with psychotic features, and bipolar disorder patients are required to explore whether or not these patients with affective psychoses may benefit from a specific intervention targeting mood disorders.

Finally, this study provides evidence for the relevance of using a categorical approach based on clinical presentation in addition to dimensional measures of symptoms. Indeed, specifying intervention based on the identification of subgroups may be useful to provide adjusted guidelines regarding specific clinical evolution and prognosis. However, our results are mixed without a clear dichotomy on clinical presentation and outcomes, pointing out the relevance of supplementing with psychopathological dimensions (Arrasate et al., 2014). This study therefore confirms previous findings suggesting the importance of combining both categorical and dimensional perspectives to map psychiatric disorders to improve identification and develop early intervention (Arrasate et al., 2014; Craddock & Owen, 2007; Keshavan et al., 2011).

Our results must be interpreted with some degree of caution due to various limitations. First, the 6 months interval between assessments may not enable to catch the complete feature of the course of symptoms through the early phase of illness. It would be interesting to study the course of mood symptoms with a greater sampling resolution and shorter time interval to better understand their temporal dynamic. Second, scores on the YMRS scale might be driven by symptoms such as delusions, insight and aggressive behaviour, rather than by specific manic symptoms, thus the similar levels of both groups on this scale must be considered with cautious. Third, we used the 2-month measures for the YMRS, MADRS and PANSS as baseline measures which may not provide a very accurate baseline clinical picture. Indeed, during the first 2 months, treatment and case management follow-up are introduced providing the first steps for stabilization. Therefore, these measures do not reflect the acute baseline symptomatic picture of first episode patients, and may thus hide some clinical differences between affective and non-affective psychosis patients. However, the PANSS, YMRS and MADRS measures were not available at baseline. Finally, differences between affective and non-affective psychosis regarding the course of symptoms might be influenced by other variables that were not tested, like the type of medication. This would require further investigation.

5 | CONCLUSION

Our study aimed to investigate the clinical relevance of a differentiation between affective and non-affective psychosis, and the results suggest that while this differentiation is challenging at baseline, it is nevertheless relevant, considering that these two groups display significant differences regarding their longitudinal trajectories and outcome. More studies are needed to explore the potential impact of a specification of intervention in both of these sub-groups.

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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REFERENCES

Alameda, L., Ferrari, C., Baumann, P. S., Gholam-Rezaee, M., Do, K. Q., & Conus, P. (2015). Childhood sexual and physical abuse: Age at exposure modulates impact on functional outcome in early psychosis patients. *Psychological Medicine*, *45*(13), 2727–2736. https://doi.org/10.1017/s0033291715000690

Alameda, L., Golay, P., Baumann, P. S., Ferrari, C., Do, K. Q., & Conus, P. (2016). Age at the time of exposure to trauma modulates the psychopathological profile in patients with early psychosis. *The Journal of Clinical Psychiatry*, *77*(5), e612–e618. https://doi.org/10.4088/JCP.15m09947

American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders (DSM)* (pp. 143–147). American Psychiatric Association.

Andreasen, N. C., Carpenter, W. T., Jr., Kane, J. M., Lasser, R. A., Marder, S. R., & Weinberger, D. R. (2005). Remission in schizophrenia: Proposed criteria and rationale for consensus. *The American Journal of Psychiatry*, *162*(3), 441–449. https://doi.org/10.1176/appi.ajp.162.3.441

Arrasate, M., Gonzalez-Ortega, I., Alberich, S., Gutierrez, M., Martinez-Cengotitabengoa, M., Mosquera, F., … Gonzalez-Pinto, A. (2014). Affective dimensions as a diagnostic tool for bipolar disorder in first psychotic episodes. *European Psychiatry*, *29*(7), 424–430. https://doi.org/10.1016/j.eurpsy.2013.07.005

Austin, S. F., Mors, O., Budtz-Jørgensen, E., Secher, R. G., Hjorthøj, C. R., Bertelsen, M., Jeppesen, P., Petersen, L., Thorup, A., & Nordentoft, M. (2015). Long-term trajectories of positive and negative symptoms in first episode psychosis: A 10 year follow-up study in the OPUS cohort. *Schizophrenia Research*, *168*(1–2), 84–91. https://doi.org/10.1016/j.schres.2015.07.021

Austin, S. F., Mors, O., Secher, R. G., Hjorthøj, C. R., Albert, N., Bertelsen, M., … Thorup, A. (2013). Predictors of recovery in first episode psychosis: The OPUS cohort at 10 year follow-up. *Schizophrenia Research*, *150*(1), 163–168. https://doi.org/10.1016/j.schres.2013.07.031

Banayan, M., Papetti, F., Palazzolo, J., Pringuey, D., & Darcourt, G. (2007). Conscience du trouble chez les sujets bipolaires euthymiques: étude transversale comparative réalisée sur 60 patients. *Annales Médico-psychologiques, revue psychiatrique*, *165*(4), 247–253. https://doi.org/10.1016/j.amp.2007.02.018

Baumann, P. S., Crespi, S., Marion-Veyron, R., Solida, A., Thonney, J., Favrod, J., Bonsack, C., Do, K. Q., & Conus, P. (2013). Treatment and early intervention in psychosis program (TIPP-Lausanne): Implementation of an early intervention programme for psychosis in Switzerland. *Early Intervention in Psychiatry*, *7*(3), 322–328. https://doi.org/10.1111/eip.12037

Berk, M., Daglas, R., Dandash, O., Yücel, M., Henry, L., Hallam, K., … Kader, L. (2017). Quetiapine v. lithium in the maintenance phase following a first episode of mania: Randomised controlled trial. *The British Journal of Psychiatry*, *210*(6), 413–421. https://doi.org/10.1192/bjp.bp.116.186833

Cannon-Spoor, H. E., Potkin, S. G., & Wyatt, R. J. (1982). Measurement of premorbid adjustment in chronic schizophrenia. *Schizophrenia Bulletin*, *8*, 470–484. https://doi.org/10.1093/schbul/8.3.470

Cawkwell, P. B., Bolton, K. W., Karmacharya, R., Öngür, D., & Shinn, A. K. (2020). Two-year diagnostic stability in a real-world sample of individuals with early psychosis. *Early Intervention in Psychiatry*, *14*, 751–754. https://doi.org/10.1111/eip.12930

Chandola, T., & Jenkinson, C. (2000). The new UKnational statistics socioeconomic classification (NS-SEC); investigating social class differences in self-reported health status. *Journal of Public Health*, *22*(2), 182–190. https://doi.org/10.1093/pubmed/22.2.182

Chia, M. F., Cotton, S., Filia, K., Phelan, M., Conus, P., Jauhar, S., Marwaha, S., McGorry, P. D., Davey, C., Berk, M., & Ratheesh, A. (2019). Early intervention for bipolar disorder - Do current treatment guidelines provide recommendations for the early stages of the disorder? *Journal of Affective Disorders*, *257*, 669–677. https://doi.org/10.1016/j.jad.2019.07.062

Conus, P. (2010). First episode of mood disorders: An opportunity for early intervention in bipolar disorders. *L'Encephale*, *36*, S71–S76.

Conus, P., Abdel-Baki, A., Harrigan, S., Lambert, M., McGorry, P. D., & Berk, M. (2010). Pre-morbid and outcome correlates of first episode mania with psychosis: Is a distinction between schizoaffective and bipolar I disorder valid in the early phase of psychotic disorders? *Journal of Affective Disorders*, *126*(1–2), 88–95. https://doi.org/10.1016/j.jad.2010.04.001

Conus, P., & Bonsack, C. (2004). Early intervention for the initial phase of psychotic disorders in Lausanne: What problems and what solutions? *Revue Médicale de la Suisse Romande*, *124*(4), 221–224.

Conus, P., Cotton, S., Abdel-Baki, A., Lambert, M., Berk, M., & McGorry, P. D. (2006). Symptomatic and functional outcome 12 months after a first episode of psychotic mania: Barriers to recovery in a catchment area sample. *Bipolar Disorders*, *8*(3), 221–231. https://doi.org/10.1111/j.1399-5618.2006.00315.x

Conus, P., Cotton, S., Schimmelmann, B. G., McGorry, P. D., & Lambert, M. (2007). The first-episode psychosis outcome study: Premorbid and baseline characteristics of an epidemiological cohort of 661 first-episode psychosis patients. *Early Intervention in Psychiatry*, *1*(2), 191–200. https://doi.org/10.1111/j.1751-7893.2007.00026.x

Conus, P., & McGorry, P. D. (2002). First-episode mania: A neglected priority for early intervention. *The Australian and New Zealand Journal of Psychiatry*, *36*(2), 158–172. https://doi.org/10.1046/j.1440-1614.2002.00994.x

Coryell, W., Grove, W., Keller, M., & Endicott, J. (1987). Outcome in RDC schizo-affective depression: The importance of diagnostic subtyping. *Journal of Affective Disorders*, *12*(1), 47–56. https://doi.org/10.1016/0165-0327(87)90060-7

Craddock, N., & Owen, M. J. (2007). Rethinking psychosis: The disadvantages of a dichotomous classification now outweigh the advantages. *World Psychiatry*, *6*(2), 84–91.

Dilling, H., & Dittmann, V. (1990). Psychiatric diagnosis following the 10th revision of the international classification of diseases (ICD-10). *Nervenarzt*, *61*(5), 259–270.

Gale-Grant, O., Dazzan, P., Lappin, J. M., Donoghue, K., Reininghaus, U., Croudace, T., … Morgan, C. (2020). Diagnostic stability and outcome after first episode psychosis. *Journal of Mental Health*, *29*(6), 1–9. https://doi.org/10.1080/09638237.2020.1818191

Ghaemi, S. N., & Rosenquist, K. J. (2004). Is insight in mania state-dependent?: A meta-analysis. *The Journal of Nervous and Mental Disease*, *192*(11), 771–775. https://doi.org/10.1097/01.nmd.0000145036.76435.c3

Henry, L. P., Amminger, G. P., Harris, M. G., Yuen, H. P., Harrigan, S. M., Prosser, A. L., Schwartz, O. S., Farrelly, S. E., Herrman, H.,

Jackson, H. J., & McGorry, P. D. (2010). The EPPIC follow-up study of first-episode psychosis: Longer-term clinical and functional outcome 7 years after index admission. *The Journal of Clinical Psychiatry*, *71*(6), 716–728. https://doi.org/10.4088/JCP.08m04846yel

Kapila, A., Fisher, H. L., Johnson, S., Major, B., Rahaman, N., Joyce, J., Chamberlain-Kent, N., Lawrence, J., Young, A. H., & Stone, J. M. (2019). Clinical and demographic differences between patients with manic, depressive and schizophrenia-spectrum psychoses presenting to early intervention Services in London. *Early Intervention in Psychiatry*, *13*(3), 509–516. https://doi.org/10.1111/eip.12511

Kay, S. R., Fiszbein, A., & Opler, L. A. (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia Bulletin*, *13*, 261–276. https://doi.org/10.1093/schbul/13.2.261

Keck, P. E., Jr., McElroy, S. L., & Strakowski, S. M. (1996). New developments in the pharmacologic treatment of schizoaffective disorder. *The Journal of Clinical Psychiatry*, *57*, 41.

Keshavan, M. S., Morris, D. W., Sweeney, J. A., Pearlson, G., Thaker, G., Seidman, L. J., Eack, S. M., & Tamminga, C. (2011). A dimensional approach to the psychosis spectrum between bipolar disorder and schizophrenia: The Schizo-Bipolar Scale. *Schizophrenia Research*, *133* (1–3), 250–254. https://doi.org/10.1016/j.schres.2011.09.005

Keshavan, M. S., Rabinowitz, J., DeSmedt, G., Harvey, P. D. F., & Schooler, N. (2004). Correlates of insight in first episode psychosis. *Schizophrenia Research*, *70*(2–3), 187–194. https://doi.org/10.1016/j.schres.2003.11.007

Kraepelin, E. (1992). Die Erscheinungsformen des Irreseins: (The manifestations of insanity). *History of Psychiatry*, *3*(12), 509–529.

Lambert, M., Conus, P., Lambert, T., & McGorry, P. D. (2003). Pharmacotherapy of first-episode psychosis. *Expert Opinion on Pharmacotherapy*, *4*(5), 717–750. https://doi.org/10.1517/14656566.4.5.717

MacBeth, A., & Gumley, A. (2008). Premorbid adjustment, symptom development and quality of life in first episode psychosis: A systematic review and critical reappraisal. *Acta Psychiatrica Scandinavica*, *117*(2), 85–99. https://doi.org/10.1111/j.1600-0447.2007.01134.x

Marshall, M., Lewis, S., Lockwood, A., Drake, R., Jones, P., & Croudace, T. (2005). Association between duration of untreated psychosis and outcome in cohorts of first-episode patients: A systematic review. *Archives of General Psychiatry*, *62*(9), 975–983. https://doi.org/10.1001/archpsyc.62.9.975

McGorry, P. D. (1994). The influence of illness duration on syndrome clarity and stability in functional psychosis: Does the diagnosis emerge and stabilise with time? *Australian & New Zealand Journal of Psychiatry*, *28*(4), 607–619. https://doi.org/10.1080/00048679409080784

McGorry, P. D., Mihalopoulos, C., Henry, L., Dakis, J., Jackson, H. J., Flaum, M., … Karoly, R. (1995). Spurious precision: Procedural validity of diagnostic assessment in psychotic disorders. *The American Journal of Psychiatry*, *152*(2), 220–223. https://doi.org/10.1176/ajp.152.2.220

Montgomery, S. A., & Asberg, M. (1979). A new depression scale designed to be sensitive to change. *The British Journal of Psychiatry*, *134*, 382–389.

Schimmelmann, B. G., Conus, P., Edwards, J., McGorry, P. D., & Lambert, M. (2005). Diagnostic stability 18 months after treatment initiation for first-episode psychosis. *The Journal of Clinical Psychiatry*, *66* (10), 1239–1246. https://doi.org/10.4088/jcp.v66n1006

Schothorst, P. F., Emck, C., & van Engeland, H. (2006). Characteristics of early psychosis. *Comprehensive Psychiatry*, *47*(6), 438–442. https://doi.org/10.1016/j.comppsych.2006.03.003

Shinn, A. K., Bolton, K. W., Karmacharya, R., Lewandowski, K. E., Yuksel, C., Baker, J. T., … Ongur, D. (2017). McLean OnTrack: A transdiagnostic program for early intervention in first-episode psychosis. *Early Intervention in Psychiatry*, *11*(1), 83–90. https://doi.org/10.1111/eip.12299

Strakowski, S. M., Keck, P. E., Jr., McElroy, S. L., West, S. A., Sax, K. W., Hawkins, J. M., … Bourne, M. L. (1998). Twelve-month outcome after a first hospitalization for affective psychosis. *Archives of General Psychiatry*, *55*(1), 49–55.

Taş, H. İ., Celik, M., & Altinbaş, K. (2019). Evaluation of four-year stability of unspecified psychosis. *Archives of Neuropsychiatry*, *56*(1), 47. https://doi.org/10.29399/npa.22903

Thaker, G. (2008). Psychosis endophenotypes in schizophrenia and bipolar disorder. *Schizophrenia Bulletin*, *34*(4), 720–721. https://doi.org/10.1093/schbul/sbn055

The WHOQOL Group. (1995). The World Health Organization qQuality of lLife assessment (WHOQOL): Position paper from the World Health Organization. *Social Science & Medicine*, *41*(10), 1403–1409.

Tohen, M., Hennen, J., Zarate, C. M., Jr., Baldessarini, R. J., Strakowski, S. M., Stoll, A. L., … Cohen, B. M. (2000). Two-year syndromal and functional recovery in 219 cases of first-episode major affective disorder with psychotic features. *The American Journal of Psychiatry*, *157*(2), 220–228. https://doi.org/10.1176/appi.ajp.157.2.220

Torrent, C., Reinares, M., Martinez-Aran, A., Cabrera, B., Amoretti, S., Corripio, I., … Vieta, E. (2018). Affective versus non-affective first episode psychoses: A longitudinal study. *Journal of Affective Disorders*, *238*, 297–304. https://doi.org/10.1016/j.jad.2018.06.005

Young, R. C., Biggs, J. T., Ziegler, V. E., & Meyer, D. A. (1978). A rating scale for mania: Reliability, validity and sensitivity. *The British Journal of Psychiatry*, *133*, 429–435.

Yung, A. R., Yuen, H. P., McGorry, P. D., Phillips, L. J., Kelly, D., Dell'Olio, M., … Buckby, J. (2005). Mapping the onset of psychosis: The comprehensive assessment of at-risk mental states. *The Australian and New Zealand Journal of Psychiatry*, *39*(11–12), 964–971. https://doi.org/10.1080/j.1440-1614.2005.01714.x

Kessing, L.V., Hansen, H.V., Hvenegaard, A., Christensen, E.M., Dam, H., Gluud, C, Wetterslev, J.J. (2013). Treatment in a specialised outpatient mood disorder clinicv.standard out-patient treatment in the early course of bipolar disorder: randomised clinical trial. *British Journal of Psychiatry*, *202*(3), 212–219. http://dx.doi.org/10.1192/bjp.bp.112.113548.

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Affective psychoses as a conceptual grouping in early psychosis: homogenous or heteronomous clinical features?

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Abstract

The concept of affective psychosis encompasses diagnostic categories of psychotic disorders with mood disturbances. This concept is applied in clinical settings but its usefulness remains questioned given the existing distinct diagnostic categories on which this conceptual grouping is based. The aim of this study was to explore whether the clinical features of the diagnostic categories within affective psychoses were homogenous enough to warrant the use of this clinical entity in the early intervention context. In our study, we examined the homogeneity of the schizoaffective disorder, the bipolar disorder, and the major depression with psychotic features in a first-episode affective psychosis cohort (N = 77; Mean age = 25.19) using Bayesian model comparison and mixed effects models repeated measures analysis of variance over a three year follow-up. Our results revealed many similarities between these diagnostic categories regarding socio-demographic variables, and outcomes as well as similar course of positive psychotic and manic symptoms. However, patients with schizoaffective disorder had more severe general and negative symptoms than bipolar disorder patients during the first 18 months, as well as less depressive symptoms during the first year. This group was also less likely to get back to work and to recover functionally at the end of the 36-month follow-up than the two other groups. These results suggest that developing clinical guidelines using the affective psychosis theoretical umbrella is relevant. However, the poor functional recovery of schizoaffective disorder requires specific attention. Further studies are required to investigate the impact of specific early intervention for affective psychoses.

Key words: affective psychosis, diagnosis, first-episode, functional outcome, symptoms

Introduction

Affective psychosis is a concept applied in both clinical and research settings that groups various psychotic disorders associated with mood disturbances including bipolar disorder with psychotic features, major depression with psychotic features, and schizoaffective disorder (Kraepelin, 1992; Lambert et al., 2003). Affective psychoses remain largely neglected in early intervention strategies and research (Chia et al., 2019; Conus and McGorry, 2002) despite poor functional outcome (Conus et al., 2006). In a recent study in a first-episode psychosis cohort we showed that the dichotomy between affective and non-affective psychosis may be useful to develop adapted guidelines considering some specificities in the clinical features of affective psychoses, such as lower severity of positive psychotic symptoms, increased variablity in manic symptoms, and a quick recovery of insight (Ramain et al., 2021). As a second step to confort this hypothesis, exploring wether the affective psychosis group is sufficiently homogeneous would be important to justify the generalisation of such a grouping, and its use when defining treatment strategies.

Indeed, the question of the clinical relevance of this concept in addition with existing diagnostic classifications on which this conceptual grouping is based remains debated. While some studies reported results for affective psychoses taken as a group (Conus and McGorry, 2002; Husted et al., 1995), and provided guidelines for the treatment of first-episode affective psychoses (Lambert et al., 2003), others focused specifically on bipolar disorder (Jauhar et al., 2019), schizoaffective disorder (Malhi et al., 2008), or major depressive disorder with psychotic features (Rothschild, 2013; Schatzberg, 2003). In addition, a previous publication suggested that in first-episode mania with psychotic features, a distinction between bipolar disorder and schizoaffective disorder was relevant on the basis of differences in negative symptoms levels and outcome (Conus et al., 2010). However, these previous papers studying the diagnostic categories separately also pointed out to commonalities and overlaps (regarding course of illness or indicated pharmacological treatment) which add support to the hypothesis that recommendations for affective psychoses as a group could be usefully developed.

Further studies are thus required to explore the clinical relevance of the concept of affective psychoses in addition or instead of existing diagnostic categories, especially with regard to the

development of early intervention strategies that may need to be different from the ones applied for first-epsiode schizophrenia spectrum disorders. The aim of this study was to explore whether the clinical features of the diagnostic categories included within the affective psychoses group (schizoaffective disorder [SAD], bipolar disorder with psychotic features [BD], major depressive disorder with psychotic features [MDP]) were homogenous enough to warrant the use of this clinical entity in the early intervention context.

Method

Sample and procedure

This prospective study examined a cohort of first-episode psychosis patients treated at a specialised early psychosis intervention program (the Treatment and Early Intervention in Psychosis Programme; TIPP) that has been implemented by Lausanne University Hospital's Department of Psychiatry in 2004 (Baumann et al., 2013; Conus and Bonsack, 2004). Patients entering the programme are aged 18–35, reside in the Lausanne catchment area and have crossed the psychosis threshold in the Comprehensive Assessment of At-Risk Mental States scale's (CAARMS; Yung et al., 2005) *Psychosis Threshold* subscale. Patients are referred to other programmes if they have been on antipsychotic medication for more than six months, have an intoxication-induced or organic brain disease-induced psychosis, or have an intelligence quotient below 70. A psychiatrist and a case manager follow every patient in the programme for three years. The TIPP favours a bio-psycho-social perspective and provides treatment including psychotherapy, psychoeducation, family support and therapy, cognitive assessment and remediation, social support, supported employment, psychological interventions for cannabis use, and pharmacological treatment. In line with international guidelines, atypical antipsychotics are a first-line pharmacological treatment used to prospectively monitor any side effects (Baumann et al., 2013). Case managers fill out a specifically designed questionnaire for the TIPP with every patient. This includes information about demographic characteristics, medical history, exposure to traumatic life events, symptomatology and usual functioning. Follow-up assessments are carried out at 2, 6, 12, 18, 24, 30 and 36 months, by a psychologist and a case manager, to explore various aspects of treatment, pharmacotherapy, the psychopathology's evolution, and functional status, as well as co-morbidities (e.g.

level of insight, treatment adherence, the presence or absence of a forensic history and substance use, intermittent exposure to trauma, suicide attempts and forensic events). The study was approved by the Human Research Ethics Committee of the Canton of Vaud (protocol #2020-00272). The data generated during follow-up were only used if patients provided written informed consent; all of them agreed that their clinical data could be used for research, yielding a highly representative sample of early psychosis patients.

Diagnostic Assessment

The diagnoses presented here were the results of an expert consensus built from discussions held at 18 and 36 months, based on the DSM-IV criteria and using information from patients' medical records or hospitalisation reports provided by their treating psychiatrists and their TIPP-assigned psychiatrists and case managers.. We used the latest consensus diagnosis available. Patients included in the affective psychoses group were diagnosed with BD, MDP or SAD.

Socio-demographic and premorbid characteristics

According to the CAARMS criteria, DUP was defined as the time elapsed from the onset of psychosis until admission to TIPP. Socioeconomic status (SES) was subdivided into three categories: low, intermediate and high (Chandola and Jenkinson, 2000). Independent living refers to patients living in independent households, living alone or with friends or family without supervision. The professional activity was subdivided into student or traineeship, active employment, which was defined as partial or full-time job, or other. The premorbid functional level was assessed with the Premorbid Adjustment Scale (PAS; Cannon-Spoor et al., 1982) using the childhood and early adolescence sub-scores (MacBeth and Gumley, 2008), and the total score. We considered that patients had a history of trauma if they had experienced at least one instance of sexual or physical abuse before the onset of psychosis (Alameda et al., 2015; Alameda et al., 2016). We defined migration in adversity as migration occurring in adverse contexts (e.g. seeking protection for political reasons, threat of death, exposure to war or extreme poverty). Past psychiatric and substance abuse or dependence diagnoses were evaluated with DSM-IV criteria (American Psychiatric Association, 1994), and past suicide attempts with the ICD-10

classification (Dilling and Dittmann, 1990). Forensic history included all types of offenses. Insight was rated by the case manager as being absent, partial, or full regarding awareness of illness and necessity of treatment.

Symptomatic and functioning data

The functional level at baseline was assessed with the Social and Occupational Functioning Assessment Scale (SOFAS; American Psychiatric Association, 1994) and the Global Assessment of Functioning (GAF; American Psychiatric Association, 1994). While the SOFAS focuses on social and occupational levels, the GAF also includes the impact of symptomatology. General, psychotic, depressive, and manic symptoms were assessed at 2, 6, 12, 18, 24, 30, 36 months follow-up. General and psychotic symptoms were assessed using the general, positive, and negative symptom subscales of the Positive and Negative Psychotic Syndrome Scale (PANSS; Kay et al., 1987). We measured the severity of depressive symptoms using the Montgomery-Asberg Depression Rating Scale (MADRS; Montgomery and Asberg, 1979), and manic symptoms with the Young Mania Rating scale (YMRS; Young et al., 1978). As the YMRS, MADRS and PANSS scores were not available at baseline in our data, we used the assessment at 2 months as a measure of the level of symptoms at the beginning of the programme.

Outcomes at discharge

We assessed quality of life at discharge with the World Health Organization Quality Of Life scale (WHOQOL; The World Health Organization, 1995). It measures satisfaction with life and self-esteem through 26 self-rated items with 5-point Likert scales ranging from 1 (low satisfaction) to 5 (high satisfaction). We used 8 items of the PANSS (delusion, unusual thought content, hallucinatory behaviour, conceptual disorganization, mannerisms, blunted affect, social withdrawal, lack of spontaneity; Andreasen et al., 2005) following Andreasen's Criteria (score $\leq$ 3) to determine symptomatic recovery. A PAS score equal or lower to the premorbid rating on four of the five PAS general scale's items defined functional recovery (Strakowski et al., 1998). The assessment of independent living recovery (head of household/living alone, with partner, or with peers/living with family with minimal supervision) was carried out using the Modified Vocational Status Index (MVSI)

and working recovery (paid or unpaid full- or part-time employment/being an active student in school or university/head of household with employed partner (homemaker)/full or part-time volunteer) using the Modified Location Code Index Independent living (MLCI; Tohen et al., 2000). Insight recovery was defined as full insight at discharge.

Statistical analysis

We compared the three affective psychosis diagnostic sub-groups (SAD, BD and MDP) using a Bayesian approach which represents an elegant alternative to the classic problem of multiple comparisons and allows evaluating the support for the null hypothesis (Golay et al., 2020; Golay et al., 2019b; Noël, 2015). All 6 possible models were estimated. The first model was the homogeneous model (1, 2, 3) stating that groups (SAD, BD, MDP) did not differ and were issued from the same distribution. It corresponds to the null hypothesis in the classical statistical testing framework. Another model was the heterogeneous model (1), (2), (3) (i.e. all the groups are different from each other and issued from a different distribution; i.e (SAD), (BD), (MDP). All other possible combinations, which adds up to 5 — that is (1, 2), (3) or (1), (2, 3) or (1, 3), (2)) were also estimated. For continuous variables, the best possible Gaussian model (μ, $\sigma 2$) was determined by using the Bayesian information criterion (Schwarz, 1978). For nominal variables, the best multinomial model was determined using the exact likelihood with a uniform prior on all parameters (Noël, 2015). An equal prior probability of 1/5 was assumed for all models so that no model was favored. The Bayes factor was also computed (Kass and Raftery, 1995) and provided a comparison between the best model and the homogenous model. A Bayes factor of 4 indicates that the best model was 4 times more likely to be true than the homogenous model. Values over 3 are generally considered sufficiently important to favor one model over another (Jeffreys, 1961; Wagenmakers et al., 2011). The course of symptoms (general, positive, negative, depressive, manic) over time were compared between the SAD, BD, and MDP groups using mixed effects models repeated measures analysis of variance (MMRM). In these models, the "within-group" factor was time and the "between-groups" factor was the diagnostical group. From the model, the main effects of the groups and time can be examined as well as their interaction. Main effects were examined only if the interaction term was not significant. We selected the optimal within-subject covariance matrix in each MMRM with the Akaike Information Criterion (AIC) coefficient. All the analyses were performed with IBM SPSS

statistics 26, , the AtelieR package for R (Noël, 2013) and the Bayes R2STATS group models online calculator (Noël, 2018).

Results

Patient sample

Our sample consisted of 77 patients (Mean age = 25.19; SD = 4.83) who met diagnostic criteria for affective psychosis (33.8% with BD, 20.8% with MDP with psychotic features, 45.5% with SAD).

Socio-demographic and premorbid characteristics

Socio-demographic and premorbid characteristics are reported in *Table 1*. Results showed that BD, MDP and SAD patients were similar regarding gender repartition, age, level of education as well as marital status. The DUP was also similar in all category. Considering their past history, all groups displayed a similar prevalence of exposure to trauma, substance abuse and dependence. They were also similar regarding their functional level during adolescence and childhood based on the PAS.

MDP patients were less likely than the two other groups to have high SES, to live independently, to have a family history of psychiatric disorder and to display full insight at baseline

Patients with BD were more likely to have an active professional/training activity at baseline and were less likely to have a past history of suicide or migration in adversity than patients with SAD or MDP

The SAD group was more likely to have a forensic history and psychiatric antecedents than BD and MDP patients.

Table 1. Comparison of socio-demographic and premorbid characteristics between diagnostic categories within affective psychoses.

	(1) Schizoaffective disorder (n = 35)	*(2) Major depression with psychotic features (n = 16)*	*(3) Bipolar disorder (n =26)*	*Best Model*[a]	*Bayes factor against null hypothesis*[b]	*Probability of the model to be true*[c]
Sex, % males (n)	**51.4 (18)**	**43.8 (7)**	**53.8 (14)**	**(1, 2, 3)**	**1.0000**	**0.4699**
Age, M (SD)	**25.17 (4.61)**	**25.38 (5.20)**	**25.12 (5.08)**	**(1, 2, 3)**	**1.0000**	**0.7367**
Level of education, M (SD)	**10.39 (2.32)**	**9.67 (2.87)**	**11.19 (2.64)**	**(1, 2, 3)**	**1.0000**	**0.5326**
SES, % (n)				(1, 3), (2)	2.7479	0.4916
Low	20.0 (7)	25.0 (4)	15.4 (4)			
Medium	42.9 (15)	62.5 (10)	30.8 (8)			
High	37.1 (13)	12.5 (2)	53.8 (14)			
Marital status, % (n)				**(1, 2, 3)**	**1.0000**	**0.5017**
Single	76.5 (26)	62.5 (10)	96.2 (25)			
Maried	11.8 (4)	31.3 (5)	0.0 (0)			
Divorced	5.9 (2)	6.3 (1)	3.8 (1)			
Cohabitation	5.9 (2)	0.0 (0)	0.0 (0)			
Professional activity, % (n)				(1, 2), (3)	1400.9766	0.7543
Active employment	8.8 (3)	12.5 (2)	33.3 (8)			
Student/traineeship	11.8 (4)	25.0 (4)	45.8 (11)			
Others	79.4 (27)	62.5 (10)	20.8 (5)			
Life style, % (n)				(1, 3), (2)	1.7265	0.4383
Independent	73.5 (25)	50.0 (8)	76.0 (19)			
Others	26.5 (9)	50.0 (8)	24.0 (6)			
DUP[d], Mdn (IQR)	**67.00 (254.00)**	**65.50 (153.00)**	**23.50 (69.75)**	**(1, 2, 3)**	**1.0000**	**0.5277**
Suicide, % (n)	17.6 (6)	25.0 (4)	3.8 (1)	(1, 2), (3)	1.1991	0.3434
Trauma, % (n)	**29.4 (10)**	**25.0 (4)**	**23.1 (6)**	**(1, 2, 3)**	**1.0000**	**0.5093**
Migration in adversity, % (n)	42.9 (15)	37.5 (6)	19.2 (5)	(1, 2), (3)	1.7126	0.3774
Forensic history, % (n)	24.1 (7)	6.7 (1)	0.0 (0)	(1), (2, 3)	5.8453	0.5464
Psychiatric antecedents, % (n)	60.0 (21)	37.5 (6)	42.3 (11)	(1), (2, 3)	1.1606	0.3214
Familial psychiatric history, % (n)	64.7 (22)	42.9 (6)	64.0 (16)	(1, 3), (2)	1.0034	0.3353
Substance abuse, % (n)	**14.7 (5)**	**6.3 (1)**	**7.7 (2)**	**(1, 2, 3)**	**1.0000**	**0.5570**
Dependence to substance, % (n)	**11.8 (4)**	**0.0 (0)**	**7.7 (2)**	**(1, 2, 3)**	**1.0000**	**0.5443**
Insight, % (n)				(1, 3), (2)	36.3186	0.7463
Null	44.1 (15)	12.5 (2)	30.8 (8)			
Partial	32.4 (11)	81.3 (13)	34.6 (9)			
Full	23.5 (8)	6.3 (1)	34.6 (9)			
PAS childhood, M (SD)	**0.29 (0.21)**	**0.25 (0.16)**	**0.24 (0.19)**	**(1, 2, 3)**	**1.0000**	**0.6386**
PAS Early adolescence M (SD)	**0.32 (0.17)**	**0.28 (0.20)**	**0.28 (0.19)**	**(1, 2, 3)**	**1.0000**	**0.6448**

Note. Lines in bold highlight homogeneity between groups. a = based on BIC coefficient; b = Bayes factor comparing the best model to the homogeneous model (1, 2, 3); c = compared to all possible models ((1, 2, 3) / (1, 2) (3) / (1) (2, 3) / (1, 3) (2) / (1) (2) (3)); d= Raw data are presented, however the test statistics were based on log10 (+constant) transformed data because of extreme positive skewness.

Clinical presentation at the beginning of the programme

Clinical presentation at the beginning of the programme is reported in *Table 2.* The groups were similar regarding the severity of the positive, manic and general symptomatology at 2 months follow-up. The SAD group was more likely to have more severe depressive symptoms at 2 months, as well as a worse level of socio-occupational and symptomatic functioning (SOFAS and GAF scores) at baseline than the two other groups. The BD group was more likely to have less severe negative symptoms at 2 months.

Table 2. Comparison of clinical data between diagnostic categories within affective psychoses at the beginning of the programme.

	(1) Schizoaffective disorder (n = 35)	*(2) Major depression with psychotic features (n = 16)*	*(3) Bipolar disorder (n = 26)*	*Best Model*[a]	*Bayes factor against null hypothesis* [b]	*Probability of the model to be true*[c]
2 months PANSS positive, M (SD)	**13.33 (4.42)**	**12.00 (3.92)**	**12.31 (4.52)**	**(1, 2, 3)**	**1.0000**	**0.6029**
2 months PANSS negative, M (SD)	17.75 (5.77)	15.14 (4.22)	12.46 (4.31)	(1, 2), (3)	3.2269	0.3766
2 months PANSS general, M (SD)	**36.50 (6.75)**	**34.57 (7.28)**	**31.61 (6.63)**	**(1, 2, 3)**	**1.0000**	**0.3627**
2 months MADRS, M (SD)	22.17 (13.25)	16.14 (7.84)	12.75 (9.62)	(1), (2, 3)	1.4780	0.3789
2 months YMRS, M (SD)	**5.42 (5.70)**	**6.14 (5.27)**	**6.50 (5.35)**	**(1, 2, 3)**	**1.0000**	**0.6186**
Baseline GAF, M (SD)	35.70 (13.07)	47.07 (17.96)	46.88 (22.37)	(1), (2, 3)	4.1898	0.6474
Baseline SOFAS, M (SD)	36.62 (12.04)	48.13 (16.98)	47.71 (19.88)	(1), (2, 3)	9.6283	0.7560

Note. Lines in bold highlight homogeneity between groups a = based on BIC coefficient; b = Bayes factor comparing the best model to the homogeneous model (1, 2, 3); c = compared to all possible models ((1, 2, 3) / (1, 2) (3) / (1) (2, 3) / (1, 3) (2) / (1) (2) (3)).

Course of symptoms over the 36 months of programme

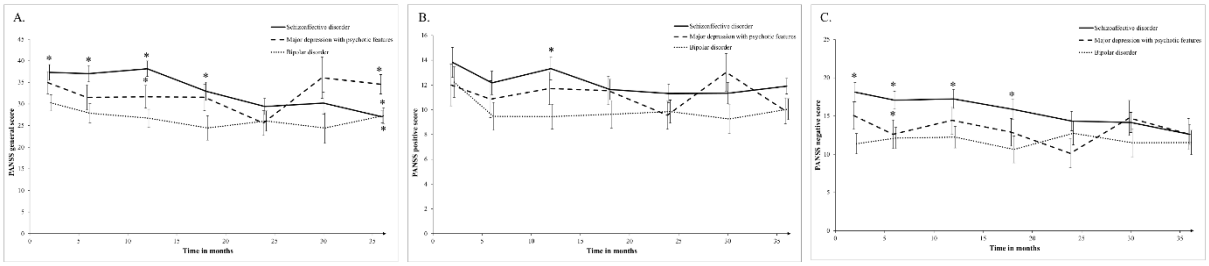
The course of general and negative symptoms differed significantly between SAD and BD patients over the first 18 months. Indeed, the SAD group had significantly more severe general symptoms (*Figure 1.*

A.) at 2 (mean difference = 7.056; df = 2.627; p =.011), 6 (mean difference = 9.142; df = 2.907; p =.003), 12 (mean difference = 11.450; df = 2.739; p <.001), 18 (mean difference = 8.492; df = 3.521; p =.021) months than the BD group. The SAD group had also significantly greater severity of negative symptomatology at 2 (mean difference = 6.731; df = 1.840; p < .001), 6 (mean difference = 4.957; df = 1.824; p =.007), 12 (mean difference = 4.995; df = 1.874; p = .008), 18 (mean difference = 5.248; df = 2.181; p =.017) months than the BD group (*Figure 1. C.).*

The SAD group had significantly more severe general symptoms at 12 months (mean difference = 6.493; df = 3.194; p =.048; *Figure 1. A.*) than the MDP group. However, general symptoms were significantly less severe at 36 months in the SAD (mean difference = -7.553; df = 2.622; p =.008; *Figure 1. A.*), and in the BD (mean difference = -7.277; df = 2.872; p =.018; *Figure 1. A.*) groups than in the MDP group. The SAD group had also significantly more negative symptoms than the MDP group at 6 months only (mean difference = 4.462; df = 2.210; p = .045; *Figure 1. C.*).

The SAD group had significantly more positive psychotic symptoms than the BD groups only at 12 months (mean difference = 3.872; df = 1.355; p =.007; *Figure 1. B.*). The three groups did not significantly differ regarding positive symptoms at any other time point.

Figure 1. The course of general (A), positive (B), and negative (C) symptoms of schizoaffective disorder, major depression with psychotic features, and bipolar disorder over the 36 months of the programme

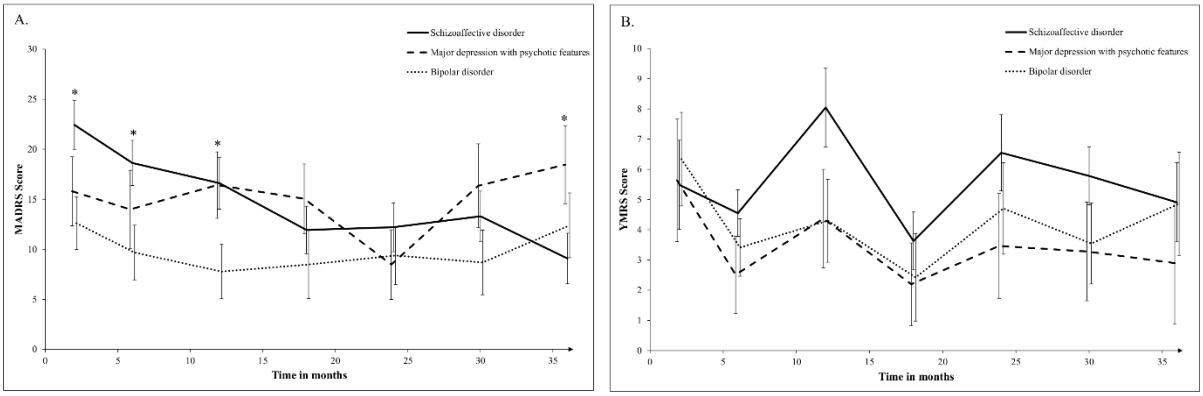


*Note. *p<.05*

The SAD group had more depressive symptoms than the BD group during the first year of the programme. Indeed, depressive symptoms were significantly more severe at 2 (mean difference = 9.844; df = 3.592; p = .007), 6 (mean difference = 8.949; df = 3.541; p = .013), and 12 (mean difference = 8.836; df = 3.757; p = .020) months (*Figure 2. A.*) in the SAD than in the BD group. The SAD group and the MDP group did not differ significantly regarding depressive symptoms until the 36 months with

more severe in the MDP group (mean difference = 9.380; df = 4.647; p = .045; *Figure 2. A.*). All the groups did not differ significantly at any time point regarding manic symptoms (*Figure 2. B.*)

Figure 2. The course of depressive (A) and manic (B) symptoms of schizoaffective disorder, major depression with psychotic features, and bipolar disorder over the 36 months of the programme



*Note. *p<.05*

Outcomes

Outcomes are reported in *Table 3*. All the groups had similar premorbid adjustment recovery, as well as insight and independent living recovery. They also had a similar perceived quality of physical health, psychological aspects, social relationships. Patients with a SAD were less likely to recover functionally and to get back to work than patients of the two other groups. Patients with BD were more likely to achieve symptomatic recovery than patients of the two other groups. They were also more likely to perceive the quality of their environment as better than patients with a SAD or a MDP.

Table 3. Comparison of outcomes between diagnostic categories within affective psychoses.

	(1) Schizoaffective disorder (n = 35)	*(2) Major depression with psychotic features (n = 16)*	*(3) Bipolar disorder (n = 26)*	*Best Model*[a]	*Bayes factor against null hypothesis* [b]	*Probability of the model to be true*[c]
Symptomatic recovery, % (n)	31.3 (5)	40.0 (2)	100.0 (10)	(1, 2), (3)	301.5605	0.6128
General functional recovery, % (n)	37.5 (12)	63.6 (7)	70.0 (14)	(1), (2, 3)	5.2093	0.4756
Premorbid adjustment recovery, % (n)	**40.0 (8)**	**50.0 (4)**	**64.3 (9)**	**(1, 2, 3)**	**1.0000**	**0.2816**
Insight recovery, % (n)	**76.7 (23)**	**63.6 (7)**	**70.6 (12)**	**(1, 2, 3)**	**1.0000**	**0.4279**
Independent living recovery, % (n)	**70.0 (21)**	**83.3 (10)**	**72.2 (13)**	**(1, 2, 3)**	**1.0000**	**0.4488**
Working recovery, % (n)	13.3 (4)	50.0 (6)	44.4 (8)	(1), (2, 3)	14.7333	0.5933
Quality of life, M (SD)						
Quality of physical health	**24.24 (5.58)**	**28.60 (5.03)**	**27.00 (2.83)**	**(1, 2, 3)**	**1.0000**	**0.3313**
Quality of psychological aspects	**21.50 (4.96)**	**22.92 (3.67)**	**21.60 (4.59)**	**(1, 2, 3)**	**1.0000**	**0.5744**
Quality of social relationships	**11.00 (2.13)**	**11.40 (1.67)**	**11.17 (2.40)**	**(1, 2, 3)**	**1.0000**	**0.5893**
Quality of environment	30.83 (6.77)	32.53 (4.32)	36.17 (3.19)	(1, 2), (3)	1.1512	0.3442

Note. Lines in bold highlight homogeneity between groups a = based on BIC coefficient; b = Bayes factor comparing the best model to the homogeneous model (1, 2, 3); c = compared to all possible models ((1, 2, 3) / (1, 2) (3) / (1) (2, 3) / (1, 3) (2) / (1) (2) (3)).

Discussion

After finding in a previous paper that a dichotomy between affective and non-affective psychoses was empirically worthwhile (Ramain et al., 2021), we studied in the current paper the degree of homogeneity among patients displaying affective psychosis, in order to further explore the clinical relevance of this conceptual grouping. In this aim, rather than relying on standard statistical tests that allow only the exclusion of statistical differences, we applied Bayesian statistic methods that permit to explore homogeneity within samples very specifically, and allow to evaluate the statistical support for the null hypothesis. Our results revealed important similarities among SAD, BD and MDP patients regarding socio-demographic variables, premorbid history, baseline clinical presentation, as well as outcomes. Based on these elements, there seems to be a sufficient homogeneity among affective psychosis patients to justify considering them as a group when developing clinical guidelines for early intervention.

Indeed, all diagnostic subgroups were homogeneous regarding many premorbid characteristics that determine outcome (gender repartition, age, level of education, marital status, rate of exposure to trauma, to substance abuse and dependence, and functional level during adolescence). In addition, severity of scores on positive, manic and general symptomatology at 2 months post entry to the programme were similar, suggesting a similar pattern of short term evolution. Moreover, the course of positive psychotic and manic symptoms did not differ significantly between groups over the 3 years. In addition, differences between groups regarding the course of depressive, negative, and general symptoms were sparse after 18 months follow-up. Finally, all affective psychosis patients had similar rate of insight development, of return to premorbid adjustment recovery and to independent living at the end of the program.

However, there were also domains where homogeneity between groups was more limited. In line with previous findings (Conus et al., 2010), SAD patients were the ones displaying the strongest divergence with both other diagnostic groups. These patients were more likely to have a forensic history and psychiatric antecedents, had more severe depressive symptoms at the beginning of the program, as well as worse level of socio-occupational and symptomatic functioning (SOFAS and GAF scores) than BD and MDP patients. During the first year of the follow-up, they displayed more enduring symptoms than

the BD group, which is somewhat understandable considering that the presence of positive symptoms for a longer period is at the basis of their clinical definition (American Psychiatric Association, 2013). SAD patients were also less likely than the two other groups to recover functionally at the end of treatment. The worse functional and professional recovery of this diagnosis group is probably not be associated with the course of symptomatology, which globally did not differ between MDP and SAD, but rather with more severe depressive symptoms and worse functioning at baseline, as well as with problematic antecedents (forensic history, psychiatric antecedents). This is in line with previous findings showing that, despite a good symptomatic recovery, functional recovery remains challenging in affective psychosis (Conus et al., 2006), and may be particularly difficult in SAD (Schöttle et al., 2012). Early intervention in affective psychoses targeting functional adjustment should therefore be intensified for patients with problematic antecedents, poor functioning and depressive symptoms at baseline, regardless of their symptomatic evolution.

Furthermore, patients with BD were more likely to have an active professional/training activity at baseline and were less likely to have attempted suicide before entering the programme and to have a history of migration in adversity than patients with SAD or MDP. As expected, they displayed lower levels of negative symptoms, both at 2 months and after 36 months. Finally, they were more likely to achieve full symptomatic recovery and to have a positive perception of their environment than MDP and SAD patients after 36 months. The reason for the better outcome we observed in BD patients is probably multi factorial, our observation that they were less likely than the two other groups to have been exposed to migration in adversity might play a role in this regard. Indeed, migration in adversity may increase the risk of exposure to traumatic events and was previously reported to be associated with an increased risk of relapse, as well as with poorer symptomatic remission in first-episode psychosis (Golay et al., 2019a). As previously suggested (Alameda et al., 2015; Golay et al., 2019a), psychological intervention targeting past traumatic events should therefore be intensified to improve symptomatic recovery, especially for patients who experienced migration in adversity.

Patients with MDP had a lower socio economic status, were less likely to have a family history of psychiatric disorder, to live independently and to display full insight at baseline. They also displayed

higher scores on the general scale of the PANSS at 36 months, mainly due to depressive symptoms being present at the end of the treatment phase. However, our study revealed a strong clinical resemblance between MDP and SAD, especially regarding their clinical baseline presentation, the course of symptoms and outcomes. While various authors have focused on a continuum between BD and schizophrenia, including an intermediate position for SAD, they often do not include MDP in such a dimensional concept (Craddock et al., 2009; Ivleva et al., 2010; Keshavan et al., 2011). In line with Keshavan et al. (2011), and based on our results, we consider indeed this as an argument to include MDP within the large concept of the psychosis spectrum.

In sum, our study shows that there is a reasonable homogeneity within the affective psychosis group as it is defined usually in the literature. Combined with our previous observation that affective and non-affective psychoses differed significantly (Ramain et al., 2021), they bring support to the relevance of this dichotomy as a practical way to group patients in order to develop guidelines that are not limited to discrete diagnoses. The issue regarding SAD remains to be clarified as it may come out as an intermediate group; however, reducing the complexity of diagnosis may contribute to promote the development of early intervention strategies that are still largely lacking for affective forms of psychoses (Chia et al., 2019; Conus and McGorry, 2002). This more simple grouping may be a complement to a completely dimensional approach where treatment would be constructed on the presence of each distinct psychopathological domain (manic, depressive, positive, negative, cognitive symptoms…), which may be justified but also has its limitations (Potuzak et al., 2012).

Our results must be interpreted with caution due to some limitations. First, the sample size is moderate, limiting the power to distinguish between groups. However, this was one motivation to use a Bayesian model comparison approach that partly circumvent the Type I and Type II error trade-off. On a more epistemological level, the Bayesian framework also allowed us to directly quantify support for the null hypothesis, which is not possible in the classical frequentist framework. However, the Bayesian approach was not directly applicable for the MMRM longitudinal modelling. Secondly, we did not compare patients on the basis of symptomatic baseline presentation; patients often being referred to our

programme after a few days and up to 3 weeks of treatment, a reliable and scale based assessment of baseline symptoms was not available. We therefore preferred to define short term (after 2 months) and 3 years symptom outcome as our focus, which is often the determinant aspect for treatment adaptation.

Conclusion

Our study revealed similar clinical features between schizoaffective disorder, major depressive disorder with psychotic features and bipolar disorder. The concept of affective psychoses may therefore be relevant for clinical purposes in order to develop treatment guidelines considering both mood and psychotic dimensions, and psychosocial intervention targeting functional adjustment. We also found some diagnosis differences that may justify some degree of treatment adaptation. In spite of this, it seems justified to conduct studies designed to explore the impact of interventions specifically developed for affective psychoses as a group in the early phase of these disorders.

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Declaration of interest

Declarations of interest: none.

References

The World Health Organization Quality of Life assessment (WHOQOL): position paper from the World Health Organization, 1995. Social science & medicine (1982) 41(10), 1403-1409.

Alameda, L., Ferrari, C., Baumann, P., Gholam-Rezaee, M., Do, K., Conus, P., 2015. Childhood sexual and physical abuse: age at exposure modulates impact on functional outcome in early psychosis patients. Psychological medicine 45(13), 2727.

Alameda, L., Golay, P., Baumann, P.S., Ferrari, C., Do, K.Q., Conus, P., 2016. Age at the time of exposure to trauma modulates the psychopathological profile in patients with early psychosis. J Clin Psychiatry 77(5), e612-618.

American Psychiatric Association, 1994. Diagnostic and statistical manual of mental disorders (DSM). Washington, DC: American psychiatric association. 143–147.

American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders - 5 (DSM-5). American Psychiatric Association 70.

Baumann, P.S., Crespi, S., Marion-Veyron, R., Solida, A., Thonney, J., Favrod, J., Bonsack, C., Do, K.Q., Conus, P., 2013. Treatment and early intervention in psychosis program (TIPP-Lausanne): Implementation of an early intervention programme for psychosis in Switzerland. Early intervention in psychiatry 7(3), 322-328.

Cannon-Spoor, H.E., Potkin, S.G., Wyatt, R.J., 1982. Measurement of premorbid adjustment in chronic schizophrenia. Schizophr Bull 8.

Chandola, T., Jenkinson, C., 2000. The new UK national statistics socio-economic classification (NS-SEC); investigating social class differences in self-reported health status. Journal of Public Health 22(2), 182-190.

Chia, M.F., Cotton, S., Filia, K., Phelan, M., Conus, P., Jauhar, S., Marwaha, S., McGorry, P.D., Davey, C., Berk, M., Ratheesh, A., 2019. Early intervention for bipolar disorder - Do current treatment guidelines provide recommendations for the early stages of the disorder? Journal of affective disorders 257, 669-677.

Conus, P., Abdel-Baki, A., Harrigan, S., Lambert, M., McGorry, P.D., Berk, M., 2010. Pre-morbid and outcome correlates of first episode mania with psychosis: is a distinction between schizoaffective and bipolar I disorder valid in the early phase of psychotic disorders? Journal of affective disorders 126(1-2), 88-95.

Conus, P., Bonsack, C., 2004. [Early intervention for the initial phase of psychotic disorders in Lausanne: what problems and what solutions?]. Revue medicale de la Suisse romande 124(4), 221-224.

Conus, P., Cotton, S., Abdel-Baki, A., Lambert, M., Berk, M., McGorry, P.D., 2006. Symptomatic and functional outcome 12 months after a first episode of psychotic mania: barriers to recovery in a catchment area sample. Bipolar disorders 8(3), 221-231.

Conus, P., McGorry, P.D., 2002. First-episode mania: a neglected priority for early intervention. The Australian and New Zealand journal of psychiatry 36(2), 158-172.

Craddock, N., O'Donovan, M.C., Owen, M.J., 2009. Psychosis genetics: modeling the relationship between schizophrenia, bipolar disorder, and mixed (or "schizoaffective") psychoses. Schizophrenia bulletin 35(3), 482-490.

Dilling, H., Dittmann, V., 1990. [Psychiatric diagnosis following the 10th revision of the International Classification of Diseases (ICD-10)]. Der Nervenarzt 61(5), 259-270.

Golay, P., Baumann, P.S., Jaton, L., Restellini, R., Solida, A., Mebdouhi, N., Conus, P., 2019a. Migration in patients with early psychosis: A 3-year prospective follow-up study. Psychiatry research 275, 108-114.

Golay, P., Laloyaux, J., Moga, M., Della Libera, C., Larøi, F., Bonsack, C., 2020. Psychometric investigation of the French version of the Aberrant Salience Inventory (ASI): differentiating patients with psychosis, patients with other psychiatric diagnoses and non-clinical participants. Annals of General Psychiatry 19(1), 1-10.

Golay, P., Morandi, S., Silva, B., Devas, C., Bonsack, C., 2019b. Feeling coerced during psychiatric hospitalization: Impact of perceived status of admission and perceived usefulness of hospitalization. International Journal of Law and Psychiatry 67, 101512.

Husted, J.A., Beiser, M., Iacono, W.G., 1995. Negative symptoms in the course of first-episode affective psychosis. Psychiatry research 56(2), 145-154.

Ivleva, E.I., Morris, D.W., Moates, A.F., Suppes, T., Thaker, G.K., Tamminga, C.A., 2010. Genetics and intermediate phenotypes of the schizophrenia--bipolar disorder boundary. Neuroscience and biobehavioral reviews 34(6), 897-921.

Jauhar, S., Ratheesh, A., Davey, C., Yatham, L.N., McGorry, P.D., McGuire, P., Berk, M., Young, A.H., 2019. The case for improved care and provision of treatment for people with first-episode mania. Lancet Psychiatry 6(10), 869-876.

Jeffreys, H., 1961. Theory of Probability (3rd edition). Clarendon, Oxford.

Kass, R.E., Raftery, A.E., 1995. Bayes factors. Journal of the american statistical association 90(430), 773-795.

Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 13.

Keshavan, M.S., Morris, D.W., Sweeney, J.A., Pearlson, G., Thaker, G., Seidman, L.J., Eack, S.M., Tamminga, C., 2011. A dimensional approach to the psychosis spectrum between bipolar disorder and schizophrenia: the Schizo-Bipolar Scale. Schizophrenia research 133(1-3), 250-254.

Kraepelin, E., 1992. Die Erscheinungsformen des Irreseins:(The manifestations of insanity).

Lambert, M., Conus, P., Lambert, T., McGorry, P.D., 2003. Pharmacotherapy of first-episode psychosis. Expert opinion on pharmacotherapy 4(5), 717-750.

MacBeth, A., Gumley, A., 2008. Premorbid adjustment, symptom development and quality of life in first episode psychosis: a systematic review and critical reappraisal. Acta Psychiatr Scand 117(2), 85-99.

Malhi, G.S., Green, M., Fagiolini, A., Peselow, E.D., Kumari, V., 2008. Schizoaffective disorder: diagnostic issues and future recommendations. Bipolar disorders 10(1 Pt 2), 215-230.

Montgomery, S.A., Asberg, M., 1979. A new depression scale designed to be sensitive to change. The British journal of psychiatry : the journal of mental science 134, 382-389.

Noël, Y., 2013. AtelieR: A GTK GUI for teaching basic concepts in statistical inference, and doing elementary bayesian tests. R package version 0.24.

Noël, Y., 2015. Psychologie statistique avec R. EDP sciences.

Noël, Y., 2018. R2STATS Group models. http://yvonnick.noel.free.fr/r2statsweb/bayes.html. (Accessed 18.08.2021 2021).

Potuzak, M., Ravichandran, C., Lewandowski, K.E., Ongür, D., Cohen, B.M., 2012. Categorical vs dimensional classifications of psychotic disorders. Compr Psychiatry 53(8), 1118-1129.

Ramain, J., Conus, P., Golay, P., 2021. Exploring the clinical relevance of a dichotomy between affective and non-affective psychosis: Results from a first-episode psychosis cohort study. Early Intervention in Psychiatry.

Rothschild, A.J., 2013. Challenges in the treatment of major depressive disorder with psychotic features. Schizophrenia bulletin 39(4), 787-796.

Schatzberg, A.F., 2003. New approaches to managing psychotic depression. The Journal of clinical psychiatry 64 Suppl 1, 19-23.

Schöttle, D., Schimmelmann, B.G., Conus, P., Cotton, S.M., Michel, C., McGorry, P.D., Karow, A., Naber, D., Lambert, M., 2012. Differentiating schizoaffective and bipolar I disorder in first-episode psychotic mania. Schizophr Res 140(1-3), 31-36.

Schwarz, G., 1978. Estimating the dimension of a model. The annals of statistics 6(2), 461-464.

Tohen, M., Hennen, J., Zarate, C.M., Jr., Baldessarini, R.J., Strakowski, S.M., Stoll, A.L., Faedda, G.L., Suppes, T., Gebre-Medhin, P., Cohen, B.M., 2000. Two-year syndromal and functional recovery in 219 cases of first-episode major affective disorder with psychotic features. The American journal of psychiatry 157(2), 220-228.

Wagenmakers, E.J., Wetzels, R., Borsboom, D., Van Der Maas, H.L., 2011. Why psychologists must change the way they analyze their data: the case of psi: comment on Bem (2011). Journal of Personality and Social Psychology 100(3).

Young, R.C., Biggs, J.T., Ziegler, V.E., Meyer, D.A., 1978. A rating scale for mania: reliability, validity and sensitivity. The British journal of psychiatry : the journal of mental science 133, 429-435.

Yung, A.R., Yuen, H.P., McGorry, P.D., Phillips, L.J., Kelly, D., Dell'Olio, M., Francey, S.M., Cosgrave, E.M., Killackey, E., Stanford, C., Godfrey, K., Buckby, J., 2005. Mapping the onset of psychosis: the Comprehensive Assessment of At-Risk Mental States. The Australian and New Zealand journal of psychiatry 39(11-12), 964-971.

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ORIGINAL ARTICLE

WILEY

Subtyping based on premorbid profile: A strategy to personalize treatment in first-episode affective psychosis

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Abstract

Aim: Premorbid history may have a major influence on the way patients cope with the onset of psychosis. This issue has been widely studied in the context of early intervention in schizophrenia but considerably less is known regarding affective psychosis. Our first goal was to investigate if subgroups could be identified among affective psychosis patients based on premorbid factors. Our second goal was to compare these subtypes according to the evolution of mood symptoms and outcomes at the end of the program.

Methods: We conducted a 3-year prospective study on a sample of 74 adults aged 18–35 with a first episode of affective psychosis. Latent class analysis (LCA) was used to reveal distinct exploratory subgroups within affective psychosis patients.

Results: Three distinct subgroups could be distinguished. One with later onset of psychosis mainly including women with more severe depressive symptoms in the first 6 months contrasting with two other subgroups with more severe manic symptoms all along the follow-up and earlier onset of psychosis, with or without many serious antecedents. The subgroup with many serious antecedents was more likely to require several hospitalizations, less likely to achieve recovery, especially regarding professional integration and return to premorbid general functioning.

Conclusions: This study provides further evidence of poor functional recovery in the early phase of affective psychosis and shows that premorbid characteristics allow the identification of subgroups with distinct outcome which may require specification of treatment.

KEYWORDS
affective, early intervention, first episode, premorbid, psychosis

1 | INTRODUCTION

Psychotic disorders are often classified in clinical settings as affective or nonaffective depending on clinical symptoms in the first episode (Torrent et al., 2018). Affective psychoses are characterized by the presence of psychotic features as well as depressive or manic episodes (Strakowski et al., 1998). These mood features impair functioning and complicate pathway to recovery (Paykel, 2008; Strakowski et al., 1998). While early nonaffective psychoses have received extensive attention, less is known about affective psychoses although they represent an important proportion of psychotic disorders (Conus et al., 2014; Salvadore et al., 2008).

Premorbid factors in early psychosis patients could account for differences between patients with different diagnosis, which hence may be composed of subjects with similar clinical presentation related however to distinct illness processes. Indeed, some sociodemographic characteristics, such as gender (Bardenstein & McGlashan, 1990; Conus et al., 2007), marital status (Benabarre et al., 2001; Conus et al., 2007), socioeconomic status (SES; Byrne et al., 2004; Eid et al., 2013) and education level (MacCabe et al., 2010), seem to differ

across diagnostic categories within psychotic disorders, and they correlate with differences regarding illness evolution and treatment response. In addition, and besides increasing the risk of psychosis (O'Donoghue et al., 2015), premorbid socioeconomic and clinical conditions of individuals are correlated to outcome and risk of chronicity (van Os et al., 1995). Finally, past personal or familial psychiatric history, exposure to traumatic events, suicide attempts, history of substance abuse (Conus et al., 2007) and migration (Zolkowska et al., 2001) are correlated to outcome. Studying premorbid factors in the initial course of psychotic disorders is therefore an opportunity to better understand how they are linked to clinical presentation and to provide clues for adjusting treatment.

This may be true for affective psychoses more specifically. Indeed, environment and life events impact mood stability in bipolar disorder (Aldinger & Schulze, 2017), suggesting that premorbid conditions may play a major role in the clinical course of affective psychoses. While sociodemographic and clinical distinctions have been made between diagnostic categories of psychoses, it remains unclear how premorbid factors could differentially affect the course of early affective psychoses. Treatment response may also be affected by sociodemographic factors, a higher SES in bipolar disorder being for example associated with better lithium response (Eid et al., 2013). Furthermore, affective psychoses have been associated with a shorter duration of untreated psychosis (DUP), an older age at onset (Benabarre et al., 2001; Conus et al., 2007; Large et al., 2008) and a better social adjustment at adolescence (Cannon et al., 1997) than nonaffective psychoses, which may influence evolution. Since premorbid factors play a role in mood evolution and treatment response in the early phase of affective psychosis, identifying subgroups of patients with different premorbid profiles may guide treatment choice.

The aims of this study are therefore (1) to identify subgroups of patients within affective-psychoses based on premorbid factors and (2) to compare their mood symptomatology and outcomes over a 3-year follow-up.

2 | METHODS

2.1 | Sample and procedure

Treatment and Early Intervention in Psychosis Program (TIPP) is a specialized early psychosis program implemented in Lausanne (Switzerland) since 2004 at the Department of Psychiatry, CHUV (Baumann et al., 2013; Conus & Bonsack, 2004). Patients entering the program are aged between 18 and 35, reside in the catchment area of Lausanne and have crossed the psychosis threshold according to the 'Psychosis threshold' subscale of the Comprehensive Assessment of At Risk Mental States scale (CAARMS; Yung et al., 2005). Patients who have more than 6 months of previous antipsychotic medication, an intoxication or an organic brain disease-induced psychosis or an intelligence quotient lower than 70 are addressed to other programs. In this program, a psychiatrist and a case manager are assigned to each patient. In a bio-psycho-social perspective, the treatment includes psychotherapy, psycho-education, family support, cognitive assessment and remediation, social support, assistance in finding employment, psychological interventions for cannabis use and pharmacological treatment. In line with international guidelines, atypical antipsychotics are first-line pharmacological treatment with a prospective monitoring of any side-effects (Baumann et al., 2013). Case managers, who have up to one hundred instances of contact with patients during the program, complete a questionnaire specially designed for the TIPP. Detailed information about demographic characteristics, past medical history, exposure to life events, symptoms and functioning are collected for each patient. A psychologist and case managers carry out follow-up assessments at 2, 6, 12, 18, 24, 30 and 36 months, exploring various aspects of treatment and comorbidities (e.g., level of insight, treatment adherence, presence or absence of forensic history and substance use, intermittent exposure to trauma, suicide attempts and forensic events), evolution of psychopathology and functional level. Every patient's file is revised by a psychologist at 18 and 36 months to collect data on hospital stays from discharge files.

This study was approved by the Human Research Ethics Committee of the Canton Vaud (protocol #2020-00272). The data generated by the follow-up of all patients were used in the study if they provided consent. Of the first 386 patients enrolled in the program, all agreed for their clinical data to be used for research.

2.2 | Diagnostic assessment

Diagnosis results from an expert consensus discussed at 18 and 36 months, based on the DSM-IV criteria using the information from medical reports from treating psychiatrists, as well as from the TIPP-assigned psychiatrist and case manager. In this study, we used the latest consensus diagnostic available. We included bipolar disorder, major depression with psychotic features and schizoaffective disorder in affective psychoses.

2.3 | Premorbid factors

Case managers collected premorbid information at entry. DUP was defined as the time between onset of psychosis defined by CAARMS and admission to TIPP. SES was subdivided into low, intermediate and high (Chandola & Jenkinson, 2000). Migration in adversity was defined as migration in adverse contexts (e.g., seeking protection for political reasons, threat of death, exposure to war or extreme poverty). Mapping of past psychiatric and substance abuse diagnoses was based on DSM-IV criteria (American Psychiatric Association, 1994) and past suicide attempts on the 10th revision of the International Classification of Diseases (ICD-10; Dilling & Dittmann, 1990). Early adolescent functional level was evaluated with the Premorbid Adjustment Scale (PAS; Cannon-Spoor et al., 1982) using the early adolescence subscore (MacBeth & Gumley, 2008). Past history of trauma

was rated by case managers (Alameda et al., 2015; Alameda et al., 2016). Patients were considered to have a history of trauma if they had experienced at least one sexual or physical abuse prior the onset of psychosis.

2.4 | Symptomatology and functioning at baseline

Manic and depressive symptoms were respectively measured with the Young Mania Rating Scale (YMRS; Young et al., 1978) and the Montgomery–Asberg Depression Rating Scale (MADRS; Montgomery & Asberg, 1979). As data were not available at baseline, we used the 2-month follow-up measures. We assessed general symptomatology with the Clinical Global Impression (CGI; Guy, 1976). The social and occupational level was assessed with the Social and Occupational Functioning Assessment Scale (SOFAS; American Psychiatric Association, 1994). We used the Global Assessment of Functioning (GAF; American Psychiatric Association, 1994) to measure functioning regarding the impact of symptomatology.

2.5 | Level of depressive and manic symptoms

Depressive and manic symptoms were assessed at 2, 6, 12, 18, 24, 30, 36 months of follow-up. We measured the severity of depressive symptoms with the MADRS, and manic symptoms with the YMRS.

2.6 | Outcomes at discharge

We classified hospital stays in three categories (none, unique, multiple) to compare the proportion of patients requiring none, one or several hospital stays. We assessed psychotic symptoms with the Positive and Negative Psychotic Syndrome Scale (PANSS; Kay et al., 1987). Symptomatic recovery was defined following Andreasen's criteria (score ≤ 3) on eight items of the PANSS (delusion, unusual thought content, hallucinatory behaviour, conceptual disorganization, mannerisms, blunted affect, social withdrawal, lack of spontaneity; Andreasen et al., 2005). Functional recovery was defined as a PAS score equal or lower to the premorbid rating on four of the five PAS general scale's items (Strakowski et al., 1998). Independent living recovery (head of household/living alone, with partner, or with peers/living with family with minimal supervision) was measured with the Modified Vocational Status Index (MVSI) and working recovery (paid or unpaid full- or part-time employment/being an active student in school or university/head of household with employed partner [homemaker]/full- or part-time volunteer) with the Modified Location Code Index Independent living (MLCI; Tohen et al., 2000). Quality of life at discharge was assessed with the World Health Organization Quality of Life assessment scale (The World Health Organization Quality of Life (WHOQOL) assessment, 1995), a 26-item self-rated scale measuring satisfaction with life and self-esteem based on 5-point Likert scales ranging from 1 (*low satisfaction*) to 5 (*high satisfaction*). The case manager assessed insight (*absence* = 0, *partial* = 1, *full* = 2). Insight recovery was defined as getting full insight at discharge, that is, awareness of illness and necessity of treatment. We also included continuous outcome measures to consider change regarding depressive and manic symptoms, general symptomatology and functioning, respectively, measured with the MADRS, the YMRS, the CGI and the SOFAS/GAF. We considered the difference between the baseline and the 36-month follow-up measures, except for the MADRS and YMRS for which the first measure was available at 2 months.

2.7 | Statistical analysis

We used LCA to identify subgroups based on premorbid factors. To determine the number of latent classes, we used the Bayesian information criterion (BIC) coefficient, the Lo–Mendell–Rubin and the bootstrapped likelihood ratio tests. We used Pearson's chi-square tests to test the repartition of diagnostic categories between classes. We used mixed-effects models repeated measures analysis of variance (MMRM) to analyse differences between subgroups over time on mood symptoms. In these models, the 'within-group' factor was time and the 'between-groups' factor was subgroups. We selected the optimal within subject covariance matrix in each MMRM based on the Akaike information criterion (AIC) coefficient. We conducted one-way analysis of variance (ANOVA) to compare subgroups regarding symptomatology and functioning at baseline. Outcome differences were assessed using logistic regression for categorical variables and one-way ANOVA or linear regression for continuous variables. We performed nonparametric Kruskal–Wallis tests to compare the number of hospital stays. We applied Bonferroni correction for post hoc analyses. The analysis was performed with IBM SPSS statistics 25 and Mplus Version 7.4.

3 | RESULTS

3.1 | Patient sample

Our final sample consisted of 74 patients (mean age = 25.16, 50.0% males) meeting diagnostic criteria for affective psychosis (24 with bipolar disorder, 17 with major depression with psychotic features, 33 with schizoaffective disorder).

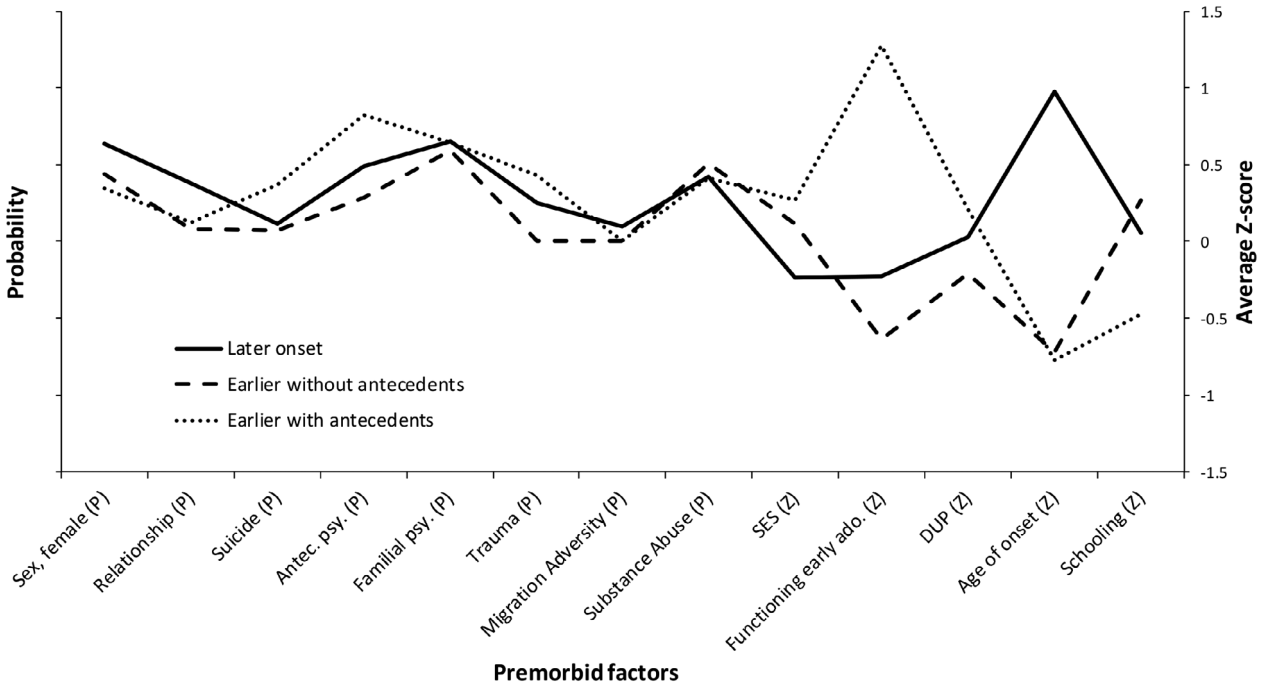
3.2 | Subgroups based on premorbid profile within affective psychosis

Models including 1–5 class were estimated (Table 1). Estimation was problematic (model under-identification) for models with more than three classes. The Lo–Mendell–Rubin test and the BIC pointed towards a one-class model while the parametric bootstrapped likelihood ratio test, which is considered the most adequate test (Nylund et al., 2008), suggested the three-class solution. Because of its

TABLE 1 Characteristics of the 1–5 latent class analysis solutions

Number of classes	Size of each class	BIC	Entropy	Model comparison *n* vs. *n* − 1 classes	
				Lo–Mendel–Rubin LRT *p*-value	Bootstrapped LRT *p*-value
1	74	1687.436			
2	15 (20.3%) 59 (79.7%)	1710.234	.799	.464	<.001
3	17 (23.0%) 25 (33.8%) 32 (43.2%)	1730.372	.838	.646	<.001
4	3 (4.1%) 19 (25.7%) 20 (27.0%) 32 (43.2%)	1759.956	.888	.282	.07
5	10 (13.5%) 12 (16.2%) 15 (20.3%) 16 (21.6%) 21 (28.4%)	1791.312	.991	.668	.10

Abbreviations: BIC, Bayesian information criterion; LRT, likelihood ratio test.



Note. P=Probability (dichotomous variable), Z=Average Z-score (continuous variable), Antec. psy. = personal psychiatric antecedents, Familial psy. = Familial psychiatric antecedents, SES = Socioeconomic status, DUP= Duration of Untreated Illness, Functioning early ado. = Functional adjustment in early adolescence.

FIGURE 1 Subgroups in affective psychosis according to premorbid factors

theoretical interpretability, we selected this three-class model to identify subgroups within affective psychosis (Figure 1).

It is important to note that the distribution of bipolar disorder, major depression with psychotic features and schizoaffective disorder was similar across subgroups ($\chi^2(4) = 2.852$, $p = .595$). The first group included 32 people with later onset psychosis. This subgroup consisted mostly of women characterized by low SES, a good level of education and past relationships, and they were more likely to have a history of migration in adversity. In the two other subgroups, patients had earlier onset of psychosis. One of these two subgroups consisted of 17 people who cumulated many serious premorbid antecedents (suicide attempt, psychiatric antecedents, trauma, low premorbid adjustment at adolescence, low education level); the other one was composed of 25 people with few premorbid antecedents. There was

TABLE 2 Sociodemographic and premorbid characteristics of subgroups within affective psychosis

	Total (*N* = 74)	Later onset (*N* = 32)	Earlier onset without antecedents (*N* = 25)	Earlier onset with antecedents (*N* = 17)
Gender, male % (*N*)	50.0 (37)	37.5 (12)	56.0 (14)	64.7 (11)
Age in year, *M* (*SD*)	25.16 (4.932)	29.94 (2.564)	21.56 (2.959)	21.47 (2.183)
Diagnosis, % (*N*)				
Schizoaffective disorder	44.6 (33)	43.8 (14)	48.0 (12)	41.2 (7)
Major depression with psychotic features	17.6 (3)	31.3 (10)	16.0 (4)	17.6 (3)
Bipolar disorder	41.2 (7)	25.0 (8)	36.0 (9)	41.2 (7)
Education in year, *M* (*SD*)	10.48 (2.566)	10.44 (2.636)	11.33 (2.436)	9.15 (2.193)
Age of onset, *M* (*SD*)	24.19 (5.090)	29.19 (2.546)	20.52 (2.535)	20.18 (2.811)
Duration of untreated psychosis (days), Mdn (IQR)	50.00 (181.50)	59.50 (129.00)	19.00 (60.00)	190.00 (377.50)
Socioeconomical level, % (*N*)				
Low	37.8 (28)	25.0 (8)	20.0 (5)	11.8 (2)
Intermediate	41.9 (31)	53.1 (17)	36.0 (9)	29.4 (5)
High	20.3 (15)	21.9 (7)	44.0 (11)	58.8 (10)
Marital status, % (*N*)				
Single	78.1 (57)	62.5 (20)	91.7 (22)	88.2 (15)
Married	12.3 (9)	21.9 (7)	4.2 (1)	5.9 (1)
Divorced	6.8 (5)	15.6 (5)	.0 (0)	.0 (0)
Cohabitation	2.7 (2)	.0 (0)	4.2 (1)	5.9 (1)
Early adolescence adjustment, *M* (*SD*)	.30 (.183)	.26 (.114)	.20 (.114)	.56 (.140)
Past suicide attempt, % (*N*)	16.4 (12)	12.5 (4)	8.0 (2)	37.5 (6)
History of trauma,[a] % (*N*)	26.8 (19)	35.5 (11)	.0 (0)	47.1 (8)
Migration in adversity, % (*N*)	37.8 (28)	50.0 (16)	16.0 (4)	29.4 (5)
Psychiatric history, % (*N*)	50.7 (37)	50.0 (16)	29.2 (7)	82.4 (14)
Familial psychiatric history, % (*N*)	62.9 (44)	64.3 (18)	60.0 (15)	64.7 (11)
Lifetime substance abuse (DSM), % (*N*)	44.6 (33)	40.6 (13)	52.0 (13)	21.2 (7)

[a]Physical or sexual abuse.

no difference across subgroups regarding prevalence of familial psychiatric history and history of premorbid substance abuse.

Sociodemographic and premorbid characteristics of subgroups are described in Table 2.

3.3 | Symptomatology and functioning at baseline

We found no difference between subgroups regarding symptomatology and functioning at baseline (Table 3).

3.4 | Evolution of depressive and manic symptoms over the program

Depressive symptoms were higher in the subgroup with later onset than in the subgroup with earlier onset and few antecedents during the first 6 months (Figure 2(a); mean difference at 6 months = 12.127, df = 138.405, p = .003, 95%IC [4.227, 20.027]). The subgroup with later onset had significantly less manic symptoms over the 36 months period than the subgroup with earlier onset and few antecedents (Figure 2(b); mean difference = −1.903, df = 61.343, p = .044, 95%IC [−3.756, −.049]), as well as than the subgroup with earlier onset and many serious antecedents (Figure 2(b); mean difference = −2.170, df = 53.000, p = .024, 95%IC [−4.041, −.300]).

3.5 | Outcomes at discharge

Results of the outcomes at discharge (Table 4) revealed that subgroups with earlier onset and few antecedents had significantly better general functional recovery (p = .038) and work-related recovery (p = .030) than the subgroup with earlier onset and many serious antecedents. Subgroups differed regarding quality of physical health (F (2, 20) = 3.992, p = .35). The subgroup earlier onset without antecedents (M = 30.33, SD = 2.94) had a significantly better physical health (mean difference = 6.167, p = .040) than the subgroup with later onset (M = 24.17, SD = 4.86). No differences were found between subgroups regarding quality of psychological aspects, environment and relationships at discharge. Analyses regarding hospitalization revealed a significant difference between subgroups regarding the number of

TABLE 3 Analysis of variance (ANOVA) between subgroups of symptomatic and functioning profiles at baseline

	Mean (*SD*)	Sum of square	df	Mean square	*F*	*p*-value
MADRS[a]		290.761	2	145.381	1.128	.339
Later onset	21.27 (13.33)					
Earlier onset without antecedents	14.17 (9.47)					
Earlier onset with antecedents	17.14 (10.93)					
YMRS[a]		49.811	2	24.905	.846	.440
Later onset	4.45 (5.03)					
Earlier onset without antecedents	6.50 (5.54)					
Earlier onset with antecedents	7.71 (5.85)					
CGI		8.371	2.61	4.185	1.565	.217
Later onset	4.48 (1.78)					
Earlier onset without antecedents	4.68 (1.64)					
Earlier onset with antecedents	5.40 (1.30)					
SOFAS		847.571	2.66	423.785	1.534	.223
Later onset	42.14 (16.56)					
Earlier onset without antecedents	45.83 (13.71)					
Earlier onset with antecedents	36.44 (20.38)					
GAF		870.043	2.64	435.022	1.330	.272
Later onset	41.36 (17.50)					
Earlier onset without antecedents	45.83 (15.83)					
Earlier onset with antecedents	36.25 (21.84)					

[a]Data for the YMRS and the MADRS were only available at 2 months.
Abbreviations: CGI, Clinical Global Impression; df, degrees of freedom; GAF, Global Assessment of Functioning; MADRS, Montgomery–Asberg Depression Rating Scale; SOFAS, Social and Occupational Functioning Assessment Scale; YMRS, Young Mania Rating Scale.

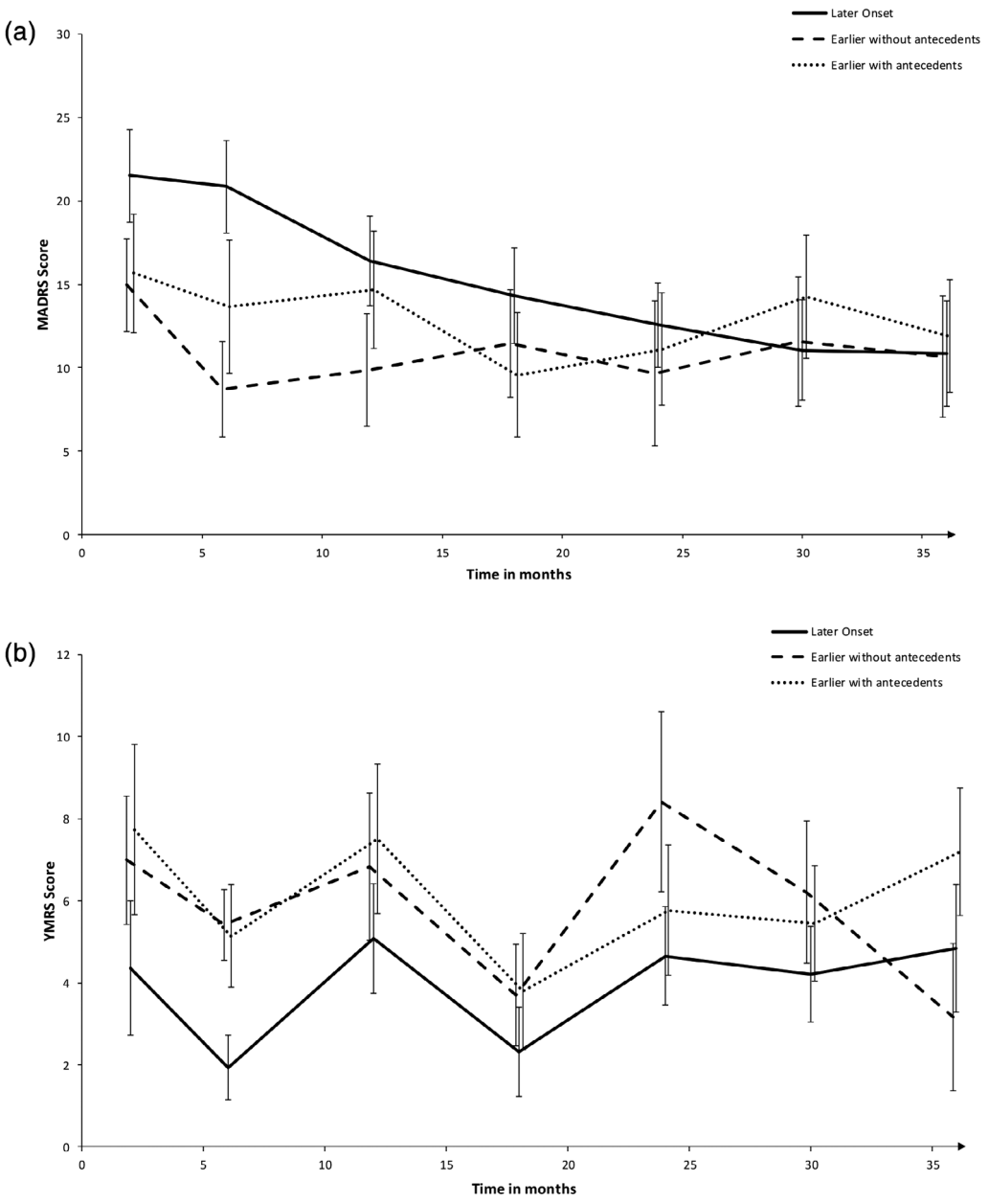
hospitalizations along the program (H(2) = 9.091, p = .011). The subgroup earlier onset with antecedents had more multiple hospitalizations (75%) compared to the subgroup earlier onset without antecedents. We did not find any difference regarding symptomatic or functional changes assessed with the 3-year difference scores.

4 | DISCUSSION

The purpose of this study was to identify potential subgroups within affective psychosis based on premorbid characteristics, and if these subgroups would have distinct outcomes. Our results showed that over and above diagnostic categories, the analysis of premorbid profile allows the detection of subgroups of patients with different course of mood symptoms and distinct functional outcome over the early phase of affective psychosis. If replicated, these results may pave the way to the specification of intervention based on characteristics that clinicians could identify in the very early phase of treatment.

The LCA we conducted on premorbid characteristics allowed the identification of three exploratory subgroups. The first one, composed of patients with a relatively late onset of psychosis, around age 30, included a majority of females who were married or in de-facto relationship and had a good educational level. They however had a low SES and the majority reported previous exposure to adverse events such as migration in adversity. The second group was composed of patients with onset of psychosis around age 20, who had hardly any exposure to adverse events and no past-history of psychiatric disorder. The third group was also composed of patients with an onset of psychosis around age 20, but who had low educational level, low premorbid adjustment, exposure to serious childhood trauma and psychiatric problems such as suicide attempts before onset of psychosis. Interestingly, these three subgroups displayed distinct patterns of symptomatic evolution and significant differences in functional outcome.

Regarding symptoms, while all three groups reached symptomatic remission at the end of the program, they differed regarding the pattern followed by mood symptoms over the 3-year follow-up. The subgroup with later onset displayed higher levels of depressive symptoms compared to the two other subgroups, mainly within the first 6 months. These symptoms should be considered when designing the treatment since previous research has shown that their presence, especially in patients previously exposed to trauma, mediates poorer functional outcome (Alameda et al., 2017). The rapid decrease of depressive symptoms in this subgroup, including a majority of females, suggests a good resilience capacity. This is in line with previous research showing a tendency of women to express more depressive symptoms (Bardenstein &



Note. The error-bars indicate +/- one standard error.

FIGURE 2 Course of depressive (a) and manic (b) symptoms over the Treatment and Early Intervention in Psychosis Program (TIPP) according to the subgroups of affective psychosis defined with premorbid factors

McGlashan, 1990), but with good resilience capacity and ability to cope with stressful events (Ochoa et al., 2012). The two other subgroups displayed higher scores of manic symptoms than the subgroup with later onset overall but with substantial variability, it would therefore require further investigation to explore to which extent they need specific mood stabilizer treatment adaptation. In addition, the subgroup with earlier onset and many serious antecedents was more likely to undergo multiple hospitalizations. Clinicians should therefore identify them early in order to provide more intensive relapse prevention and probably more support.

The three subgroups differed significantly regarding functional outcome at discharge despite similar symptomatic outcome. Many studies have shown that in affective psychoses, while symptomatic outcome is favourable in the vast majority of patients, functional recovery remains challenging (Conus et al., 2006; Conus et al., 2010; Conus & McGorry, 2002). Our data suggest that subtyping premorbid profiles might allow the identification of a subgroup at high risk of poor functional outcome. Indeed, patients with early onset and many serious antecedents showed significantly more difficulty to recover premorbid functioning, and less than 10% of them had employment at discharge. This is in line with previous studies showing that premorbid history with comorbidities, poor adjustment and traumatic events are associated with poor functional outcome (Conus et al., 2007), an earlier age of onset and risk of chronicity

TABLE 4 Comparison of outcomes between subgroups at the end of the program

	% (*N*)	Odds ratio (OR)	95%CI of OR		*p*-value
			LCI	UCI	
Symptomatic recovery					
Earlier onset with antecedents	50.0 (5)	Ref cat.	–	–	
Later onset	44.4 (4)	.800	.131	4.874	.809
Earlier onset without antecedents	62.5 (5)	1.667	.251	11.071	.597
General functional recovery					
Earlier onset with antecedents	28.6 (4)	Ref cat.	–	–	
Later onset	57.7 (15)	3.409	.844	13.774	.085
Earlier onset without antecedents	66.7 (12)	5.000	1.096	22.820	.038*
Premorbid adjustment recovery					
Earlier onset with antecedents	66.7 (6)	Ref cat.	–	–	
Later onset	33.3 (6)	.250	.046	1.365	.109
Earlier onset without antecedents	69.2 (9)	1.125	.183	6.935	.899
Working recovery					
Earlier onset with antecedents	7.1 (1)	Ref cat.	–	–	
Later onset	24.0 (6)	4.105	.441	38.234	.215
Earlier onset without antecedents	47.4 (9)	11.700	1.265	108.200	.030*
Independent living recovery					
Earlier onset with antecedents	64.3 (9)	Ref cat.	–	–	
Later onset	84.0 (21)	2.917	.632	13.459	.170
Earlier onset without antecedents	68.4 (13)	1.204	.280	5.182	.803
Insight recovery					
Earlier onset with antecedents	69.2 (9)	Ref cat.	–	–	
Later onset	76.0 (19)	1.407	.316	6.265	.654
Earlier onset without antecedents	66.7 (12)	.889	.192	4.114	.880
			95%CI of OR		
	M (*SD*)	*B*	LCI	UCI	*p*-value
ΔMADRS					
Earlier onset with antecedents	3.00 (2.828)	Ref cat.	–	–	
Later onset	−8.00 (20.347)	−11.000	−38.648	16.648	.378
Earlier onset without antecedents	−2.00 (2.944)	−5.000	−32.648	22.648	.682
ΔYMRS					
Earlier onset with antecedents	−5.00 (7.071)	Ref cat.	–	–	
Later onset	−1.50 (7.047)	3.500	−9.990	16.990	.559
Earlier onset without antecedents	−4.25 (5.909)	.750	−12.740	14.240	.899
ΔCGI					
Earlier onset with antecedents	−1.75 (.957)	Ref cat.	–	–	
Later onset	−.43 (2.070)	1.321	−.983	3.626	.237
Earlier onset without antecedents	−1.60 (1.517)	.150	−2.317	2.617	.897
ΔSOFAS					
Earlier onset with antecedents	24.85 (24.344)	Ref cat.	–	–	
Later onset	20.83 (12.984)	−4.020	−16.182	8.142	.510
Earlier onset without antecedents	21.50 (16.671)	−3.346	−16.104	9.411	.601
ΔGAF					
Earlier onset with antecedents	22.67 (28.308)	Ref cat.	–	–	
Later onset	21.52 (13.853)	−1.145	−14.895	12.605	.868
Earlier onset without antecedents	18.00 (17.773)	−4.667	−19.225	9.892	.522

Abbreviations: CGI, Clinical Global Impression; CI, confidence interval; LCI, lower confidence interval; UCI, upper confidence interval; GAF, Global Assessment of Functioning; MADRS, Montgomery–Asberg Depression Rating Scale; SOFAS, Social and Occupational Functioning Assessment Scale; YMRS, Young Mania Rating Scale.

*$p < .05$.

(Aldinger & Schulze, 2017; van Os et al., 1995). Future research should explore if the early implementation of strategies aiming at promoting functional recovery, like cognitive remediation, supported employment, would help these patients to improve their functional recovery. Despite displaying a better functional outcome, both other subgroups did not do well either. Indeed, only 56% of patients in the group with later onset returned to their premorbid functioning, and only 24% returned to work at discharge. This is in line with previous findings (Golay et al., 2017) showing that bringing patients back to work is challenging despite employment before psychosis onset, suggesting specific strategies are needed to protect competencies patients acquired before the disorder emerges.

Although this study provides useful insights for early intervention in affective psychoses, it has limitations. First, the TIPP program only includes patients aged between 18 and 35, excluding patients with very early and late onset of psychosis. Second, patients were including in affective psychoses according to their diagnosis over the entire treatment period. Diagnosis could sometimes change across follow-up making the use of these premorbid subtypes challenging in clinical settings. Fourth, our sample size was relatively limited. Different class structures may emerge with other larger or more heterogeneous samples. Selected premorbid variables were considered in the LCA based on previous literature; thus, different class structures may also emerge with the use of other data (e.g., neurocognition).

In conclusion, our data confirm that functional outcome is relatively poor in affective psychosis patients and suggest it is possible to identify subgroups with distinct outcome profiles among these patients. Considering the clinical relevance of this way of identifying subgroups of patients, it would be interesting to investigate premorbid subtyping in nonaffective psychosis in further study. More research is also required to see if specification of treatment according to these profiles could improve outcome.

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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REFERENCES

Alameda, L., Ferrari, C., Baumann, P. S., Gholam-Rezaee, M., Do, K. Q., & Conus, P. (2015). Childhood sexual and physical abuse: Age at exposure modulates impact on functional outcome in early psychosis patients. *Psychological Medicine*, *45*(13), 2727–2736. https://doi.org/10.1017/s0033291715000690

Alameda, L., Golay, P., Baumann, P. S., Ferrari, C., Do, K. Q., & Conus, P. (2016). Age at the time of exposure to trauma modulates the psychopathological profile in patients with early psychosis. *Journal of Clinical Psychiatry*, *77*(5), e612–e618. https://doi.org/10.4088/JCP.15m09947

Alameda, L., Golay, P., Baumann, P. S., Progin, P., Mebdouhi, N., Elowe, J., … Conus, P. (2017). Mild depressive symptoms mediate the impact of childhood trauma on long-term functional outcome in early psychosis patients. *Schizophrenia Bulletin*, *43*(5), 1027–1035. https://doi.org/10.1093/schbul/sbw163

Aldinger, F., & Schulze, T. G. (2017). Environmental factors, life events, and trauma in the course of bipolar disorder. *Psychiatry and Clinical Neurosciences*, *71*(1), 6–17. https://doi.org/10.1111/pcn.12433

American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders (DSM)* (pp. 143–147). Washington, DC: Author.

Andreasen, N. C., Carpenter, W. T., Jr., Kane, J. M., Lasser, R. A., Marder, S. R., & Weinberger, D. R. (2005). Remission in schizophrenia: Proposed criteria and rationale for consensus. *American Journal of Psychiatry*, *162*(3), 441–449. https://doi.org/10.1176/appi.ajp.162.3.441

Bardenstein, K. K., & McGlashan, T. H. (1990). Gender differences in affective, schizoaffective, and schizophrenic disorders: A review. *Schizophrenia Research*, *3*(3), 159–172. https://doi.org/10.1016/0920-9964(90)90034-5

Baumann, P. S., Crespi, S., Marion-Veyron, R., Solida, A., Thonney, J., Favrod, J., Bonsack, C., Do, K. Q., & Conus, P. (2013). Treatment and early intervention in psychosis program (TIPP-Lausanne): Implementation of an early intervention programme for psychosis in Switzerland. *Early Intervention in Psychiatry*, *7*(3), 322–328. https://doi.org/10.1111/eip.12037

Benabarre, A., Vieta, E., Colom, F., Martinez-Aran, A., Reinares, M., & Gasto, C. (2001). Bipolar disorder, schizoaffective disorder and schizophrenia: Epidemiologic, clinical and prognostic differences. *European Psychiatry*, *16*(3), 167–172.

Byrne, M., Agerbo, E., Eaton, W. W., & Mortensen, P. B. (2004). Parental socio-economic status and risk of first admission with schizophrenia—A Danish national register based study. *Social Psychiatry and Psychiatric Epidemiology*, *39*(2), 87–96. https://doi.org/10.1007/s00127-004-0715-y

Cannon, M., Jones, P., Gilvarry, C., Rifkin, L., McKenzie, K., Foerster, A., & Murray, R. M. (1997). Premorbid social functioning in schizophrenia and bipolar disorder: Similarities and differences. *American Journal of Psychiatry*, *154*(11), 1544–1550. https://doi.org/10.1176/ajp.154.11.1544

Cannon-Spoor, H. E., Potkin, S. G., & Wyatt, R. J. (1982). Measurement of premorbid adjustment in chronic schizophrenia. *Schizophrenia Bulletin*, *8*, 470–484. https://doi.org/10.1093/schbul/8.3.470

Chandola, T., & Jenkinson, C. (2000). The new UK national statistics socio-economic classification (NS-SEC); investigating social class differences in self-reported health status. *Journal of Public Health*, *22*(2), 182–190. https://doi.org/10.1093/pubmed/22.2.182

Conus, P., Abdel-Baki, A., Harrigan, S., Lambert, M., McGorry, P. D., & Berk, M. (2010). Pre-morbid and outcome correlates of first episode mania with psychosis: Is a distinction between schizoaffective and bipolar I disorder valid in the early phase of psychotic disorders? *Journal of Affective Disorders*, *126*(1–2), 88–95. https://doi.org/10.1016/j.jad.2010.04.001

Conus, P., & Bonsack, C. (2004). Early intervention for the initial phase of psychotic disorders in Lausanne: What problems and what solutions? *Revue Médicale de la Suisse Romande*, *124*(4), 221–224.

Conus, P., Cotton, S., Abdel-Baki, A., Lambert, M., Berk, M., & McGorry, P. D. (2006). Symptomatic and functional outcome

12 months after a first episode of psychotic mania: barriers to recovery in a catchment area sample. *Bipolar Disorders*, *8*(3), 221–231. https://doi.org/10.1111/j.1399-5618.2006.00315.x

Conus, P., Cotton, S., Schimmelmann, B. G., McGorry, P. D., & Lambert, M. (2007). The first-episode psychosis outcome study: Premorbid and baseline characteristics of an epidemiological cohort of 661 first-episode psychosis patients. *Early Intervention in Psychiatry*, *1*(2), 191–200. https://doi.org/10.1111/j.1751-7893.2007.00026.x

Conus, P., Macneil, C., & McGorry, P. D. (2014). Public health significance of bipolar disorder: Implications for early intervention and prevention. *Bipolar Disorders*, *16*(5), 548–556. https://doi.org/10.1111/bdi.12137

Conus, P., & McGorry, P. D. (2002). First-episode mania: A neglected priority for early intervention. *Australian and New Zealand Journal of Psychiatry*, *36*(2), 158–172. https://doi.org/10.1046/j.1440-1614.2002.00994.x

Dilling, H., & Dittmann, V. (1990). Psychiatric diagnosis following the 10th revision of the International Classification of Diseases (ICD-10). *Nervenarzt*, *61*(5), 259–270.

Eid, L., Heim, K., Doucette, S., McCloskey, S., Duffy, A., & Grof, P. (2013). Bipolar disorder and socioeconomic status: What is the nature of this relationship? *International Journal of Bipolar Disorders*, *1*, 9–9. https://doi.org/10.1186/2194-7511-1-9

Golay, P., Alameda, L., Mebdouhi, N., Baumann, P., Ferrari, C., Solida, A., Progin, P., Elowe, J., & Conus, P. (2017). Age at the time of onset of psychosis: A marker of specific needs rather than a determinant of outcome? *European Psychiatry*, *45*, 20–26. https://doi.org/10.1016/j.eurpsy.2017.06.002

Guy, W. (1976). *ECDEU assessment manual for psychopharmacology*. US Department of Health, Education, and Welfare, Public Health Service.

Kay, S. R., Fiszbein, A., & Opler, L. A. (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia Bulletin*, *13*, 261–276. https://doi.org/10.1093/schbul/13.2.261

Large, M., Nielssen, O., Slade, T., & Harris, A. (2008). Measurement and reporting of the duration of untreated psychosis. *Early Intervention in Psychiatry*, *2*(4), 201–211. https://doi.org/10.1111/j.1751-7893.2008.00080.x

MacBeth, A., & Gumley, A. (2008). Premorbid adjustment, symptom development and quality of life in first episode psychosis: a systematic review and critical reappraisal. *Acta Psychiatrica Scandinavica*, *117*(2), 85–99. https://doi.org/10.1111/j.1600-0447.2007.01134.x

MacCabe, J. H., Lambe, M. P., Cnattingius, S., Sham, P. C., David, A. S., Reichenberg, A., Murray, R. M., & Hultman, C. M. (2010). Excellent school performance at age 16 and risk of adult bipolar disorder: National cohort study. *British Journal of Psychiatry*, *196*(2), 109–115. https://doi.org/10.1192/bjp.bp.108.060368

Montgomery, S. A., & Asberg, M. (1979). A new depression scale designed to be sensitive to change. *British Journal of Psychiatry*, *134*, 382–389.

Nylund, K. L., Asparouhov, T., & Muthén, B. O. (2008). Deciding on the number of classes in latent class analysis and growth mixture modeling: A Monte Carlo simulation study. *Erratum: Structural Equation Modeling*, *15*(1), 182–182. https://doi.org/10.1080/10705510701793320

Ochoa, S., Usall, J., Cobo, J., Labad, X., & Kulkarni, J. (2012). Gender differences in schizophrenia and first-episode psychosis: A comprehensive literature review. *Schizophrenia Research and Treatment*, *2012*, 916198. https://doi.org/10.1155/2012/916198

O'Donoghue, B., Lyne, J., Madigan, K., Lane, A., Turner, N., O'Callaghan, E., & Clarke, M. (2015). Environmental factors and the age at onset in first episode psychosis. *Schizophrenia Research*, *168*(1–2), 106–112. https://doi.org/10.1016/j.schres.2015.07.004

Paykel, E. S. (2008). Partial remission, residual symptoms, and relapse in depression. *Dialogues in Clinical Neuroscience*, *10*(4), 431–437.

Salvadore, G., Drevets, W. C., Henter, I. D., Zarate, C. A., & Manji, H. K. (2008). Early intervention in bipolar disorder, part I: Clinical and imaging findings. *Early Intervention in Psychiatry*, *2*(3), 122–135. https://doi.org/10.1111/j.1751-7893.2008.00071.x

Strakowski, S. M., Keck, P. E., Jr., McElroy, S. L., West, S. A., Sax, K. W., Hawkins, J. M., … Bourne, M. L. (1998). Twelve-month outcome after a first hospitalization for affective psychosis. *Archives of General Psychiatry*, *55*(1), 49–55.

The World Health Organization Quality of Life (WHOQOL) assessment. (1995). Position paper from the World Health Organization. *Social Science & Medicine*, *41*(10), 1403–1409.

Tohen, M., Hennen, J., Zarate, C. M., Jr., Baldessarini, R. J., Strakowski, S. M., Stoll, A. L., … Cohen, B. M. (2000). Two-year syndromal and functional recovery in 219 cases of first-episode major affective disorder with psychotic features. *American Journal of Psychiatry*, *157*(2), 220–228. https://doi.org/10.1176/appi.ajp.157.2.220

Torrent, C., Reinares, M., Martinez-Aran, A., Cabrera, B., Amoretti, S., Corripio, I., … Vieta, E. (2018). Affective versus non-affective first episode psychoses: A longitudinal study. *Journal of Affective Disorders*, *238*, 297–304. https://doi.org/10.1016/j.jad.2018.06.005

van Os, J., Takei, N., Castle, D. J., Wessely, S., Der, G., & Murray, R. M. (1995). Premorbid abnormalities in mania, schizomania, acute schizophrenia and chronic schizophrenia. *Social Psychiatry and Psychiatric Epidemiology*, *30*(6), 274–278.

Young, R. C., Biggs, J. T., Ziegler, V. E., & Meyer, D. A. (1978). A rating scale for mania: Reliability, validity and sensitivity. *British Journal of Psychiatry*, *133*, 429–435.

Yung, A. R., Yuen, H. P., McGorry, P. D., Phillips, L. J., Kelly, D., Dell'Olio, M., … Buckby, J. (2005). Mapping the onset of psychosis: The Comprehensive Assessment of At-Risk Mental States. *Australian and New Zealand Journal of Psychiatry*, *39*(11–12), 964–971. https://doi.org/10.1080/j.1440-1614.2005.01714.x

Zolkowska, K., Cantor-Graae, E., & McNeil, T. F. (2001). Increased rates of psychosis among immigrants to Sweden: Is migration a risk factor for psychosis? *Psychological Medicine*, *31*(4), 669–678.

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