UNIVERSIDAD COMPLUTENSE DE MADRID
FACULTAD DE MEDICINA

TESIS DOCTORAL

Síndromes con alto riesgo clínico de desarrollar trastornos psicóticos: avances en caracterización, pronóstico y factores terapéuticos

MEMORIA PARA OPTAR AL GRADO DE DOCTOR

PRESENTADA POR

Gonzalo Salazar de Pablo

Directores

Carmen Moreno Ruiz
Christoph U. Correll
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Madrid

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MEMORIA PARA OPTAR AL GRADO DE DOCTOR INTERNACIONAL

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CLINICAL SYNDROMES AT HIGH RISK OF DEVELOPING PSYCHOTIC DISORDERS: ADVANCES IN CHARACTERIZATION, PROGNOSIS AND THERAPEUTIC FACTORS

Doctoral dissertation authored and presented by

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Madrid, 2021

“There comes a point where we need to stop just pulling people out of the river.

We need to go upstream and find out why they are falling in”

Desmond Tutu

Para mi familia

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LIST OF ABBREVIATIONS

LIST OF ABBREVIATIONS

Various abbreviations and acronyms have been used throughout the doctoral dissertation. This is the meaning of the abbreviations:

ADHD: Attention-deficit hyperactivity disorder

AFP: Affective psychosis

APS: Attenuated Psychosis Syndrome

APSS: Attenuated Psychotic Symptoms Syndrome

ATPD: Acute and Transient Psychotic Disorders

BAR: Bipolar At Risk

BD-I: Bipolar disorder type I

BD-II: Bipolar disorder type II

BD-NOS: Bipolar disorder not otherwise specified

BPD: Brief psychotic disorder

BLIPS: Brief Limited Intermittent Psychotic Symptoms

BIPS: Brief Intermittent Psychotic Symptom

BPRS: Brief Psychiatric Rating Scale

BS: Basic symptoms CHR-P designation

BSABS: Bonn Scale for the Assessment of Basic Symptoms

BSIP: Basel Screening Instrument for Psychosis

CAARMS: Comprehensive Assessment of At-Risk Mental States

CASH: Comprehensive Assessment of Symptoms and History

CBT: Cognitive Behavioral Therapy

CGI-S: Clinical Global Impression– Severity

CHR-P: Clinical High Risk for Psychosis

COGDIS: Cognitive Disturbances

COPER: Cognitive-Perceptive Basic Symptoms

DSM: Diagnostic and Statistical Manual of mental disorders

DSM-5–APS: Attenuated Psychosis Syndrome as per the Diagnostic and Statistical Manual of mental disorders

FEP: First-episode psychosis

GAF: Global Assessment of Functioning

GRD: Genetic Risk and Deterioration

K-SADS-PL: Kiddie-Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version

ICD: International Statistical Classification of Diseases and Related Health Problems

IQ: Intelligence Quotient

IQR: Interquartile Range

MADRS: Montgomery Åsberg Depression rating scale

MD-NOS: Mood disorder not otherwise specified

MDD: Major depressive disorder

MOOSE: Meta-analysis of Observational Studies in Epidemiology

NICE: National Institute for Health and Care Excellence

NOS: Not otherwise specified

OCD: Obsessive compulsive disorder

ODD: Oppositional defiant disorder

PANSS: Positive and Negative Symptom Scale

PQ: Prodromal Questionnaire

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses

PTSD: Post-traumatic stress disorder

RCT: Randomized clinical trial

SCID: Structured Clinical Interview for DSM

SIBARS: Semistructured Interview of At Risk Bipolar States

SIPS: Structured Interview for Prodromal Syndromes

SPI: Schizophrenia Proneness Instrument

UHR: Ultra-high risk

WHO: World Health Organization

YMRS: Young Mania Rating Scale

INTRODUCTION

1. INTRODUCTION

1.1. BRIEF HISTORICAL OVERVIEW AND CONCEPTUAL FOUNDATIONS

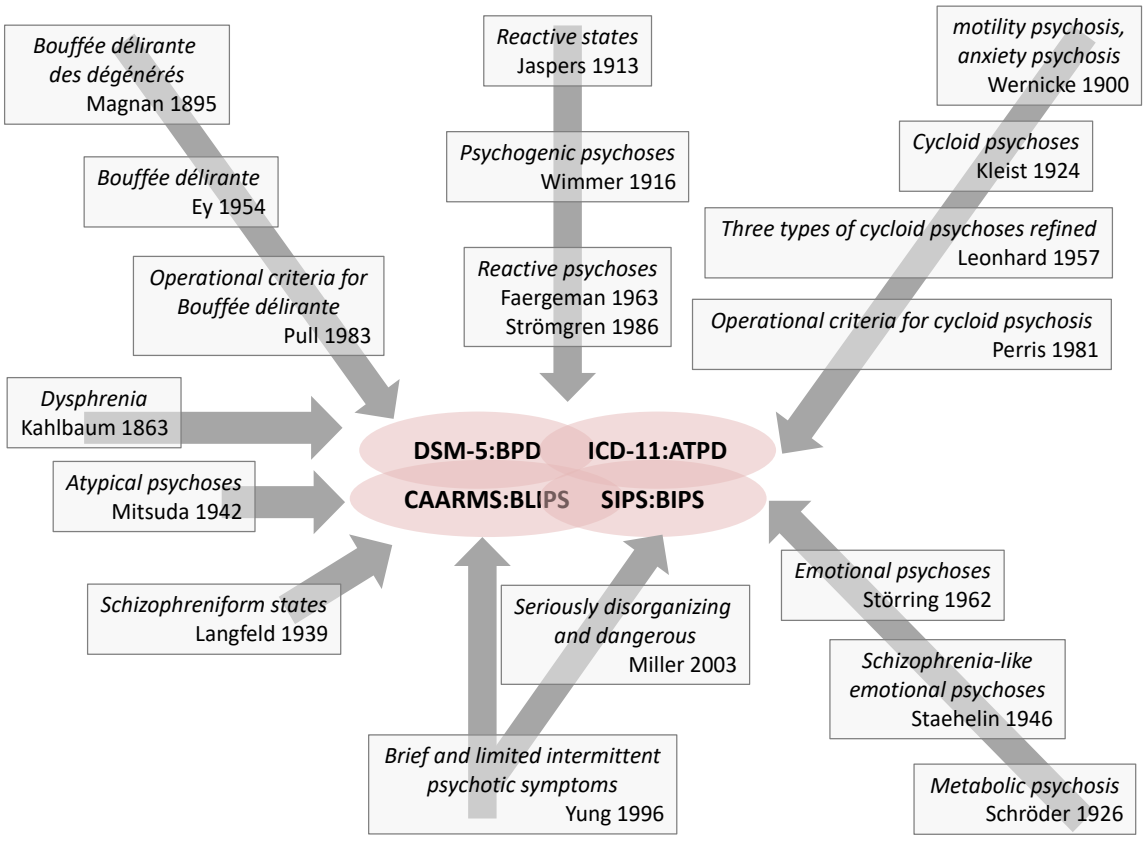
The recognition of a subsyndromal phase that preceded the first episode of psychosis was acknowledged as early as in the first half of the 20th century (Sullivan, 1994). The term prodromal was introduced to the literature in 1932 (Mayer-Gross, 1932). However, the prevention of psychotic disorders field has only recently advanced to the point of becoming one of the most established preventive approaches in clinical psychiatry (Yung et al., 2005).

The first longitudinal study on the early identification of schizophrenia was published in 1989, three decades ago, and referred to the basic symptoms (BS) criteria (Huber and Gross, 1989). Around 25 years ago, the term "at-risk mental state" was introduced (Yung et al., 1996). Three groups were defined (Yung et al., 1996), which compose the ultra-high risk (UHR) criteria: 1) attenuated psychotic symptoms, with individuals with recent subthreshold, attenuated positive symptoms; 2) “Brief Limited Intermittent Psychotic Symptoms” (BLIPS) with individuals with short but frank psychotic symptoms; 3) trait and state risk factor [now referred to as “Genetic Risk and Deterioration syndrome” (GRD)], with individuals with a first-degree relative with a psychotic disorder or a personal history of schizotypal personality disorder in addition to a decreased functioning during the previous year (Nelson et al., 2011). At the moment, the combination of UHR criteria and BS criteria compose the Clinical High Risk for Psychosis (CHR-P) designation, which is currently the most widely used designation in the literature for individuals at risk of psychosis (Fusar-Poli et al., 2020b).

BLIPS individuals [“Brief Intermittent Psychotic Symptom” (BIPS) as per the “Structured Interview for Prodromal Syndromes” (SIPS); BLIPS as per the “Comprehensive Assessment of At-Risk Mental States” (CAARMS); BLIPS hereafter] are considered the research-based operationalizations of brief psychotic disorders (BPD) (Fusar-Poli et al., 2021). Their historical development has been parallel to other CHR-P criteria (Marneros and Pillmann, 2004, Fusar-Poli et al., 2016a).

The conceptual foundations of brief psychotic episodes have been marked by different historical landmarks and denominations, including the “dysphrenia” (Kahlbaum, 1863) and the "bouffée délirante des dégénérés" (Magnan, 1895), among others (see the conceptual foundations of brief psychotic episodes in Figure 1).

Figure 1. Conceptual foundations of brief psychotic episodes



(adapted from (Fusar-Poli et al., 2021, Marneros and Pillmann, 2004, Fusar-Poli et al., 2016a))

While “Brief Reactive Psychosis” was added to the “Diagnostic and Statistical Manual of Mental Disorders” (DSM) in the DSM-III and the “International Classification of Diseases” (ICD) incorporated the “Acute and Transient Psychotic Disorders” (ATPD) to the ICD-10 in the "schizophrenia, schizotypal and delusional disorders" group (Castagnini and Berrios, 2009), a diagnostic category

based on the attenuated psychotic symptoms criteria was not introduced into the DSM until 2013, when the DSM-5 introduced the diagnosis of Attenuated Psychosis Syndrome (DSM-5–APS) in Research Appendix Section and briefly in the Main Section of the manual (Salazar de Pablo et al., 2020a).

In the bipolar disorders field, psychotic features, particularly delusions, have been described as part of melancholia and mania since ancient Greece (Glovinsky, 2002). However, manic depression was not considered a distinct entity until the nineteenth century (Falret, 1854). A half-century later, Kraepelin established a clear distinction between manic depressive illness and schizophrenia (dementia praecox) (Kraepelin, 1921).

Clinicians have been diagnosing mania in children and adolescents since as early as 1763 (Glovinsky, 2002). At the beginning of the 20th century, 0.4% of the patients Kraepelin studied had symptoms before ten years of age (Kraepelin, 1921). Not long after, Kasanin described mania's clinical picture while studying affective psychoses in adolescents (Carlson and Glovinsky, 2009). The bipolar prodrome has been less studied than the psychosis prodrome (Conroy et al., 2018). However, in the last decade, it has received increasing attention (Geoffroy and Scott, 2017, Conroy et al., 2018), resulting in the introduction of bipolar spectrum disorders in classification systems like the ICD (World Health Organization, 2018) or the DSM (American Psychiatric Association, 2013).

1.2. CHARACTERIZATION OF PREVENTION OF PSYCHOTIC DISORDERS IN INDIVIDUALS AT RISK

1.2.1. Classification of prevention of mental disorders

The high personal, clinical, and social burden associated with psychosis has led to an interest in preventing psychotic disorders. The objectives of preventive interventions vary depending on the approaches carried out. Two main classifications are usually followed to characterize preventive approaches in psychiatry: the classic public health classification of prevention (WHO, 2004) and the classification by Gordon (Gordon, 1983) (Table 1).

The classic public health classification of prevention differentiates primary prevention, secondary prevention, and tertiary prevention depending on whether the final goal is to have an effect on the incidence (primary), the prevalence (secondary), or the complications that may appear after the disorder is established (tertiary). Gordon's classification of prevention of physical illness differentiates interventions depending on which individuals they target, either individuals without a-priori risk or the general population (universal), subgroups with a high risk of developing a certain disorder (selective), or individuals who have developed minimal or subthreshold symptoms but noticeable symptoms (indicated) (Table 1).

Table 1. Classification of preventive approaches in psychiatry

Classic public health classification of prevention (World Health Organization, 2004)	**Gordon's classification of prevention of physical illness** (Gordon, 1983)
Primary prevention seeks to prevent the onset (incidence) of a disorder or illness	**Universal prevention** targets either the general public or a whole population group that has not been identified based on increased risk
Secondary prevention seeks to lower the rate of established cases of the disorder or illness in the population (prevalence)	**Selective prevention** targets individuals or subgroups of the population whose risk of developing a mental disorder is significantly higher than average, as evidenced by biological, psychological, or social risk factors
Tertiary prevention includes interventions that reduce disability, enhance rehabilitation, and prevent relapses and recurrences of the illness	**Indicated prevention** targets high-risk people who are identified as having minimal but detectable signs or symptoms foreshadowing a mental disorder or biological markers indicating predisposition for a mental disorder but who do not meet

	diagnostic criteria for the disorder at that time

1.2.2. Clinical high risk for psychosis (CHR-P) criteria

In the prevention of psychotic disorders field. interventions are usually primary (seeking to prevent the incidence of psychosis) and indicated (directed towards individuals with subthreshold or minimal symptoms, typically at CHR-P) (Fusar-Poli et al., 2016c, Fusar-Poli et al., 2013b). CHR-P individuals present with attenuated psychotic symptoms (Fusar-Poli et al., 2013b), negative symptoms (Lencz et al., 2004), low functioning (Addington et al., 2008), poor quality of life (Bechdolf et al., 2005), and help-seeking behavior (Fusar-Poli et al., 2013b). CHR-P individuals also have a high risk of developing psychosis (Fusar-Poli et al., 2016b) and a high risk of developing other poor mental health outcomes (Fusar-Poli et al., 2013b).

The two most frequent CHR-P criteria are attenuated psychotic symptoms, representing 85% of the CHR-P individuals (Fusar-Poli et al., 2016b) and BLIPS, representing 10% of the CHR-P individuals (Fusar-Poli et al., 2016b). However, other criteria as GRD and BS are included within this category (see Table 2 and Figure 2).

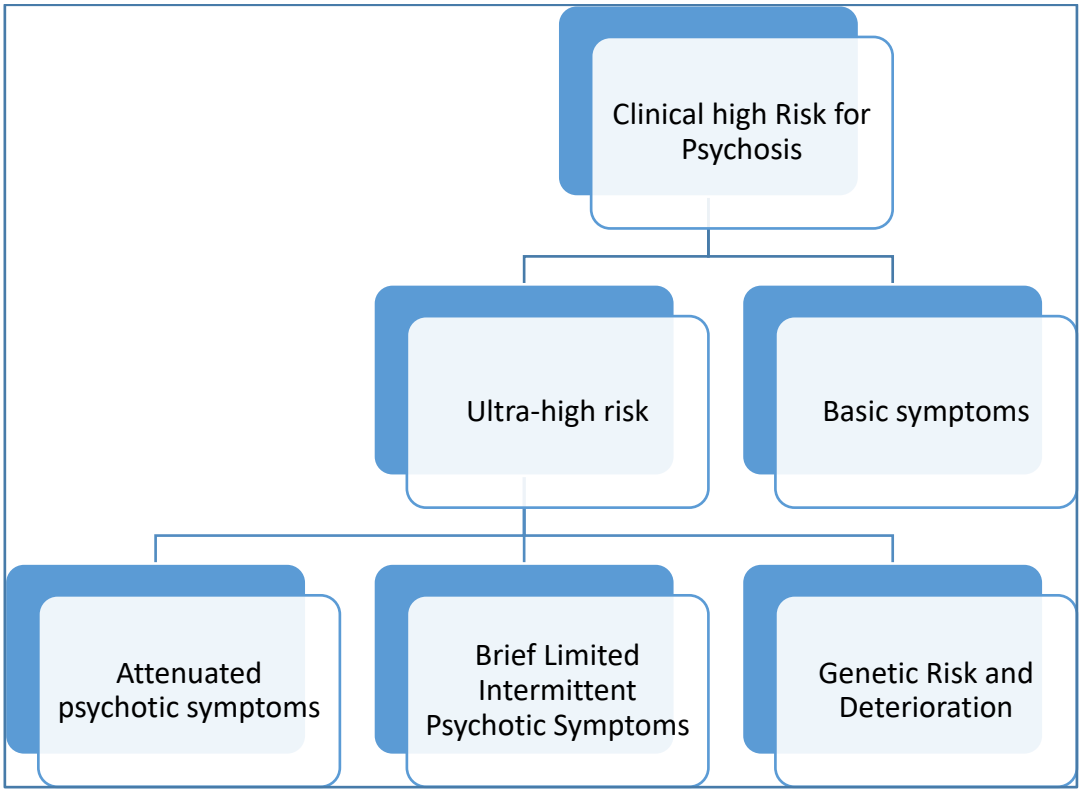
Table 2. Clinical-High-Risk Criteria

CRITERIA	CHARACTERISTICS
Attenuated psychotic symptoms	-Presence of at least one of the following attenuated/subthreshold symptoms: ideas of reference, odd beliefs, perceptual abnormalities, paranoid ideation, odd thinking and speech, odd behavior, and appearance. - Frequency of symptoms at least several times per week. - Symptoms present within the last year. - Symptoms present for at least one week and no longer than five years.
Brief Limited Intermittent Psychotic Symptoms	- Presence of at least one of the following symptoms: ideas of reference, odd beliefs, perceptual abnormalities, paranoid ideation, odd thinking, or speech. - Duration of episode less than one week. - Frequency of symptoms at least several times per week. - Symptoms occurred within the last year. - Symptoms resolve spontaneously.
Genetic Risk and Deterioration	- First-degree relative with a psychotic disorder or personal history of schizotypal personality disorder. - Significant decline in mental state or functioning, maintained for at least one month and no longer than five years. - Decline in functioning occurred within the past year.

Basic symptoms	- Subtle, subjectively experienced disturbances in mental processes, including thinking, attention, perception, speech, stress tolerance, and affect. • Cognitive-Perceptive Basic Symptoms (COPER) criteria: presence of at least one of ten basic symptoms (thought interference, thought perseveration, thought pressure, thought blockages, disturbance of receptive speech, decreased ability to discriminate between ideas and perception, fantasy and true memories, unstable thoughts of reference, derealization, visual perception disturbances, acoustic perception disturbances), with at least weekly occurrence within the last three months and first occurrence at least 12 months ago. • Cognitive Disturbances (COGDIS): presence of at least two of nine basic symptoms (inability to divide attention, thought interference, thought pressure, thought blockages, disturbance of receptive speech, disturbance of expressive speech, unstable thoughts of reference, disturbances of abstract thinking, captivation of attention by details of the visual field), with at least weekly occurrence within the last three months.

Adapted from (Schultze-Lutter, 2016, Fusar-Poli et al., 2016b, Nelson et al., 2011).

Figure 2. Clinical-High Risk for Psychosis Criteria



1.2.1.1. Attenuated psychotic symptoms and Attenuated Psychosis Syndrome

The most frequent CHR-P designation, attenuated psychotic symptoms, is typically characterized by subthreshold psychotic symptoms (Yung et al., 2006), such as perceptual disturbances, ideas of reference, paranoid ideation, and disorganization, with mostly intact insight (Fusar-Poli et al., 2013b).

The “Structured Interview for Psychosis-Risk Syndrome” (SIPS) operationalized the "Attenuated Psychotic Symptoms Syndrome” (APSS) criteria. In contrast, the “Comprehensive Assessment of At-Risk Mental States” (CAARMS) operationalized "attenuated psychotic symptoms" (see annex 1 for APSS-SIPS and CAARMS-APS criteria). Hereafter, patients who fulfill Attenuated Psychosis Syndrome criteria will be referred to as APS or DSM-5–APS. The denomination attenuated psychotic symptoms will be spelled consistently along the text to avoid any confusion.

As a consequence of the clinical research conducted on attenuated psychotic symptoms, Attenuated Psychosis Syndrome diagnosis was introduced in the DSM-5 in Section III, in the "Conditions for Further Study” section. These are the criteria for DSM-5–APS:

A. At least one of the following symptoms is present in an attenuated form, with relatively intact reality testing, and is of sufficient severity or frequency to warrant clinical attention:
    1. Delusions.
    2. Hallucinations.
    3. Disorganized speech.
B. Symptom(s) must have been present at least once per week for the past month.
C. Symptom(s) must have begun or worsened in the past year.
D. Symptom(s) is/are sufficiently distressing and disabling for the individual to warrant clinical attention.

E. Symptom(s) is/are not better explained by another mental disorder, including a depressive or bipolar disorder with psychotic features, and is not attributable to a substance or another medical condition's physiological effects.
F. Criteria for any psychotic disorder have never been met.

DSM-5–APS was also introduced in the main section under "other specified schizophrenia spectrum and other psychotic disorders," defined as "characterized by psychotic-like symptoms that are below a threshold for full psychosis (e.g., the symptoms are less severe and more transient, and insight is relatively maintained)."

While roadmaps for the inclusion of this diagnostic category in the DSM-5.1 are already being traced (Fusar-Poli et al., 2014a), no systematic review has summarized the available evidence regarding the clinical validity of DSM-5–APS.

1.2.2.2. Brief Limited Intermittent Psychotic Symptoms and Brief Psychotic Episodes

The definition of brief psychotic episodes is based on two competing approaches (each of which is internally characterized by two additional competing definitions): standard psychiatric classification and research-based operationalization.

While standard psychiatric classifications of brief psychotic episodes include DSM-5 defined BPD (American Psychiatric Association, 2013) and ICD-11 defined Acute and Transient Psychotic Disorders (ATPD) (Reed et al., 2019), new research-based operationalizations of brief psychotic episodes have been introduced, leveraging the CHR-P criteria and clinical staging paradigm (Fusar-Poli et al., 2017a).

BLIPS operationalization identifies young people at risk of psychosis due to a recent history of frank psychotic symptoms such as delusions, hallucinations, and disorganization, limited in duration and with spontaneous remission (without antipsychotic medication) within one week (Fusar-Poli et al., 2013b). Symptoms must occur during the past year, and there must be a drop in social functioning or low functioning in the previous year (Yung et al., 2006). The BLIPS operationalization was modified into the BIPS in the SIPS (Miller et al., 2003), excluding seriously disorganizing and dangerous features, extending the duration of short-lived psychotic symptoms to up to 3 months, and allowing the use of antipsychotics.

Table 3. Current classification of Brief Intermittent Psychotic Symptom as per SIPS and Brief Limited Intermittent Psychotic Symptoms as per CAARMS

	Brief Intermittent Psychotic Symptom (BIPS) - SIPS Version 5.6 (Woods et al., 2014)	**Brief Limited Intermittent Psychotic Symptoms (BLIPS) - CAARMS Version 12/2006** (Yung et al., 2006)
Symptoms	At least one of the SIPS P1-P5 Severity Scales scored as 6.	At least one of the CAARMS P1, P2, or P4 Severity Scales is scored 6, or P3 is scored ≥ 5.
Age	14-35 years.	14-35 years.
Onset	Symptoms should have been present the past month and have begun in the previous 3 months.	Symptoms should have been present in the previous 12 months and for no longer than 5 years.
Duration and frequency	Up to 3 months, at a frequency of at least several min per day at least once per month but less than one hour per day for 4 days per week in the past month.	Up to 7 days, at a frequency of at least 3–4 times per week when lasting at least 1 hour, or at least a daily presence when lasting less than 1 hour.
Level of functioning	No social/occupational dysfunction requirement.	30% drop in SOFAS score from premorbid level, sustained for a month, within past 12 months or SOFAS score <50 for the past 12 months or more.

Specifiers	-BIPS lifetime. -BIPS progressive. -BIPS persistent. -BIPS partial remission. -BIPS full remission.	No specifiers.
Exclusion criteria	- Symptoms are strongly intertwined temporally with substance use episodes. - Substance-induced psychosis. - Symptoms are better accounted for by another DSM diagnosis (including substance intoxication and including cannabis). - Previous psychotic episodes (but lifetime BIPS are not exclusion criteria). - Symptoms are seriously disorganizing and dangerous.	-Symptoms occur only during peak intoxication from a substance known to be associated with psychotic experiences. -Symptoms are rated regardless of how the symptoms developed. Any non-psychotic comorbidity is allowed. - Previous psychotic episode above BLIPS threshold. - Symptoms do not resolve spontaneously without antipsychotic medication.

1.2.2.3. Other clinical high risk for psychosis (CHR-P) and psychosis clinical risk criteria

The other two main CHR-P criteria are GRD and BS. For individuals to fulfill GRD criteria according to the established instruments (Fusar-Poli et al., 2016c), either a Schizotypal Personality Disorder or a family history of psychosis in a first-degree relative must be accompanied with a decreased functioning (Yung et al., 2006, McGlashan T, 2010).

BS target an even earlier phase. Two different criteria have been proposed: COPER criteria and COGDIS criteria (see Table 2). Basic symptoms are subclinical disturbances in mental processes, considered the phenomenological expression of the brain aberrations underlying the development of psychosis (Schultze-Lutter, 2016). They may be related to affect, thinking, language, perception, stress tolerance, memory, and other cognitive processes, among others (Miret et al., 2016).

Other risk criteria include the “unspecific risk category” as per the “Basel Screening Instrument for Psychosis” (BSIP) (Riecher-Rössler et al., 2008) to identify patients with less specific prodromal symptoms and risk factors for psychosis. This category has a lower risk of transition to psychosis than the others described in this dissertation (Peralta et al., 2018).

1.2.3. Bipolar spectrum disorders and antecedent conditions

Bipolar disorder type I (BD-I) is characterized by at least one episode of mania (American Psychiatric Association, 2013). Although depressive episodes are common, an episode of mania without depression is enough for a BD-I diagnosis, as long as there is no other cause that explains the symptoms better (American Psychiatric Association, 2013).

While full syndromal BD-I is relatively uncommon in children and adolescents, more children and adolescents present subsyndromal mood disturbances and nonspecific manic-type symptoms than BD-I (Hafeman et al., 2013). These disturbances and symptoms put them at high risk of developing BD-I. Several antecedent conditions have been described, and different categories and criteria to define the bipolar prodrome have been proposed (Hauser and Correll, 2013) (for a comprehensive description, see annex 2). Still, it has been challenging to characterize the high risk state for developing bipolar disorder (Saraf et al., 2020). The offspring of individuals with bipolar disorder are at high risk of developing psychotic disorders as bipolar psychotic disorder (Duffy, 2000). However, having familial risk is not typically enough to be considered at high risk according to the established classifications (Malhi et al., 2014).

Another approach involves identifying people with subsyndromal affective symptoms (Saraf et al., 2020). “At Risk for Mania Syndrome” criteria (Correll et al., 2014) are based on the “Bipolar Prodrome Symptom Scale” and differentiate two prodromal stages according to clinical criteria (manic symptoms, depressive symptoms, and general symptoms) and functioning: an early prodromal stage

characterized by subclinical, attenuated nonspecific manic symptoms, and a late prodromal stage including individuals with bipolar disorder not otherwise specified (BD-NOS). Also, subsyndromal stages include individuals with cyclothymia or hypomania (Lambert et al., 2016).

Other criteria for individuals at risk of developing bipolar disorder, aged between 15 and 25 years, include the "Bipolar At Risk" (BAR) criteria (Bechdolf et al., 2010), with three groups of individuals: a) individuals with sub-threshold mania; b) individuals with depression and cyclothymic features; c) individuals with depression and a genetic risk -i.e., first-degree relatives with bipolar disorder-. The "Semistructured Interview of At Risk Bipolar States" (SIBARS) (Fusar-Poli et al., 2018b) considers within the criteria to be considered at-risk of developing bipolar disorders the three previous groups (a-c) plus d) individuals with cyclothymic features and genetic risk; e) individuals with sub-threshold mixed episodes; f) individuals with mood swings. The criteria need to be fulfilled in the last year (Fusar-Poli et al., 2018b). All these criteria require a lack of previous full-blown manic or psychosis episodes.

BD-not otherwise specified (BD-NOS), renamed "unspecified BD" in the DSM-5 (American Psychiatric Association, 2013), is characterized by symptoms that lack sufficient duration or severity for a BD-I or BD-II diagnosis. This group includes periods of abnormally elevated or irritable mood with other symptoms, lasting at least 4 hours on four cumulative days (Birmaher et al., 2006).

Patients with mood disorder NOS (MD-NOS) named "other specified BD" in the DSM-5 (American Psychiatric Association, 2013) have characteristic symptoms

of BD and related disorders that do not meet the full criteria for any category previously mentioned. Individuals with MD-NOS are characterized by subthreshold periods of mania or hypomania that, unlike BD-NOS, last <4 hours per day for less than four cumulative days (Salazar de Pablo et al., 2020b) (full criteria for BD-NOS and MD-NOS can be found in annex 3).

The efforts to characterize prodromal and subsyndromal bipolar mania and depression states and ultimately prevent psychotic affective disorders like BD-I have been even more limited, particularly in underage individuals.

1.3. PSYCHOMETRIC INSTRUMENTS

While the CHR-P criteria were first operationalized using the “Comprehensive Assessment of Symptoms and History” (CASH) (Andreasen et al., 1992) and the “Brief Psychiatric Rating Scale” (BPRS) (McGorry et al., 1988), at the moment, CHR-P criteria are mainly established using the “Comprehensive Assessment of At-Risk Mental States” (CAARMS) (Yung et al., 2005) and the “Structured Interview for Prodromal Syndromes” (SIPS) (Miller et al., 2003) (for a comprehensive list of established psychometric instruments for CHR-P criteria see annex 4).

The CAARMS and the SIPS are semi-structured interviews carried out by trained professionals, which share some similarities and have a significant diagnostic agreement towards identifying UHR individuals (Fusar-Poli et al., 2016c). BS criteria were initially operationalized with the “Bonn Scale for the Assessment of Basic Symptoms” (BSABS) (Vollmer-Larsen et al., 2007), but can also be defined by the “Basel Screening Instrument for Psychosis” (BSIP) (Riecher-Rössler et al., 2008), and the “Schizophrenia Proneness Instrument” (SPI) (Fux et al., 2013).

Regarding individuals at risk of developing bipolar disorder, depending on the categories and concepts that are intended to be characterized (for a comprehensive description, see annex 2), different instruments can be used. Two of the most comprehensive are the “Bipolar Prodrome Symptom Interview and Scale-Prospective” (BPSS-P) (Correll et al., 2014) and the SIBARS (Fusar-Poli et al., 2018b).

1.3.1. The Structured Interview for Psychosis-Risk Syndromes (SIPS)

The SIPS (Miller et al., 1999, Miller et al., 2003) is a semi-structured interview used to diagnose psychosis-risk syndromes in the last month. According to the symptoms evaluated, it includes four primary sections: positive symptoms, negative symptoms, disorganized symptoms, and general symptoms (Cornblatt et al., 2015). As part of the SIPS, the "Scale of Prodromal Symptoms" (SOPS) is used to determine whether participants meet the research criteria for APSS or not.

Positive symptoms include the following five symptoms: unusual thought content/delusional ideas, suspiciousness/persecutory ideas, grandiosity, perceptual abnormalities/hallucinations, and disorganized communication; negative symptoms include the following six symptoms: social isolation and withdrawal, avolition, expression of emotion, experience of emotions and self, ideational richness and occupational functioning; disorganized symptoms include the following four symptoms: odd behavior or appearance, bizarre thinking, trouble with focus and attention, and personal hygiene; general symptoms include the following four symptoms: sleep disturbances, dysphoric mood, motor disturbances and impaired tolerance to normal stress.

For positive symptoms, frequency is relevant. Mainly, whether symptoms were present for at least several minutes per day at a frequency of at least once per month, whether symptoms were present with an average frequency of several minutes per day at least once per week in the past month, and whether symptoms occurred for at least one hour per day at an average frequency of four days per

week over one month. Furthermore, symptoms onset, frequency, and past year history are also recorded.

1.3.2. The Bipolar Prodrome Symptom Interview and Scale-Prospective (BPSS-P)

The BPSS-P (Correll et al., 2014) has a similar structure to the SIPS. It intends to characterize prodromal and subsyndromal bipolar mania and depression states and assess the evolution of BD at any stage. It is designed to evaluate the lifetime presence and severity of prodromal/subsyndromal and syndromal manic, depressive, and general symptoms. It includes 10 manic symptoms, 12 depression symptoms, and 9 general symptoms (Correll et al., 2014). Manic symptoms include mood elevation, irritability, inflated self-esteem/grandiosity, decreased need for sleep, over talkativeness, racing thoughts/flight of ideas, distractibility, increased energy/goal-directed activity, increased psychomotor activity, and reckless or dangerous behavior; depressive symptoms include depressed mood, anhedonia, decreased appetite, increased appetite, insomnia, hypersomnia, decreased psychomotor activity, decreased energy, worthlessness/guilt, decreased concentration, indecision, and suicidality; general symptoms include mood lability, oppositionality, anger/aggressiveness, anxiety, self-injurious behavior, obsessions and compulsions, positive psychotic symptoms, negative psychotic symptoms, and disorganized symptoms. The last three symptoms are optional.

Symptom severity is rated using an ordinal scale with 0=absent, 1=questionably present, 2=mild, 3=moderate, 4=moderately severe, 5=severe, 6=extreme, with a rating of “moderate” (rating=3) being the lowest subsyndromal rating [i.e., symptoms are “beginning to be noticed by others” and are not just “fully explained by external factors,” (rating=2), but not yet “beginning to interfere with functioning” (rating=4)]. In addition, the frequency of these symptom episodes is recorded on a Likert scale, as follows: 0=none, 1=<once/month, 2=once/month, 3=2–3 times/month, 4=4–7 times/month, 5=8–27 times/month, 6≥28 times/month. Furthermore, the duration, onset, and pattern of these symptoms are also recorded.

1.3.3. Global Assessment of Functioning (GAF)

GAF (Piersma and Boes, 1997) assesses global functioning ranging from 0 to 100. Scores 100-91 indicate no symptoms; 90-81 absent or minimal symptoms; 80-71 some transient symptoms; 70-61 some persistent mild symptoms; 60-51 moderate symptoms; 50-31 some serious symptoms or impairment in functioning; 30-21 inability to function in almost all areas; 20-11 in some danger of hurting self or others; 10-1 in persistent danger of severely hurting self or others.

1.4. DEMOGRAPHICS AND EPIDEMIOLOGY IN INDIVIDUALS AT RISK OF DEVELOPING PSYCHOTIC DISORDERS

Psychosis and psychotic-like experiences are common in the general population (McGorry et al., 1995). It has been estimated that psychotic-like experiences appear in around 5% of the individuals in the general population (van Os et al., 2009). Adolescence and young adulthood are the most common periods for developing psychotic disorders (Fusar-Poli et al., 2020b). The mean age at the time of psychosis onset is typically later in female individuals than in male individuals (Brucato et al., 2017). Meta-analytical evidence found a significant association between cannabis use and a 2.7 years earlier age at the onset of psychosis (Large et al., 2011).

Different characterizations within CHR-P individuals and CHR-P samples, which can lead to biased samples, have been observed (Fusar-Poli et al., 2016d, Fusar-Poli et al., 2016e). Furthermore, significant differences in the prevalence of individuals at risk of developing psychotic disorders among the different settings appear. An additional challenge of epidemiological research in individuals at risk of developing psychotic disorders in the general population is that outreach strategies may dilute the level of pre-test psychosis risk (Fusar-Poli et al., 2016e) and difficult the identification of CHR-P individuals (Fusar-Poli et al., 2019d, Oliver et al., 2019a).

2.4% of individuals aged 16-40 meet psychosis-risk criteria, according to previous evidence (Schultze-Lutter et al., 2018). Considering individual designations, the prevalence of individuals meeting the SIPS-APSS criteria was 1.3% in the

general population (Schimmelmann et al., 2015) and 3.5% in college students (Chen et al., 2014). The prevalence of non–help-seeking young individuals meeting DSM-5–APS criteria was estimated to be 0.3% (Schultze-Lutter et al., 2014). A systematic review evaluated the presence of CHR-P in educational settings, finding a prevalence of 1-8% (Howie et al., 2019).

1.5. RISK FACTORS FOR INDIVIDUALS AT RISK OF DEVELOPING PSYCHOTIC DISORDERS

Several risk factors for the CHR-P state have been identified. Among them, there is meta-analytical evidence for a significant association between CHR-P individuals and obstetric complications, physical inactivity, male gender, single status, unemployment, and low educational level (Fusar-Poli et al., 2017d).

CHR-P individuals showed abnormal personality and character traits, including higher harm avoidance, lower reward dependence and persistence, and lower self-directedness and cooperativeness (Song et al., 2013).

The prevalence of trauma in CHR-P individuals was estimated to be 86.8% (Kraan et al., 2015). Childhood trauma, childhood emotional abuse, childhood physical neglect, and high perceived stress have been associated with the CHR-P state (Fusar-Poli et al., 2017d). Childhood trauma was more severe in CHR-P individuals than in controls, and bullying victimization was also more frequently reported (Peh et al., 2019).

While an association between tobacco use and the CHR-P state has been found (Fusar-Poli et al., 2017d), meta-analytical evidence has also observed that CHR-P individuals were less likely to consume alcohol than healthy controls (Fusar-Poli et al., 2017d). There are no existing studies on the association between genetic or epigenetic risk factors and the CHR-P state (Oliver et al., 2019a).

A recent meta-analysis has explored the risk factors and the protective factors associated with the risk of developing psychosis in CHR-P individuals (Oliver et

al., 2019b). Of the 26 factors that were retrieved, for none of them convincing level of evidence of an association with transition to psychosis was found. Increased severity of attenuated psychotic symptoms (SMD=0.348) and decreased global functioning (SMD=−0.291) were associated with transition to psychosis with highly suggestive evidence, and increased severity of negative psychotic symptoms was associated with transition to psychosis with suggestive evidence (Oliver et al., 2019b). There was weak but significant evidence for an association between transition to psychosis and male gender (OR=1.178), stress/trauma (OR=1.146), living alone (OR=1.557), being unemployed (OR=1.808), or being right-handed (OR=1.602). Also, there was evidence of a higher risk of transition to psychosis in individuals with higher severity of disorganized/cognitive symptoms (SMD=0.317), general symptoms (SMD=0.227), and total symptoms (SMD=0.307) (Oliver et al., 2019b). However, height and BMI were not statistically significant risk factors (Oliver et al., 2019b).

Bipolar patients with psychosis have higher rates and more severe anxiety and affective symptoms, higher rates of suicidality, higher rates of psychiatric hospitalizations, higher rates of sexual/physical abuse, and poorer psychosocial functioning than bipolar patients without psychosis (Shalev et al., 2020). Paternal age >40 years, early or late gestational age, childhood adversity, substance misuse, and being from an ethnic minority have been associated with affective psychosis (AFP), suggesting that non-affective and affective psychosis may share an environmental load (Rodriguez et al., 2021). These findings highlight the importance of carrying out preventive approaches for both individuals with subthreshold affective and psychotic symptoms. Furthermore, the following

factors have been identified as risk factors for developing bipolar disorder in young people: depression, disruptive behavior disorders, psychosis, antidepressant-induced manic symptoms, anxiety, family history of bipolar disorder, and subsyndromal symptoms of mania and depression (DelBello, 2018, Marangoni et al., 2018).

1.6. OUTCOMES AND PROGNOSIS IN THE PREVENTION OF PSYCHOTIC DISORDERS

A precise assessment of the prognosis and risk of developing psychotic disorders and poor mental health outcomes has the potential to maximize the benefits of early interventions in psychosis (Fusar-Poli et al., 2018c). This prognosis, the course of the illness, and the evolution of outcomes have high importance to inform clinical care (Fusar-Poli et al., 2018c).

Transition to psychosis has classically represented the core outcome in prediction and preventive research in the prevention of psychotic disorders field (Fusar-Poli et al., 2012). The reason for this is that prognostication of the likelihood of transitioning from a CHR-P designation to psychosis is highly important for the clinical care of these individuals (Fusar-Poli et al., 2018c). Meta-analytical transition to psychosis from a CHR-P stage was estimated as 18% after 6 months, 22% after 12 months, 29% after 24 months, and 36% after ≥36 months of follow-up (Fusar-Poli et al., 2012). Transition to psychosis is associated with several clinically meaningful real-world outcomes (Fusar-Poli et al., 2020a).

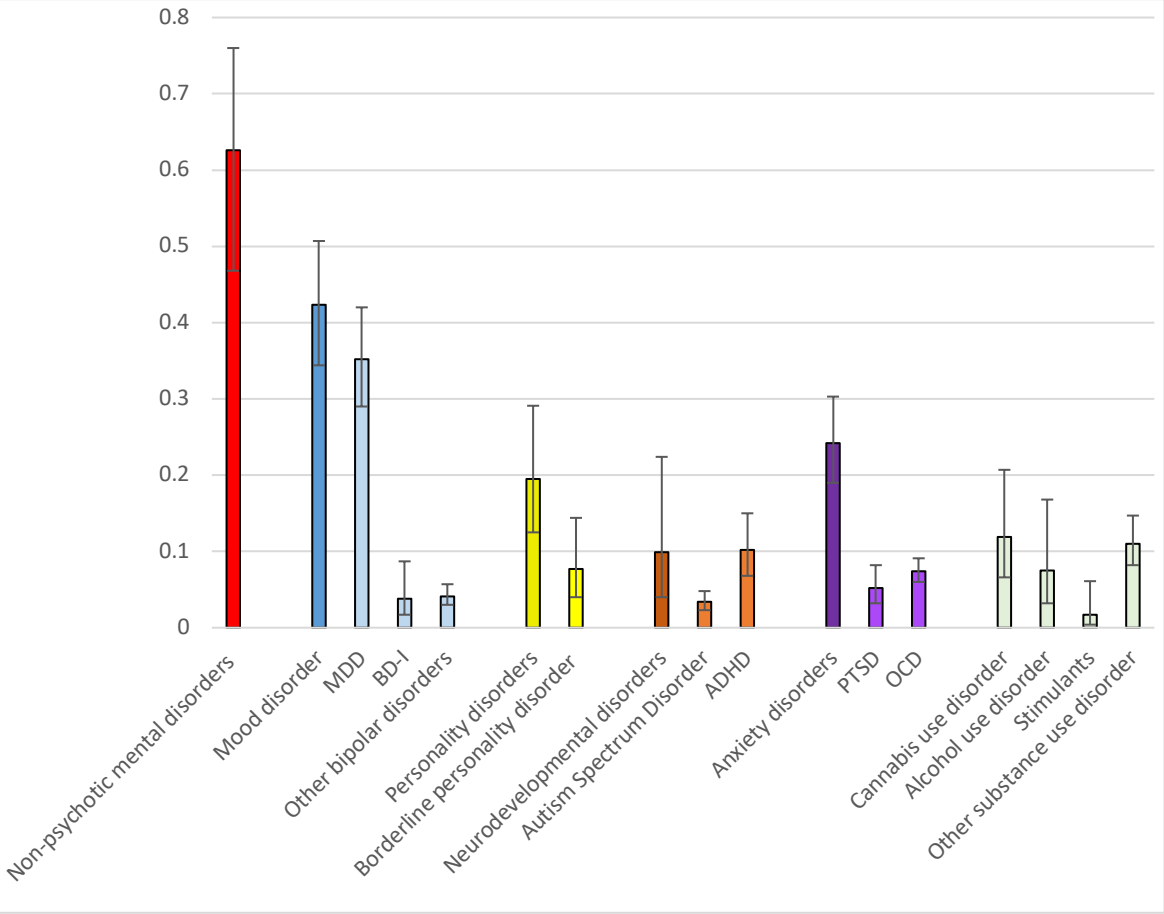
The risk of transition appears to be significant for all the CHR-P individuals, but several characteristics may affect this risk, which may also be different in children and adolescents. Although updated meta-analytical evidence does not exist, previous evidence shows that individuals with BLIPS may be at particularly high risk compared to other subgroups (Fusar-Poli et al., 2017a, Fusar-Poli et al., 2016a).

Transition to psychosis, defined by the severity of positive psychotic symptoms, has classically represented the core outcome in prediction and preventive research in this field. However, other outcomes are essential and may be even more prevalent (Fusar-Poli et al., 2013b). In fact, CHR-P individuals frequently present with high levels of negative symptoms -particularly social isolation (Lencz et al., 2004)-, associated with low functioning (Lencz et al., 2004). Meta-analytical evidence has evaluated baseline functioning (Fusar-Poli et al., 2015, Fusar-Poli et al., 2017d), cognitive functioning (Bora and Murray, 2014), and quality of life (Fusar-Poli et al., 2015) in CHR-P individuals, comparing them to control individuals and to individuals with other mental disorders. It has been concluded that CHR-P individuals frequently develop different poor mental health outcomes, even those who do not transition to psychosis (Beck et al., 2019).

Comorbid disorders are also common, including depressive disorders (Albert et al., 2018, Fusar-Poli et al., 2014b), bipolar disorders (Albert et al., 2018), anxiety disorders (Albert et al., 2018, Fusar-Poli et al., 2014b), obsessive-compulsive disorders (Albert et al., 2018) and eating disorders (Albert et al., 2018, Tay et al., 2015) among other conditions. In longitudinal studies, 62.6% (95%CI: 46.8%–76%) had non-psychotic mental disorders including the following: mood disorders (42.3%, 95%CI: 34.4%–50.7%) including major depressive disorder (35.2%, 95%CI: 29%–42%), bipolar disorder-I (3.8%, 95%CI: 1.7%–8.7%) and other bipolar disorders (4.1%, 95%CI: 3.0–5.7%); personality disorders (19.5%, 95%CI: 12.5–29.1%) including borderline personality disorder (7.7%, 95%CI: 4–14.4%); neurodevelopmental disorders (9.9%, 95%CI: 4–22.4%) including attention-deficit hyperactivity disorder (ADHD) (10.2%, 95%CI: 6.8–15%); anxiety

disorders (24.2%, 95%CI: 19–30.3%) including post-traumatic stress disorder (PTSD) (5.2%, 95%CI: 3.2–8.2%), and obsessive compulsive disorder (OCD) (7.4%, 95%CI: 6–9.1%). Substance use disorders are common in individuals at CHR-P, including cannabis use disorder (11.9%, 95%CI: 6.6–20.7%), alcohol use disorder (7.5%, 95%CI: 3.2–16.8%), stimulant use disorder (1.7%, 95%CI: 0.4–6.1%) and other substance use disorder (11%, 95%CI: 8.2–14.7%) (Figure 3).

Figure 3: Comorbidity in CHR-P

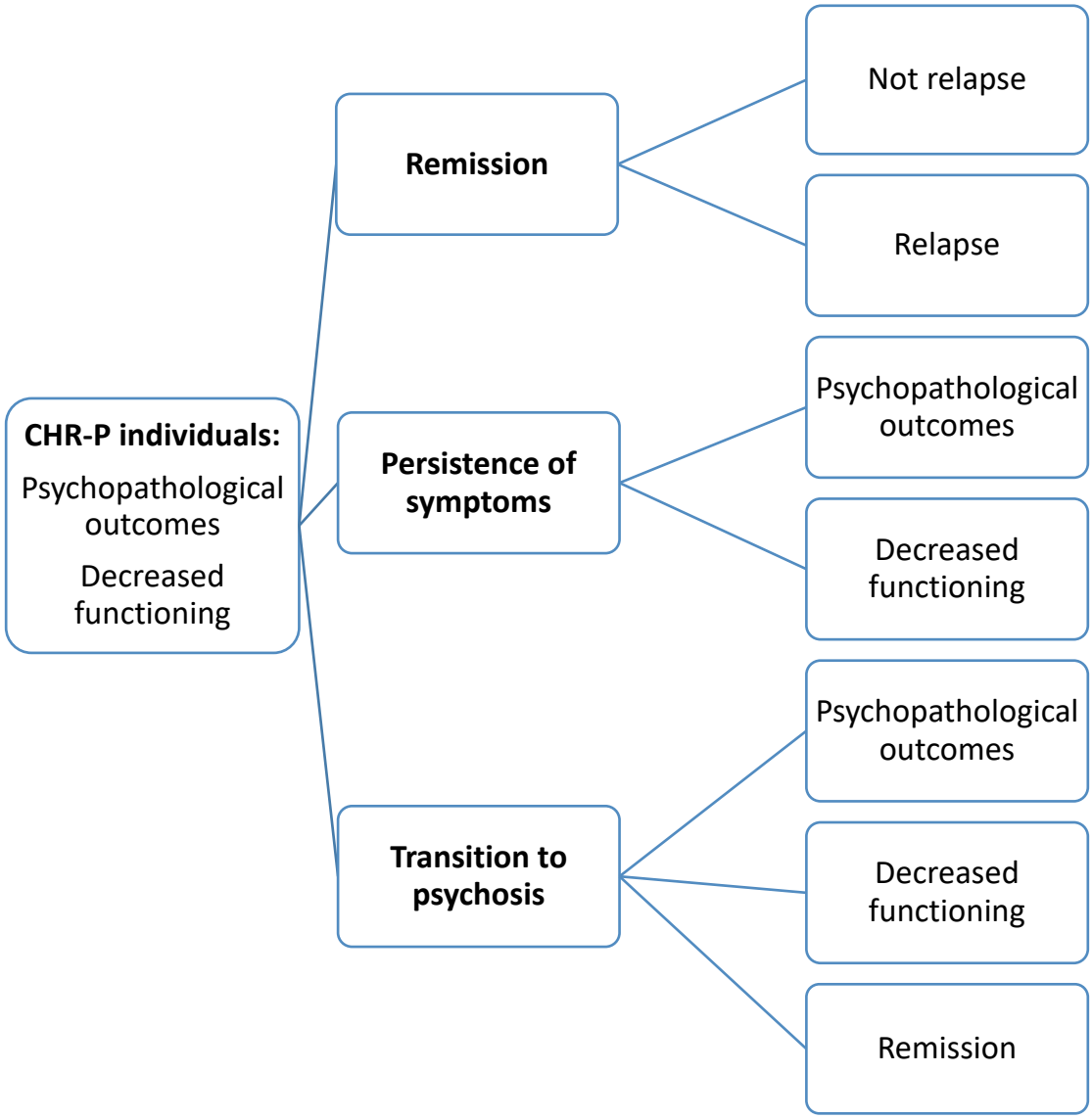


MDD: major depressive disorder; BD-I: bipolar disorder Type I; ADHD: attention-deficit hyperactivity disorder; PTSD: post-traumatic stress disorder: OCD: oppositional defiant disorder.

Self-harm (Taylor et al., 2015) and suicide attempts (Taylor et al., 2015) are also prevalent. Importantly, non-psychotic comorbid disorders and a family history of psychiatric disorders have been identified as risk factors associated with suicide in the CHR-P population (Pontillo et al., 2020).

Several longitudinal trajectories are possible in CHR-P individuals, each likely associated with a different prognosis. Some individuals may reach remission, although some of them may also relapse. Others continue experiencing poor mental health outcomes, including psychopathological outcomes and decreased functioning. Finally, some may transition to psychosis (see Figure 4). In this state, complete remission is less likely to occur.

Figure 4. Longitudinal trajectories in CHR-P individuals



The study of outcomes in individuals at risk of developing AFP has been developed in parallel. In particular, the study of the bipolar prodrome has slowly gained traction. It has been meta-analytically reported that the bipolar prodrome may last 27 months (Van Meter et al., 2016). During this period, mood and affective symptoms, but also subthreshold psychotic symptoms, may appear (Correll et al., 2014). However, only a minority (11%) of CHR-P individuals develop an affective psychotic disorder (Fusar-Poli et al., 2013a).

Other individuals at increased risk of developing AFP, different from the individuals at CHR-P, play an essential role in the transition to bipolar affective psychosis. After two years of follow-up, 25% of the individuals with BD-NOS (considered in the late prodromal period) develop bipolar I or II disorder (Birmaher et al., 2006). This proportion increased to 38% after four years (Birmaher et al., 2009). Additionally, 22.5% of adolescents with major depressive disorder followed up for 12-18 years developed BD (Ratheesh et al., 2017). This transition risk was particularly high in the first five years (Ratheesh et al., 2017). To date, conversion rates and patterns in individuals diagnosed with mood disorder NOS have not been reported (Hauser and Correll, 2013).

Several factors may influence these conversion rates. For instance, individuals with comorbid subclinical psychosis among individuals with subclinical mania transition to a bipolar disorder more frequently than those without psychosis (Kaymaz et al., 2007). Other risk factors for transition from MDD to BD have been identified: earlier age of onset of depression (g=-0.33), a family history of BD

(OR=2.9), and the presence of psychotic symptoms (OR=4.8) (Ratheesh et al., 2017).

Finally, among the outcomes that individuals with psychosis and individuals at risk of developing psychotic disorders may suffer, physical health outcomes should be considered. Coronary heart diseases and cerebrovascular diseases, among other physical conditions, appear more frequently in these individuals than in the general population (Correll et al., 2017). The early phase of psychosis is considered a critical period for acquiring and preventing cardiometabolic risk (Carney et al., 2016). This consideration is important for both individuals at risk of developing affective and non-affective psychosis. By systematically monitoring cardiometabolic risk factors and by establishing early intervention strategies that improve physical health outcomes in these patients, this increased risk can be substantially reverted (Samaras et al., 2016). Thus, early detection and settlement of not only mental health but also physical health strategies that target cardiometabolic risk factors may have an impact on physical health outcomes, including mortality.

Antipsychotics are associated with metabolic disturbances, particularly some of them (e.g., olanzapine and clozapine) (Pillinger et al., 2020). The response to antipsychotic medication is better in the earlier stages of psychotic disorders. Besides, individuals at risk of developing psychotic disorders are more likely to receive psychosocial interventions as clinical monitoring or psychological interventions (Yung et al., 1996). However, they are less likely to receive high

doses of antipsychotics with significant side effects (see 1.8 in this doctoral dissertation).

In spite of this, antipsychotics are commonly used in some young people at risk of developing psychotic disorders (Gerstenberg et al., 2015), even in adolescents.

1.7. PRECISION MEDICINE

Precision medicine is an emerging approach for disease detection, prognostication, prevention, and intervention (Fusar-Poli et al., 2018c). The main rationale is that each patient is different: their environment and lifestyle are different, and they have different genes (Genetics Reference, 2019). This variability has been studied in prediction models and risk calculators. Prediction models can be used to prognosticate at an individual level the probability of a determinant disorder being present (diagnostic models), the likelihood of a particular outcome to happen (prognostic models), or the probability of observing a determined response to an intervention (predictive models) (Salazar de Pablo et al., 2020d). The need to personalize preventive interventions for psychotic disorders (Davies et al., 2018a) has stimulated the investigation on prediction models. The main objective of prediction models is to forecast outcomes in subgroups of patients (stratified medicine) or at the individual subject level (precision medicine). The development of clinical prediction models may enable stratified and precision medicine approaches to individualize treatments for these patients.

The most frequently evaluated outcome in individuals at risk of developing psychotic disorders has been the transition to psychosis, particularly in CHR-P individuals (Cannon et al., 2016, Fusar-Poli et al., 2017c, Koutsouleris et al., 2020, Oliver et al., 2020, Sanfelici et al., 2020, Lee et al., 2020, Perkins et al., 2020). However, while a plethora of prediction models have been developed, none of them has been fully implemented into the clinical routine (Salazar de

Pablo et al., 2020d). Only two prediction models have evaluated other outcomes in CHR-P individuals, the first one using MRI measures in CHR-P adolescents to predict their long-term clinical outcomes and level of functioning (de Wit et al., 2017), and the second one combining clinical and imaging-based variables to predict social and role functioning (Koutsouleris et al., 2018).

A further risk calculator for the offspring of patients with bipolar disorder detected the following predictors for developing bipolar disorder: psychosocial functioning; parental age at mood disorder; dimensional measures of mania, depression, anxiety and mood lability (Hafeman et al., 2017). These prediction models and precision psychiatry may ultimately facilitate obtaining essential information on which patients are at high risk of developing poor mental health outcomes and the best way to address this risk therapeutically. For that, a comprehensive characterization of the predictors most frequently used and with the most robust evidence of an association with poor mental health outcomes is essential.

Precision medicine and psychiatry also face some challenges for the patients (e.g., accepting the outputs of the risk calculators), clinicians (e.g., adhere to the recommendations made by risk prediction models), providers (e.g., confidentiality and accessibility of data), and organizations (e.g., implementing an infrastructure that enables risk prediction procedure).

1.8. PREVENTIVE INTERVENTIONS FOR INDIVIDUALS AT RISK OF DEVELOPING PSYCHOTIC DISORDERS

It is essential to disentangle who should access and who would benefit more from preventive interventions (Fusar-Poli et al., 2019a) and the type of outreach and referrals that may lead to an appropriate level of psychosis risk (pre-test risk) for individuals that undergo CHR-P assessments (Fusar-Poli et al., 2018d, Fusar-Poli et al., 2016e). Interventions aim to prevent or delay psychosis onset (Fusar-Poli et al., 2013a) but also reduce complications, reduce the duration of untreated psychosis (see point 1.10 of this doctoral dissertation), and improve functioning in CHR-P individuals (Schultze-Lutter et al., 2015, Addington et al., 2017a, Fusar-Poli et al., 2017a).

In research settings, several clinical trials have been conducted. One peculiarity is that interventions in the CHR-P field are frequently compared against need-based interventions. Need-based interventions have been defined as the interventions that encompass supportive psychotherapy (focusing on social relationships and vocational or family problems), case management (providing psychosocial assistance with accommodation, education, or employment), or brief family psychoeducation and support (Salazar de Pablo et al., 2021b). Arguably, need-based Interventions could be considered active interventions.

The first double-blind, placebo-controlled RCT developed in the CHR-P field compared a combination of risperidone and cognitive behavioral therapy (CBT) with need-based interventions (McGorry et al., 2002). Since then, different

interventions have evaluated pharmacological interventions as well as psychosocial interventions.

Within the pharmacological interventions, second-generation antipsychotics have been the most frequently evaluated. Administration of olanzapine led to an improvement in attenuated psychotic symptoms compared to placebo after eight weeks (Woods et al., 2003). However, in the longer-term, statistically significant differences were not found between the groups in the severity of attenuated psychotic symptoms or the transition to psychosis (McGlashan et al., 2006). Amisulpride improved attenuated psychotic symptoms, global functioning, depressive symptoms, negative symptoms, and basic symptoms compared to placebo (Ruhrmann et al., 2007). Ziprasidone was also able to improve attenuated psychotic symptoms but did not decrease the number of transitions to psychosis (Woods et al., 2017).

Similarly, in an open-label pilot study, aripiprazole reduced attenuated psychotic symptoms (Woods et al., 2007). Interestingly, a naturalistic study found significantly higher transition rates in patients treated with antipsychotics than in patients treated with antidepressants (Cornblatt et al., 2007). However, transitions were associated with antipsychotic nonadherence (Cornblatt et al., 2007), so further research is needed.

Other experimental treatments have been used, particularly omega-3 (Amminger et al., 2010, Amminger et al., 2015, Cadenhead et al., 2017, McGorry et al., 2017). Results, however, have been conflicting. While a study found a reduced risk of transition, reduced positive and negative symptoms, and improved

functioning in the omega-3 group compared to the placebo group (Amminger et al., 2015), other studies did not replicate these positive results (Cadenhead et al., 2017, McGorry et al., 2017). D-serine led to a significant reduction in negative symptoms compared to placebo after 16 weeks (Kantrowitz et al., 2015); N-acetylcysteine has been piloted as well (Miyake et al., 2016). Still, the evidence on their efficacy (or lack of efficacy) is scarce.

Within the psychosocial interventions, CBT has been the most studied (Morrison et al., 2012). Enhanced CBT with psychoeducation for six months reduced transition to psychosis and the distress associated with psychotic symptoms compared to treatment as usual (van der Gaag et al., 2012). In another study, CBT plus monitoring was compared to monitoring only (Morrison et al., 2012). Although the number of transitions to psychosis was not reduced, the severity of psychotic symptoms improved at 12 months in the CBT group (Morrison et al., 2012). Another study found no differences between CBT, placebo, or aripiprazole in the transition to psychosis rates (Bechdolf et al., 2017). Other psychosocial interventions have been piloted, including cognitive remediation (Loewy et al., 2016), integrated psychological interventions (Bechdolf et al., 2012), and family-focused therapy (Miklowitz et al., 2014, Landa et al., 2016).

For individuals at risk of developing bipolar disorders, pharmacological and psychosocial interventions have been studied as well. In youths with cyclothymia and BD-NOS, a double-blind placebo-controlled trial of aripiprazole found reduced symptoms of mania in children and adolescents (Findling et al., 2017). In another study, valproate did not improve mood symptoms or psychosocial

functioning over time compared to placebo in young people at high risk for developing bipolar disorder (Findling et al., 2007). Quetiapine also showed preliminary efficacy for mood symptoms in individuals at risk of developing bipolar disorder (DelBello et al., 2007).

For the same group of youths with cyclothymia and BD-NOS, “individual family psychoeducational psychotherapy” plus omega-3 reduced depressive symptoms but not manic symptoms (Fristad et al., 2015). Among other psychosocial interventions, family-focused therapy (Miklowitz et al., 2020), mindfulness-based cognitive therapy (Cotton et al., 2020, Strawn et al., 2016), and “interpersonal and social rhythm therapy” (Goldstein et al., 2014) have been piloted, among others, in individuals at risk of developing bipolar disorder, with variable/ inconclusive results.

At the moment, interventions for individuals at risk of developing psychotic disorders are usually carried out in specialized services, which are expanding globally (Kotlicka-Antczak et al., 2020). An early intervention service is a multidisciplinary community mental health service that provides treatment and support to people experiencing or at high risk of developing psychosis (NHS-England, 2016). Early intervention consists of two components that the same service may deliver: early detection during the initial phases of the illness and early intervention to positively impact the illness and reduce the DUP, among other outcomes (McDaid et al., 2016). Prevention of psychosis clinical services should provide both (Fusar-Poli et al., 2020b) as well as treatment and support to people at risk of developing psychotic disorders (NHS-England, 2016).

Interventions provided in these services vary. For instance, in “Outreach and Support in South London” (OASIS), Europe's largest prevention of psychosis service and one of the oldest in the world, 69.8% of CHR-P individuals were treated with CBT, 46.2% with antidepressants, and 39.2% with antipsychotics (Fusar-Poli et al., 2020c). The knowledge regarding CHR-P services has been limited, and guidelines for translational implementation scarce. However, the configuration, outreach strategy and referrals, service user characteristics, interventions and outcomes in these clinical services are essential.

1.9. PREVENTION OF PSYCHOTIC DISORDERS IN ADOLESCENTS

The prevalence of mental conditions has been estimated to be more than 13% in children and adolescents (Polanczyk et al., 2015). Furthermore, once established, mental disorders have negative effects on young people's functioning and quality of life (Catalan et al., 2020). Additionally, they result in a substantial economic burden on our society (Fatori et al., 2018).

One-third of psychotic disorders have an onset before 18 years (Madaan et al., 2008). Besides, the prevalence of psychotic symptoms is also high: around 7.5% in adolescents (Kelleher et al., 2012a). However, most evidence in the prevention of psychotic disorders field in individuals at risk has been developed either in adult populations or in populations with a low % of adolescents. Additionally, studies in CHR-P children and adolescents report inconclusive findings across the mainstream clinical research areas: characterization/diagnosis, prognosis, and intervention (Welsh and Tiffin, 2014, Schlosser et al., 2012). Besides, the evidence on individuals at risk of developing psychotic disorders is even more limited in adolescents. Few efforts have been made to characterize and describe DSM-5–APS, excluding other risk criteria, and advance knowledge specifically in adolescents.

1.9.1. Characterization

CHR-P criteria appear to be frequently met in clinical populations of adolescents (Gerstenberg et al., 2015). CHR-P adolescents suffer a broad range of clinical symptoms and disorders, including affective features (Pelizza et al., 2020), impulse-control disorders (Gerstenberg et al., 2015), and personality disorder traits (Gerstenberg et al., 2015). Negative symptoms are also frequent and comparable to adolescents with FEP (Pelizza et al., 2020).

Suicidal ideation is common in adolescents at CHR-P, and suicide attempts more frequent than in adolescents not fulfilling these criteria (Pelizza et al., 2019b). According to a recent study, 7.5% of the UHR adolescents had engaged in suicidal ideation, some of them suffering severe suicidal behaviors (Poletti et al., 2019, Pelizza et al., 2020). Self-injurious behaviors are particularly common in CHR-P adolescents (Taylor et al., 2015). It has been suggested that high levels of suicidality in CHR-P adolescents and young adults might precede the onset of frank psychosis (Taylor et al., 2015).

Adolescents at CHR-P suffer traumatic events more frequently than healthy controls (Morelli et al., 2019). They have worse socioeconomic status, premorbid academic performance, and global functioning than healthy controls (Dolz et al., 2018). They also show poorer social adjustment (Simeonova et al., 2015) and poorer quality of life (Nitka et al., 2016) than individuals who are not at CHR-P.

Lower IQ scores have been found in CHR-P adolescents compared to controls (Ziermans et al., 2014). Adolescents at CHR-P have mild to moderate impairments in neurocognitive performance (Koren et al., 2019), maladaptive metacognitive beliefs (Welsh et al., 2014), and impairments in labeling facial expressions of others (van Rijn et al., 2011a). CHR-P adolescents also have difficulties identifying and verbalizing their emotions (van Rijn et al., 2011c). Furthermore, CHR-P adolescents show neurological soft signs (Pitzianti et al., 2019), increased stress and cortisol secretion (Moskow et al., 2016), and low testosterone levels (van Rijn et al., 2011b).

Bipolar spectrum disorders beginning in childhood/adolescence can be challenging to diagnose due to the symptomatic overlap with other childhood disorders, including ADHD, oppositional defiant disorder (ODD), unipolar depression, and anxiety (Youngstrom et al., 2008). Symptoms of mania are common in children and adolescents with bipolar spectrum disorders, particularly increased energy, distractibility, and pressured speech (Van Meter et al., 2016, Kowatch et al., 2005). Furthermore, adolescents at risk of developing bipolar disorders suffer impaired functionality and quality of life (Luby and Navsaria, 2010, Carlson and Pataki, 2016). Suicide attempts and suicide are also frequent (Goldstein et al., 2005).

Levels of clinical severity, including suicidality and psychosis, appear to be similar in BD-NOS, BD-II. and BD-I, in line with evidence on the bipolar spectrum disorders continuum (Hirneth et al., 2015). Instruments that not only evaluate the

presence of symptoms but rate their severity might be able to detect more subtle differences between the groups.

1.9.2. Prognosis

The validation of different psychometric instruments in CHR-P individuals has been attempted, including tools to characterize both main CHR-P criteria: UHR criteria (Pelizza et al., 2019a, Spada et al., 2016) and BS (Fux et al., 2013). Also, the validation of instruments for global functioning have been piloted (Lo Cascio et al., 2017). The most commonly evaluated outcome in CHR-P individuals has been the transition to psychosis, but rates have been variable (Poletti et al., 2019, Pelizza et al., 2018, Spada et al., 2016).

While many adolescents show improvements in symptoms after two years (Welsh and Tiffin, 2014), less than half appear to remit from the CHR-P state (Ziermans et al., 2011). Baseline characteristics do not clearly differ between individuals who remit and those who do not (de Wit et al., 2014), which complicates detecting those who might be at particularly high risk or may need particularly intensive clinical care. However, it seems that higher SIPS scores (Simeonova et al., 2011) and lower IQ might predict conversion to psychosis, while no other neurocognitive variables seem to discriminate between the groups (Ziermans et al., 2014). A higher rate of BLIPS has also been associated with higher conversion risk in children and adolescents at CHR-P (Armando et al., 2015).

Youths with bipolar spectrum disorders are more time symptomatic and have more mixed/cycling episodes, mood symptom changes, and polarity switches compared to adults (Birmaher et al., 2006). Early age of onset was found to be associated with longer delays to treatment, greater severity of depression (Hedges' g=0.42), and higher levels of comorbid anxiety (OR=2.34) and substance use (OR=1.80) in bipolar disorder. However, no association has been found between early age of onset and clinical characteristics such as psychotic symptoms or mixed episodes as defined by the DSM-IV (Joslyn et al., 2016).

1.9.3. Therapeutic factors

Few clinical or therapeutic trials, particularly RCTs, have been conducted in adolescents at risk of developing psychotic disorders. In CHR-P individuals, one clinical trial found that a community-oriented family-based intervention was associated with improved functioning and affective symptoms compared with adolescent psychiatric treatment (Grano et al., 2016). Another trial found an improvement in visuospatial abilities but not in attention, memory, or psychopathology when comparing computer-assisted cognitive remediation with regular computer games in CHR-P individuals (Holzer et al., 2014). Finally, family-focused therapy was associated with a greater improvement in attenuated psychotic symptoms than a brief intervention oriented toward symptom prevention after six months. However, no differences between the groups were found in social and role functioning (Miklowitz et al., 2014).

Although adolescents are frequently included along with young adults in CHR-P services (Fusar-Poli et al., 2013c, Pelizza et al., 2020, Nelson et al., 2013), early intervention services for adolescents at CHR-P are not common. One early intervention service did describe the clinical care they provided for adolescents (Tiffin and Hudson, 2007). This care included an initial assessment and a specialist assessment before the CHR-P designation was established. Once adolescents were accepted into the service, the care coordination included psychoeducation, substance misuse work, family work, CBT, supportive counseling, relaxation training, and social skills. A low-dose antipsychotic trial was also considered, including either 25–75mg quetiapine or 0.5–1mg risperidone twice a day (Tiffin and Hudson, 2007).

In individuals at risk of developing bipolar disorder, one RCT, including only adolescents, evaluated the efficacy of a combination of interpersonal and social rhythm therapy, with promising results (Goldstein et al., 2018). To our knowledge, six further RCTs conducted in children and adolescents at risk of developing bipolar disorders have evaluated the efficacy of other interventions (Saraf et al., 2020). Within pharmacological interventions, these included lithium (Geller et al., 1998), valproate (Findling et al., 2007), and aripiprazole (Findling et al., 2017); within psychological interventions, two studies evaluated family-focused therapy (Miklowitz et al., 2013, Miklowitz et al., 2020). A further study looked at the efficacy of psychoeducation and omega-3, comparing them separately and altogether with placebo and active monitoring (Fristad et al., 2015). Further research is needed to identify which are the most effective interventions.

1.10. DURATION OF UNTREATED PSYCHOSIS

Delays in access to clinical care are frequent at the moment until an appropriate intervention is provided, even in individuals with established psychotic disorders (Perkins et al., 2005, Lloyd-Evans et al., 2011). Duration of untreated psychosis (DUP) is defined as the period between the onset of psychosis and the start of treatment (Hegelstad et al., 2012). DUP is an important prognostic factor that has been associated with poor mental health outcomes (Howes et al., 2021), highlighting the importance of an early (if possible preventive) intervention. According to a recent umbrella review, there is highly suggestive evidence for a relationship between longer DUP and more severe positive symptoms, more severe negative symptoms, and lower remission (Howes et al., 2021). Furthermore, there is suggestive evidence for the association of longer DUP with poorer overall functioning and more severe global psychopathology (Howes et al., 2021).

The World Health Organization and the International Early Psychosis Association produced a consensus statement fifteen years ago. They recommended active efforts to reduce mean DUP to less than three months in individuals with a FEP (Bertolote and McGorry, 2005). However, meta-analytical evidence reported mean DUPs way over this threshold (61.3 weeks) (Penttila et al., 2014). DUP distribution is usually skewed as there are some individuals with very long DUP, which are challenging to detect with current strategies (Johannessen et al., 2001).

Implementing services for individuals at risk of developing psychotic disorders has been considered the most effective method for lowering DUP (Oliver et al.

, 2018), since individuals can receive preventive interventions before they transition to psychosis. Furthermore, the detection of individuals at CHR-P and the development of preventive interventions can maximize the benefits of early intervention in psychosis (Correll et al., 2018, Fusar-Poli et al., 2017b). However, currently, only a small proportion of FEP had been previously seen at CHR-P services (Ajnakina et al., 2017), so additional strategies to impact DUP are needed.

Efforts to intervene in individuals with clinical syndromes that put them at high risk of developing affective or non-affective psychotic disorders have the potential to intervene before the consequences of DUP occur and potentially relieve other poor mental health outcomes (Fusar-Poli et al., 2013b, Lencz et al., 2004, Addington et al., 2008, Bechdolf et al., 2005) and promote good mental health (Petros et al., 2020).

OBJECTIVES

2. OBJECTIVES

A. Provide state-of-the-art evidence on the CHR-P paradigm and the prevention of psychotic disorders' field by reviewing the advances in the characterization, prognostic and therapeutic factors, both in adult populations and adolescents.

B. Evaluate with prodromal symptom scales the proportion of non-psychotic adolescents admitted into an inpatient unit who meet Attenuated Psychosis Syndrome criteria. Compare their sociodemographic, illness, and intervention peculiarities with other adolescents admitted into the same inpatient unit without that designation.

C. Evaluate a clinical sample of adolescents with bipolar spectrum disorders, including adolescents at-risk of developing bipolar disorder type I, with scales designed to characterize the bipolar prodrome. Describe their sociodemographic, illness, and intervention peculiarities and compare them with adolescents with bipolar disorder type I.

D. Provide current evidence on the clinical validity of DSM-5 Attenuated Psychosis Syndrome, recently introduced into the DSM-5. Assess the most recent advances in diagnosis, prognosis, and treatment in individuals with DSM-5 Attenuated Psychosis Syndrome and closely related criteria.

E. Evaluate the prognosis of individuals at risk of developing psychotic disorders, providing transition to psychosis rates for individuals with DSM-5 Attenuated Psychosis Syndrome, individuals with Brief Limited Intermittent Psychotic Symptoms, and adolescents at CHR-P.

HYPOTHESIS

3. HYPOTHESIS

A. Advances in the characterization and prognostic factors in CHR-P individuals will be substantial, while therapeutic advances will be limited. Some of the clinical characteristics including comorbidity rates and the prognosis including transition rates will be similar in adult populations and adolescents. Families will have a particularly important role in adolescents.

B. Adolescents with Attenuated Psychosis Syndrome will represent a significant proportion of the adolescents with non-psychotic psychiatric disorders admitted into an inpatient unit. They will have more comorbid conditions and will be more clinically and functionally impaired than adolescents not fulfilling these criteria.

C. Adolescents at risk of developing bipolar disorder type I (fulfilling BD-NOS or MD-NOS criteria), admitted into an inpatient unit, will report relevant threshold and subthreshold affective and psychotic symptoms as well as clinical and functional impairment. Some of these symptoms will be less severe compared to adolescents with BD-I.

D. We expect to confirm the potential clinical validity of DSM-5 Attenuated Psychosis Syndrome by summarizing the evidence on antecedent, concurrent, and prognostic validators. We expect concurrent and

prognostic validation from the psychosis prevention research field to be substantial for this syndrome.

E. The meta-analytical risk of transition to psychosis will be significant in CHR-P individuals, including those meeting DSM-5 Attenuated Psychosis Syndrome criteria. The risk will be particularly high in individuals with Brief Limited Intermittent Psychotic Symptoms and similar to DSM-5 Attenuated Psychosis Syndrome in CHR-P adolescents.

METHODS

4. METHODS

This thesis incorporates several manuscripts authored by the doctoral student.

The main publications that contain the core of this dissertation include two original articles and one systematic review and meta-analysis.

In addition, to provide a more comprehensive view of the work carried out by the doctoral student in the field during this period, two additional systematic reviews and meta-analyses, one systematic review and meta-regression, one systematic review, and one umbrella review are presented and discussed.

All the publications, including the complementary publications (annexes 5-9), were published during the doctorate, fulfill the authorship criteria, and have been published or accepted before the presentation of this dissertation.

A summary of the methodology of the main articles of the doctoral thesis can be found below.

PUBLICATION 1

Salazar de Pablo G, Guinart D, Cornblatt BA, Auther AM, Carrión RE, Carbon M, Jiménez-Fernández S, Vernal DL, Walitza S, Gerstenberg M, Saba R, Lo Cascio N, Brandizzi M, Arango C, Moreno C, Van Meter D, Fusar-Poli P, Correll CU. DSM-5 Attenuated Psychosis Syndrome in Adolescents Hospitalized With Non-psychotic Psychiatric Disorders Front. Psychiatry Oct 21;11:568982.

The "Adolescent Mood Disorder and Psychosis Study" (AMDPS) is an ongoing study interviewing help-seeking, hospitalized adolescents (aged 12–18 years) and their caregivers at the Adolescent Child and Adolescent Inpatient Unit at the Zucker Hillside Hospital, New York, USA, using established research instruments.

Diagnoses were established in research consensus conferences and confirmed by the study lead. DSM-5 clinical criteria and SIPS, a semi-structured interview to diagnose psychosis-risk syndromes, were used. Additional rating scales included the "Clinical Global Impression– Severity" (CGI-S) scale to assess the overall severity of illness, the GAF to assess global functioning, the "Global Functioning: Social" and the "Global Functioning: Role" to assess social and role functioning, and the "Scale to Assess Unawareness of Mental Disorder" to assess insight.

First, we evaluated the presence of DSM-5–APS among non-psychotic adolescents. Second, we compared adolescents fulfilling DSM-5–APS criteria and adolescents not fulfilling DSM-5–APS criteria regarding sociodemographic,

illness, and intervention characteristics. Third, we correlated psychopathology with levels of functioning and severity of illness. Finally, we investigated the influence of individual clinical, functional, and comorbidity variables on the likelihood of participants to be diagnosed with DSM-5–APS.

PUBLICATION 2

Salazar de Pablo G, Guinart D, Cornblatt BA, Auther AM, Carrión RE, Carbon M, Jiménez-Fernández S, Vernal DL, Walitza S, Gerstenberg M, Saba R, Lo Cascio N, Brandizzi M, Arango C, Moreno C, Van Meter A, Correll CU. Demographic and Clinical Characteristics, Including Subsyndromal Symptoms Across Bipolar-Spectrum Disorders in Adolescents. J Child Adolesc Psychopharmacol. 2020 May;30(4):222-234.

This study recruited adolescents (age: 12–18 years) with bipolar spectrum disorders, between September 2009 and July 2017, from the adolescent inpatient unit at the "Zucker Hillside Hospital," from the ongoing "Adolescent Mood and Psychosis Study" (AMDPS), an observational study aiming to characterize the bipolar prodrome prospectively.

Inclusion criteria were as follows: (1) age: 12–18 years; (2) research diagnosis, using the SCID and the K-SADS-PL of either (a) BD-1, (b) BD-NOS, or (c) MD-NOS; (3) currently admitted into a psychiatric hospital; (4) subject and parent (if subject <18 years) willing and able to provide written, informed consent/assent. Exclusion criteria were: (1) an estimated premorbid IQ <70; (2) fulfilling DSM-IV criteria for pervasive developmental disorder or autism spectrum disorders; (3) a history of any medical condition known to affect the brain.

Assessments included the validated BPSS-P to evaluate syndromal and subsyndromal psychopathology. We compared phenomenology across patients with a research consensus conference-confirmed DSM-IV diagnoses of BD-I,

BD-NOS, or MD-NOS. Additional rating scales were administered to adolescents and their caregivers. They included the CGI-S for overall severity of illness, the GAF for functioning, the “Montgomery Åsberg Depression Rating Scale” (MADRS) for symptoms of depression, and the “Young Mania Rating Scale” (YMRS) for symptoms of mania.

PUBLICATION 3

Salazar de Pablo G, Catalan A, Fusar-Poli P. Clinical Validity of DSM-5 Attenuated Psychosis Syndrome: Advances in Diagnosis, Prognosis, and Treatment. JAMA Psychiatry. 2020 Mar 1;77(3):311-320.

A literature search of the Web of Science database, the Cochrane Central Register of Reviews, Ovid/PsychINFO, conference proceedings, and trial registries from inception until June 2019 was conducted. This systematic review follows the “Preferred Reporting Items for Systematic Reviews and Meta-analyses” (PRISMA) and the “Meta-analysis of Observational Studies in Epidemiology” (MOOSE) reporting guidelines.

The following inclusion criteria were used: (1) original studies with no restriction on the topic investigated; (2) conducted in individuals meeting DSM-5–APS criteria, SIPS-APSS operationalization, or SIPS version 5.6 operationalization of DSM-5–APS criteria; (3) published in English. The following exclusion criteria were used: (1) reviews, editorials, or clinical cases; (2) unpublished data; (3) studies measuring other operationalizations; (4) studies that do not report specific information on the SIPS-APSS or CAARMS-APS group alone but reported composite results.

The results of the systematic review were narratively synthesized against established evidence-based validators, including antecedent validators, concurrent validators, and prognostic validators.

A random-effects meta-analysis was conducted to explore the cumulative risk of psychosis onset at 6, 12, 24, and ≥36 months in individuals with DSM-5–APS. Publication bias was assessed with the metafunnel and with the Egger test. Heterogeneity among study point estimates was assessed using Q statistics. The proportion of the total variability in the effect size estimates was evaluated with the I^2 index. Meta-regressions were planned when there was substantial heterogeneity (>50%) and at least ten studies per each outcome. P values were 2-sided, and the level of significance was set at a $p<0.05$.

PUBLICATIONS

5. PUBLICATIONS

5.1. PUBLICATION 1

Salazar de Pablo G, Guinart D, Cornblatt BA, Auther AM, Carrión RE, Carbon M, Jiménez-Fernández S, Vernal DL, Walitza S, Gerstenberg M, Saba R, Lo Cascio N, Brandizzi M, Arango C, Moreno C, Van Meter D, Fusar-Poli P, Correll CU. DSM-5 Attenuated Psychosis Syndrome in Adolescents Hospitalized With Non-psychotic Psychiatric Disorders Front. Psychiatry Oct 21;11:568982. doi:10.3389/fpsyt.2020.5689.

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DSM-5 Attenuated Psychosis Syndrome in Adolescents Hospitalized With Non-psychotic Psychiatric Disorders

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Introduction: Although attenuated psychotic symptoms often occur for the first time during adolescence, studies focusing on adolescents are scarce. Attenuated psychotic symptoms form the criteria to identify individuals at increased clinical risk of developing psychosis. The study of individuals with these symptoms has led to the release of the DSM-5 diagnosis of Attenuated Psychosis Syndrome (APS) as a condition for further research. We aimed to characterize and compare hospitalized adolescents with DSM-5-APS diagnosis vs. hospitalized adolescents without a DSM-5-APS diagnosis.

Methods: Interviewing help-seeking, hospitalized adolescents (aged 12–18 years) and their caregivers independently with established research instruments, we (1) evaluated the presence of APS among non-psychotic adolescents, (2) characterized and compared APS and non-APS individuals regarding sociodemographic, illness and intervention characteristics, (3) correlated psychopathology with levels of functioning and severity of illness and (4) investigated the influence of individual clinical, functional and comorbidity variables on the likelihood of participants to be diagnosed with APS.

Results: Among 248 consecutively recruited adolescents (age=15.4 ± 1.5 years, females = 69.6%) with non-psychotic psychiatric disorders, 65 (26.2%) fulfilled APS criteria and 183 (73.8%) did not fulfill them. Adolescents with APS had higher number

of psychiatric disorders than non-APS adolescents (3.5 vs. 2.4, $p < 0.001$; Cohen's d = 0.77), particularly, disruptive behavior disorders (Cramer's V = 0.16), personality disorder traits (Cramer's V = 0.26), anxiety disorders (Cramer's V = 0.15), and eating disorders (Cramer's V = 0.16). Adolescents with APS scored higher on positive (Cohen's d = 1.5), negative (Cohen's d = 0.55), disorganized (Cohen's d = 0.51), and general symptoms (Cohen's d = 0.84), and were more severely ill (Cohen's d = 1.0) and functionally impaired (Cohen's d = 0.31). Negative symptoms were associated with lower functional levels (Pearson $\rho = -0.17$ to -0.20; $p = 0.014$ to 0.031). Global illness severity was associated with higher positive, negative, and general symptoms (Pearson $\rho = 0.22$ to 0.46; $p = 0.04$ to $p < 0.001$). APS status was independently associated with perceptual abnormalities (OR = 2.0; 95% CI = 1.6–2.5, $p < 0.001$), number of psychiatric diagnoses (OR = 1.5; 95% CI = 1.2–2.0, $p = 0.002$), and impaired stress tolerance (OR = 1.4; 95% CI = 1.1–1.7, $p = 0.002$) ($r^2 = 0.315$, $p < 0.001$).

Conclusions: A considerable number of adolescents hospitalized with non-psychotic psychiatric disorders meet DSM-5-APS criteria. These help-seeking adolescents have more comorbid disorders and more severe symptoms, functional impairment, and severity of illness than non-APS adolescents. Thus, they warrant high intensity clinical care.

Keywords: Attenuated Psychosis Syndrome (APS), adolescence, epidemiology, risk, psychosis, prevention

INTRODUCTION

Psychotic disorders, such as schizophrenia, are usually preceded by a clinical high-risk for psychosis (CHR-P) state (1), which is characterized by subtle symptoms, functional impairment and help-seeking behavior (2–4), as well as non-psychotic comorbidity (5, 6). The CHR-P state, which includes individuals at ultra-high risk for psychosis and/or those with basic symptoms, has allowed preventive efforts to be implemented (7, 8). This area of clinical research has grown until it has become one of the most established preventive approaches in psychiatry (7, 8).

The achievements and challenges of the CHR-P paradigm have been recently appraised by an umbrella review (9). In brief, three CHR-P subgroups have been established: attenuated psychotic symptoms; brief limited and intermittent psychotic symptoms (BLIPS) and genetic risk and deterioration (GRD) syndrome (9, 10). There are substantial diagnostic (11), prognostic (10, 12), clinical (13), and therapeutic (14) differences across these three subgroups. For example, psychosis risk is higher in the BLIPS group (38%) than in the attenuated psychotic symptoms group (24%) and higher in both groups than in the GRD group (8%) at >48 months follow-up (10).

Although most research and clinical studies have evaluated the three groups together (15–17), the most common group by far is the attenuated psychotic symptoms group, which includes 85% of CHR-P individuals (10). Psychosis-risk syndromes, including attenuated psychotic symptoms, are usually characterized using semi-structured interviews as the Structured Interview for Psychosis-Risk Syndromes (SIPS) (18, 19) or the Comprehensive Assessment of At-Risk Mental States (CAARMS) (1), which have comparable prognostic accuracy (20). In the SIPS, the characterization used is Attenuated Positive Symptoms Syndrome (APSS). Seven years ago, the DSM-5 introduced the Attenuated Psychosis Syndrome (APS) diagnosis in the research appendix, listed in both section II and section III (21) (**Figure 1**). This diagnosis is defined by the presence of delusions, hallucinations, or disorganized speech in attenuated form, but with sufficient severity and frequency to warrant clinical attention (23, 24) (**Figure 1**). The diagnostic, prognostic, and therapeutic characteristics of this diagnosis have been recently appraised by a systematic review and meta-analysis (21). This review concluded that DSM-5-APS criteria have received substantial concurrent and prognostic validation, mostly driven by research in adult populations (21). A previous study looking at the agreement between CAARMS and DSM-5-APS criteria found that the agreement was only moderate (kappa 0.59) (25). Meanwhile, as findings from other studies point out (26, 27), SIPS and DSM criteria for APS are more similar (**Figure 1**).

While most reports to date on APS are based on cohorts that also include adults (25, 28–30), APS features often occur for the first time in adolescence (31, 32). Broadly speaking, studies that focus on DSM-5-APS in adolescents are scarce (21, 22), and there are few studies on APS in adolescents in clinical care and hospital settings.

To our knowledge, only a few efforts have been made (22, 33, 34) to characterize APS, excluding other ultra-high risk criteria, and advance knowledge specifically in children and adolescents, comparing them to other help-seeking individuals. Among them, 22 APS individuals were compared to other treatment-seeking individuals and healthy controls regarding clinical and cognitive features (34), finding that APS was associated with impaired

Criteria	DSM-5-APS Section III (American Psychiatric Association, 2013)	DSM-5-APS Section II (American Psychiatric Association, 2013)	APSS SIPS (Miller et al., 1999;Miller et al., 2003;McGlashan T, 2010)
Severity	A. At least one of the following symptoms is present in attenuated form, with relatively intact reality testing, and is of sufficient severity or frequency to warrant clinical attention: 1. Delusions 2. Hallucinations 3. Disorganized speech	Examples of presentations that can be specified using this designation include APS. This syndrome is defined by psychotic-like symptoms below a threshold for full psychosis (e.g., they are less severe and more transient, and insight is relatively maintained)	SOPS-positive symptom scales P1. unusual thought content, P2. suspiciousness, P3. grandiose ideas, P4. perceptual abnormalities, P5. disorganized communication, with at least one of these symptoms rated 3, 4, or 5 indicating clinically significant disturbance below a psychotic level of intensity
Frequency	B. Symptom(s) must have been present at least once per week for the past month	Not specified	Symptoms ever been present at an average frequency of at least once/week over a month
New onset and worsening	C. Symptom(s) must have begun or worsened in the past year	Not specified	Begin within the past year, or any currently rate one or more scale points higher compared to 12 months ago; rated only symptoms that occurred over the past month
Distress/disability	D. Symptom(s) is sufficiently distressing and disabling to the individual to warrant clinical attention	Symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.	Attenuated positive symptoms sufficiently distressing and disabling to the patient to warrant clinical attention
Differential diagnosis	E. Symptom(s) is not better explained by another mental disorder, including a depressive or bipolar disorder with psychotic features, and is not attributable to the physiological effects of a substance or another medical condition	Symptoms do not meet the full criteria for any of the disorders in the schizophrenia spectrum and other psychotic disorders diagnostic class	Symptoms ever not been explained better by another DSM disorder

FIGURE 1 | DSM-5-APS Attenuated Psychosis Syndrome diagnostic criteria compared with SIPS operationalization [adapted from (Gerstenberg et al. (22); Salazar De Pablo et al. (21)]. APS, Attenuated Psychosis Syndrome; APSS, Attenuated Positive Symptoms Syndrome; SIPS, Structured Interview for Psychosis-Risk Syndromes.

neurocognition. Also, APS was associated with self-reported internalizing problems and thought problems in a study with 7 APS adolescents (33). One further study without a comparison group found that an older age of APS presentation in adolescents (comparing 9–14 years vs. 15–18 years) was associated with better social and role functioning and fewer depressive symptoms (35).

There is little evidence on how many help-seeking adolescents accessing inpatient care meet APS criteria. Our preliminary data from the Adolescent Mood Disorder and Psychosis Study (AMDPS) clinical study compared the first 21 APS and 68 non-APS adolescents who were recruited and found that APS was present in 23.6% of psychiatrically hospitalized adolescents, who suffered from a broad range of psychiatric symptoms and disorders (22).

Although specific knowledge for APS is limited, CHR-P individuals show impairments in work, educational and social functioning as well as poor quality of life (9, 36). Furthermore, psychopathology can adversely influence functioning (37). Negative symptoms have been associated with functioning, both daily (38), work related (39) and real-world functioning (40). Among CHR-P individuals, the severity of attenuated positive and negative symptoms has been associated with some outcomes [e.g., transition to psychosis (9, 21)] but not with others [e.g., cannabis use (9)]. Our preliminary results showed that poorer functioning in adolescents with APS was associated with more severe attenuated positive, negative, and general symptoms (22).

In the CHR-P field, the influence of sociodemographic and clinical variables on diagnostic and treatment outcomes has been widely studied, particularly regarding the transition to psychosis (41–45). Unusual thought content and suspiciousness have been found to predict conversion to psychosis along with decline in social functioning, lower verbal learning and memory performance (46). However, there is no convincing evidence of the association between any variable and the onset of psychotic disorders according to a meta-analysis, and only attenuated positive psychotic symptoms and global functioning show suggestive evidence (47). The influence of demographic and clinical variables on the presence of APS, particularly in adolescents, is even less known. In the first 89 individuals recruited into AMDPS, lowest GAF score in the past year, and social isolation were independently associated with APS (22).

The current study analyzes the final sample of this cohort of hospitalized adolescents to (1) assess how many non-psychotic, help-seeking adolescents accessing inpatient care meet APS criteria, (2) describe and compare both groups regarding sociodemographic, illness and intervention characteristics, (3) correlate attenuated positive, negative, general and disorganized symptoms with the level of functioning and severity of illness, and (4) investigate the influence of individual clinical, functional and comorbidity variables, selected empirically, on the likelihood of participants to be diagnosed with APS.

Based on prior literature, we hypothesized that (1) a significant number of adolescents with non-psychotic psychiatric disorders would fulfill APS criteria, (2) APS individuals would report significant comorbidity, clinical burden and functional impairment that would exceed those of non-APS individuals, (3) severity of negative symptoms would be significantly associated with the level of functioning and severity of illness, and (4)

APS status would be associated with specific attenuated positive symptoms and other clinical variables.

MATERIALS AND METHODS

Design and Setting

AMDPS was registered at ClinicalTrials.gov (NCT01383915).

Participants were recruited consecutively into AMDPS between September 2009 and July 2017 from the Adolescent Child and Adolescent Inpatient Unit of The Zucker Hillside Hospital, New York, USA (48, 49). AMDPS is an ongoing, prospective study that aims to assess predictors of the development of bipolar disorder and psychotic disorders in hospitalized adolescents. Analyses for this study are restricted to baseline data. The protocol was approved by the Institutional Review Board of the North Shore-Long Island Jewish Health System in accordance with the Helsinki Declaration of 1975 and the UNESCO Universal Declaration on human rights. Written informed consent was obtained from subjects aged 18 or the guardians/legal representatives of minors, obtaining written assent from the minors.

Participants

Inclusion criteria for AMDPS study were: (1) age 12–18 years; (2) hospitalized at the adolescent inpatient unit of The Zucker Hillside Hospital, a self-standing psychiatric hospital; (3) admission chart diagnosis of any bipolar-spectrum disorder, cyclothymia, major depressive disorder, depressive disorder not otherwise specified (NOS), dysthymia or mood disorder NOS, schizophrenia, schizoaffective disorder, schizophreniform disorder or psychotic disorder NOS, re-evaluated by research interview, using the Structured Clinical Interview for DSM Disorders (SCID) (50), supplemented for missing pediatric diagnoses by the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version (K-SADS-PL) (51); (4) subject and guardian/caregiver (if subject<18) willing and able to provide written, informed consent/assent. Exclusion criteria were: (1) an estimated premorbid IQ<70; (2) DSM-5 clinical criteria for autism spectrum disorders or pervasive developmental disorder and (3) history of any neurological or medical condition known to affect the brain.

For the purpose of this study, we also excluded patients: (1) with a psychotic disorder according to DSM-5 criteria; (2) in whom the Structured Interview for Psychosis-Risk Syndromes, version 4.0 (52) was not completed (**Figure 2**).

Psychiatric diagnoses were established in diagnostic research consensus conferences based on in-person independent interview assessments of the adolescents and caregivers whenever possible. The interviews were typically conducted a few days after hospital admission. In consensus conferences, both assessments were integrated assuming that symptoms are more likely forgotten or hidden than invented or exaggerated. Also, SIPS items were discussed one by one for both interviews to reach to the correct value, and every psychiatric primary or comorbid diagnosis, including APS, was discussed among all the attendees and confirmed by the study lead (CUC). In order to conduct AMDPS assessments, experienced clinicians had to be certified by the study PI (CUC) after having gone through a structured training program, which involved observing several assessments, followed by conducting several assessments in front of one of the certified trainers, and presenting their ratings as part of a diagnostic consensus conference led by the study PI. All raters continually took part in the diagnostic consensus conference, during which all interview ratings were discussed and finalized as part of a group consensus, which served to assure validity of the ratings, facilitate interrater reliability via consensual rating, and avoid rater drift after completion of the initial training and certification.

Diagnostic Assessments

The Structured Interview for Psychosis-Risk Syndromes (SIPS) (18, 19) is a semi-structured interview used to diagnose psychosis-risk syndromes in the last month. We used SIPS Version 4.0 (53). It includes four primary sections according to the symptoms evaluated: attenuated positive symptoms, negative symptoms, disorganized symptoms, and general symptoms. As part of the SIPS, the Scale of Prodromal Symptoms (SOPS) is used to determine whether participants meet research criteria for APSS. SIPS/SOPS psychometric instruments and DSM-5 criteria were both used to diagnose DSM-5-APS in a precise way.

Clinical and Functional Assessments

Additional rating scales were administered to both adolescents and their caregivers, including the Clinical Global Impression–Severity scale (CGI-S; range = 1–7) to assess the overall severity of illness (54) and Global Assessment of Functioning (GAF) scale (55) to assess global functioning. Social and role functioning were assessed as well, using the Global Functioning: Social (GF: Social) and the Global Functioning: Role (GF: Role) (56, 57) scales. Insight was assessed using the Scale to Assess Unawareness of Mental Disorder (SUMD) (58), using three general awareness items: mental disorder, social consequences of mental disorder, and achieved effect of medication. Suicidality was assessed as the % of individuals who reported suicidal ideation lifetime and those with a history of at least one suicide attempt prior to admission.

Data Analysis

We used descriptive statistics to characterize the study population, including diagnosis according to DSM-5 criteria, demographic variables, clinical characteristics and treatment characteristics. Between-group comparisons of categorical variables were performed using χ^2-test or Fisher's exact test, whenever at least one cell contained $\leq$5 patients. For comparisons of continuous variables, we used *t*-test. The following effect sizes were calculated: (a) Cramer's V for χ^2 (59), which was interpreted as follows: 0.1=small; 0.3=moderate; 0.5=large effect size; and (b) Cohen's d (60) for *t*-test, which was interpreted as follows: 0.2=small; 0.5=moderate; 0.8=large effect size, using effect size calculator for *t*-test (61). We correlated attenuated positive, negative, general and disorganized symptoms with the level of functioning and severity of illness using Pearson's correlation. We finally conducted a multivariable, backward logistic regression analysis, entering into the model

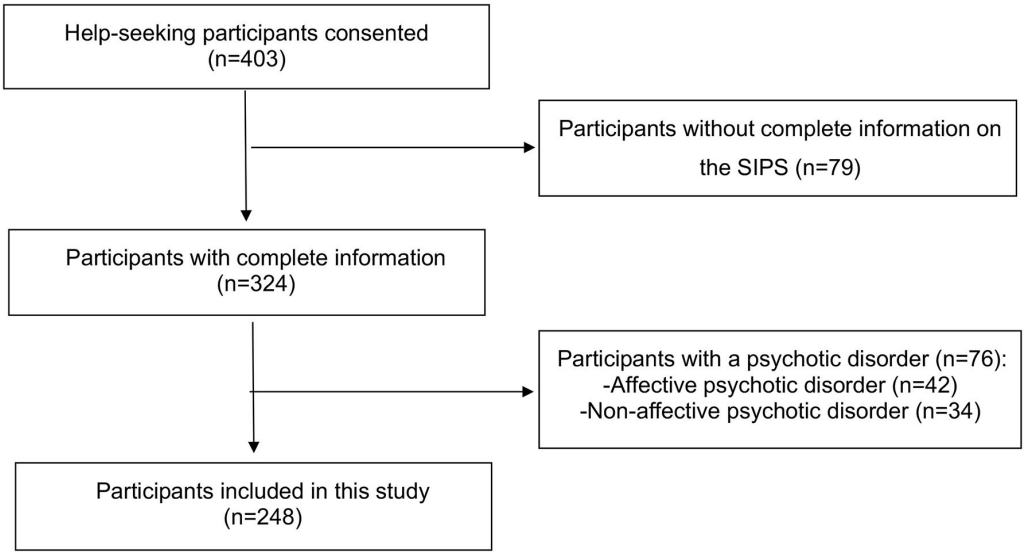

FIGURE 2 | Flowchart outlining selection of study population. SIPS, Structured Interview for Psychosis-Risk Syndromes.

variables that were significantly different ($p < 0.05$) between APS vs. non-APS groups in univariate analyses with data in >67% of subjects. For DSM-5 diagnoses, we entered into the multivariable model broad diagnostic categories (e.g., anxiety disorders), instead of single diagnoses (e.g., panic disorder), that were significantly different between the APS and non-APS group, in order to maximize power for the analyses. For the SIPS psychopathology symptoms, we included only individual items and not subscale sum scores to identify potentially clinically relevant symptoms that can guide clinical identification of APS status. The percent variance explained by the significant variables retained in the final multivariable logistic regression model was expressed as r^2. Significance level was set at alpha=0.05, and all tests were two-tailed. Statistical analyses were performed with SPSS 21 for Windows software (IBM) (62).

RESULTS

Demographic, Comorbidity and Treatment Characteristics

Altogether, 403 help-seeking adolescents and their guardians/legal representatives were consented into AMDPS. Of those, 79 (16.9%) were excluded from this study due to incomplete information on the SIPS, and of the remaining 324 patients, 76 (23.5%) had a psychotic disorder and were therefore also excluded. Finally, 248 hospitalized adolescents with non-psychotic psychiatric disorders were included in this study. Of those, 65 (26.2%) fulfilled DSM-5-APS criteria and 183 (83.8%) did not fulfill APS criteria (**Figure 2**). Agreement was 100% between DSM-5 clinical criteria and the SIPS.

Table 1 shows the demographic, illness and baseline treatment characteristics of the sample at the time of the interview. The average age of participants was 15.4 years (SD=1.5). Most participants were female (69.4%) and white (54.6%). There were no significant differences between the two groups in any of the demographic characteristics (**Table 1**).

APS individuals had a higher number of comorbid disorders (3.5 vs. 2.4, $p < 0.001$; Cohen's d = 0.77) compared to non-APS individuals. The most frequent in the total sample (APS plus non-APS) were depressive disorders (77.0%), particularly major depressive disorder (55.2%), followed by anxiety disorders (42.7%), and disruptive behavior disorders (39.1%). The following disorders were significantly more common in individuals with APS vs. non-APS: disruptive behavior disorders ($p = 0.011$; Cramer's V = 0.16), including oppositional defiant disorder ($p = 0.03$; Cramer's V = 0.14), and conduct disorder ($p = 0.049$; Cramer's V = 0.12); bipolar disorders ($p = 0.002$, Cramer's V = 0.20), including other specified bipolar and related disorders ($p = 0.005$; Cramer's V = 0.18)—also known as bipolar disorder NOS as defined by the COBY study criteria (63)–; personality disorder traits ($p < 0.001$; Cramer's V = 0.26), including borderline personality disorder traits ($p = 0.002$; Cramer's V = 0.20) and other personality disorder traits ($p < 0.001$; Cramer's V = 0.27); anxiety disorders ($p = 0.016$; Cramer's V = 0.15), including panic disorder ($p = 0.031$; Cramer's V = 0.14), generalized anxiety disorder ($p = 0.011$; Cramer's V = 0.16) and specific phobia ($p = 0.005$; Cramer's V = 0.18); and eating disorders ($p = 0.012$; Cramer's V = 0.16). The two groups did not differ in comorbid depressive disorders, substance use

TABLE 1 | Demographic, comorbidity and treatment characteristics.

	Total (*n* = 248)	**APS (*n* = 65)**	**Non-APS (*n* = 183)**	***P*-value**	**Effect size**
Demographic characteristics					
Sex, male, *n* (%)	76 (30.6)	16 (24.6)	60 (32.8)	0.22	0.078
Age (years) mean ± SD	15.4 ± 1.5	15.5 ± 1.3	15.4 ± 1.5	0.63	0.070
Race/ethnicity, *n*, (%)[a]				0.60	0.11
White	124 (54.6)	32 (55.2)	92 (54.4)		
Black or African American	41 (18.1)	13 (22.4)	28 (16.6)		
Other	31 (13.7)	8 (13.8)	23 (13.6)		
Asian or Pacific Islander	28 (12.3)	5 (8.6)	23 (13.6)		
Indian American	3 (1.3)	0 (0.0)	3 (1.8)		
Estimated IQ, mean ± SD	108.4 ± 18.9	107.2 ± 17.8	108.8 ± 19.3	0.56	0.088
Lifetime consensus diagnoses, *n* (%)					
Number of psychiatric diagnoses	2.6 ± 1.5	3.5 ± 1.5	2.4 ± 1.4	**<0.001**	**0.77**
Depressive disorders	191 (77.0)	52 (80.0)	139 (76.0)	0.51	0.042
Major depressive disorder	137 (55.2)	42 (64.6)	95 (51.9)	0.077	0.11
Other specified depressive disorder	53 (21.4)	10 (15.4)	43 (23.5)	0.170	0.087
Persistent depressive disorder	18 (7.3)	5 (7.7)	13 (7.1)	0.87	0.010
Disruptive, impulse-control and conduct disorders	97 (39.1)	34 (52.3)	63 (34.4)	**0.011**	**0.16**
Attention-deficit/hyperactivity disorder	58 (23.4)	13 (20.0)	45 (24.6)	0.45	0.048
Oppositional defiant disorder	40 (16.1)	16 (24.6)	24 (13.1)	**0.03**	**0.14**
Conduct disorder	26 (10.5)	11 (16.9)	15 (8.2)	**0.049**	**0.12**
Disruptive behavior disorder not otherwise specified	11 (4.4)	4 (6.2)	7 (3.8)	0.43	0.050
Bipolar disorders	57 (23.0)	24 (36.9)	33 (18.0)	**0.002**	**0.20**
Other specified bipolar and related disorder	41 (16.5)	18 (27.7)	23 (12.6)	**0.005**	**0.18**
Bipolar I disorder	12 (4.8)	6 (9.2)	6 (3.3)	0.055	0.12
Bipolar II disorder	8 (3.2)	3 (4.6)	5 (2.7)	0.46	0.047
Personality disorder traits	48 (19.4)	24 (36.9)	24 (13.1)	**<0.001**	**0.26**
Borderline personality disorder traits	42 (16.9)	19 (29.2)	23 (12.6)	**0.002**	**0.20**
Other personality disorder traits	13 (5.2)	10 (15.4)	3 (1.6)	**<0.001**	**0.27**
Substance use disorders	39 (15.7)	13 (20.0)	26 (14.2)	0.27	0.070
Cannabis use disorder	31 (12.5)	9 (13.8)	22 (12.0)	0.70	0.024
Alcohol use disorder	14 (5.6)	6 (9.2)	8 (4.4)	0.14	0.093
Others	6 (2.4)	2 (3.1)	4 (2.2)	0.67	0.026
Trauma- and stressor-related disorders	38 (15.3)	8 (12.3)	30 (16.4)	0.43	0.050
Posttraumatic stress disorder	20 (8.1)	7 (10.8)	13 (7.1)	0.35	0.059
Adjustment disorder	19 (7.7)	2 (3.1)	17 (9.3)	0.11	0.10
Anxiety disorders	106 (42.7)	36 (55.4)	70 (38.3)	**0.016**	**0.15**
Panic disorder	63 (25.4)	23 (35.4)	40 (21.9)	**0.031**	**0.14**
Generalized anxiety disorder	37 (14.9)	16 (24.6)	21 (11.5)	**0.011**	**0.16**
Social phobia	24 (9.7)	10 (15.4)	14 (7.7)	0.07	0.11
Others	20 (8.1)	5 (7.7)	15 (8.2)	0.90	0.008
Obsessive-compulsive disorder	13 (5.2)	6 (9.2)	7 (3.8)	0.093	0.11
Specific phobia	9 (3.6)	6 (9.2)	3 (1.6)	**0.005**	**0.18**
Other diagnostic categories					
Eating disorders	20 (8.1)	10 (15.4)	10 (5.5)	**0.012**	**0.16**
Enuresis (not due to a general medical condition)	9 (3.6)	3 (4.6)	6 (3.3)	0.62	0.031
Treatment characteristics at time of the interview *n* (%)[b]					
Antipsychotics[c]	118 (53.6)	37 (66.1)	81 (49.4)	**0.031**	**0.15**
Antidepressants[d]	112 (50.9)	24 (42.9)	88 (53.7)	0.16	0.094
Mood stabilizers[e]	55 (25.0)	14 (25.0)	41 (25.0)	1.0	0.000

(Continued)

TABLE 1 | Continued

	Total (n = 248)	APS (n = 65)	Non-APS (n = 183)	*P*-value	Effect size
Lithium	41 (18.6)	9 (16.1)	32 (19.5)	0.57	0.038
Anxiolytics[f]	23 (10.5)	7 (12.5)	16 (9.8)	0.56	0.039
Others[h]	21 (9.5)	7 (12.5)	14 (8.5)	0.38	0.059
Antiepileptic drugs	18 (8.2)	6 (10.7)	12 (7.3)	0.42	0.054
ADHD medication[g]	4 (1.8)	0 (0.0)	4 (2.4)	0.24	0.080
Two or more drugs	91 (41.4)	22 (39.3)	69 (42.1)	0.71	0.025
Three or more drugs	25 (11.4)	7 (12.5)	18 (11.0)	0.76	0.021

ADHD, Attention Deficit Hyperactivity Disorder; APS, Attenuated Psychosis Syndrome.
[a] *Information available for 227 individuals.*
[b] *Information available for 220 individuals.*
[c] *Antipsychotics: aripiprazole, molindone, quetiapine, risperidone, lurasidone, ziprasidone, olanzapine, haloperidol, chlorpromazine, clozapine.*
[d] *Antidepressants: amitriptyline, nortriptyline, bupropion, citalopram, escitalopram, duloxetine, fluoxetine, paroxetine, sertraline, venlafaxine, mirtazapine.*
[e] *Mood stabilizers: lamotrigine, lithium, valproic acid.*
[f] *Anxiolytics/tranquilizers: clonazepam, lorazepam, hydroxyzine, buspirone.*
[g] *Anti-ADHD medications: atomoxetine, lisdexamphetamine, methylphenidate, modafinil, clonidine, guanfacine.*
[h] *Others: zolpidem, melatonin, propranolol, diphenhydramine, amlodipine.*
Bold values indicate $p < 0.05$ for between-groups analysis.

disorders, trauma and stressor-related disorders or enuresis (all $p > 0.05$).

Overall, the most used psychotropic medications at the time of the interview were antipsychotics (53.6%; $p = 0.031$), followed by antidepressants (50.9%; $p = 0.16$), and mood stabilizers (25.0%; $p = 1.0$). Antipsychotics, which were more common in the APS group ($p = 0.031$; Cramer's V = 0.15), were the only medication class that was significantly different between the groups. The use of multiple medications (use of two or more drugs or use of three or more drugs) was equally frequent in both groups ($p = 0.71$ to 0.76).

Severity of Symptoms and Symptom Domains

Total attenuated positive ($p < 0.001$; Cohen's d = 1.5), negative ($p < 0.001$; Cohen's d = 0.55), disorganized ($p < 0.001$; Cohen's d = 0.51), and general ($p < 0.001$; Cohen's d = 0.84) symptom scores were significantly higher in APS individuals vs. non-APS hospitalized adolescents. All group-defining SIPS attenuated positive symptoms (unusual thought content, suspiciousness, grandiosity, perceptual abnormalities and disorganized communication) were significantly more severe in the APS group (Cohen's d = 0.39 to 1.3), with the largest effect size for perceptual abnormalities (Cohen's d = 1.3) (**Table 2**). Additionally, the following symptoms were more severe in the APS vs. non-APS group: social anhedonia ($p < 0.001$; Cohen's d = 0.57), avolition ($p = 0.002$; Cohen's d = 0.51), experiences of emotions and self ($p < 0.001$; Cohen's d = 0.54), bizarre thinking ($p < 0.001$; Cohen's d = 0.60), trouble with focus and attention ($p = 0.001$; Cohen's d = 0.53), sleep disturbances ($p = 0.002$; Cohen's d = 0.38), dysphoric mood ($p = 0.004$; Cohen's d = 0.34) and impaired stress tolerance ($p < 0.001$; Cohen's d = 0.63).

Illness Severity, Functional Level, Illness Insight and Suicidality

Overall illness severity (CGI-S) was higher in the APS group ($p<0.001$) and the effect size was large (Cohen's d = 1.0). The mean current GAF score was 23.0 ± 11.9 in the APS group and 28.1 ± 17.9 in the non-APS group ($p = 0.012$; Cohen's d = 0.31). Scores for the highest functioning in the past year ($p = 0.002$; Cohen's d = 0.52) and lowest functioning in the past year ($p = 0.002$; Cohen's d = 0.38) were lower in the APS group as well (i.e., poorer functioning in the APS group). Unlike current role functioning, which did not differ significantly between the groups ($p = 0.35$), current social functioning was better in the non-APS group ($p = 0.003$; d = 0.66). Both groups did not differ regarding awareness of mental disorder or social consequences, suicidal ideation or suicidal attempts (all $p > 0.05$) (**Table 3**).

Correlation Between Symptom Domains and Functioning (GAF)–Severity of Illness (CGI-S)

Total negative symptoms were significantly correlated with lower current functioning (Pearson $\rho = -0.17$; $p = 0.031$), lower lowest functioning in the past year (Pearson $\rho = -0.20$; $p = 0.014$) and lower highest functioning reached in the past year (Pearson $\rho = -0.19$; $p = 0.022$). Functioning was not significantly correlated with attenuated positive symptoms, disorganized symptoms or general symptoms. The severity of illness was associated with more severe SIPS positive, negative, disorganized and general symptoms (Pearson $\rho = 0.22$ to 0.46; $p = 0.04$ to $p < 0.001$) (**Table 4**).

Multivariable Logistic Regression Analysis

Independent correlates of APS in the final model were perceptual abnormalities (OR = 2.0; 95% CI = 1.6–2.5, $p < 0.001$), number of psychiatric diagnoses (OR = 1.5; 95% CI = 1.2–2.0, $p = 0.002$),

TABLE 2 | Severity of structured interview of prodromal syndromes (SIPS) assessed symptoms and symptom domains.

	Total (n = 248)	APS (n = 65)	Non-APS (n = 183)	P-value	Effect size
Structured interview of prodromal syndromes mean± SD					
Positive symptoms					
Total positive symptom score	3.2 ± 4.1	7.4 ± 4.6	1.9 ± 3.3	**<0.001**	**1.5**
Highest positive symptom score	1.8 ± 1.8	3.5 ± 1.3	1.2 ± 1.6	**<0.001**	**1.5**
P1 unusual thought content	0.73 ± 1.4	1.6 ± 1.6	0.41 ± 1.1	**<0.001**	**0.95**
P2 suspiciousness	0.84 ± 1.3	1.8 ± 1.6	0.48 ± 0.93	**<0.001**	**1.2**
P3 grandiosity	0.54 ± 1.2	0.89 ± 1.5	0.41 ± 1.1	**0.024**	**0.39**
P4 perceptual abnormalities/hallucinations	0.99 ± 1.7	2.3 ± 1.9	0.47 ± 1.2	**<0.001**	**1.3**
P5 disorganized communication	0.29 ± 0.86	0.63 ± 1.1	0.16 ± 0.68	**<0.001**	**0.58**
Negative symptoms					
Total negative symptom score	8.0 ± 6.22	10.4 ± 6.7	7.1 ± 5.8	**<0.001**	**0.55**
Highest negative symptom score	3.4 ± 1.83	3.8 ± 1.6	3.2 ± 1.9	**0.012**	**0.33**
N1 social anhedonia	1.5± 1.79	2.2 ± 1.9	1.2 ± 1.7	**<0.001**	**0.57**
N2 avolition	2.1 ± 2.0	2.9 ± 1.7	1.9 ± 2.0	**0.002**	**0.51**
N3 expression of emotions	0.88 ± 1.5	1.2 ± 1.6	0.75 ± 1.4	0.061	0.31
N4 experience of emotions and self	0.87 ± 1.7	1.6 ± 2.3	0.65 ± 1.4	**<0.001**	**0.54**
N5 ideational richness	0.20 ± 0.65	0.18 ± 0.18	0.21 ± 0.75	0.88	0.050
N6 occupational functioning	2.4 ± 2.1	2.5 ± 2.4	2.3 ± 2.0	0.31	0.11
Disorganized symptoms					
Total disorganized symptom score	3.1 ± 3.2	4.3 ± 3.7	2.7 ± 2.9	**<0.001**	**0.51**
Highest disorganized symptom score	2.2 ± 1.9	2.9 ± 1.7	2.03 ± 1.9	**0.003**	**0.47**
D1 odd behavior or appearance	0.16 ± 0.94	0.14 ± 1.4	0.17 ± 0.71	0.297	−0.03
D2 bizarre thinking	0.18 ± 0.7	0.48 ± 1.1	0.08 ± 0.4	**<0.001**	**0.60**
D3 trouble with focus and attention	1.9 ± 1.8	2.6 ± 1.7	1.66 ± 1.81	**0.001**	**0.53**
D4 impairment in personal hygiene	0.76 ± 1.7	0.86 ± 2.1	0.73 ± 1.54	0.45	0.08
General symptoms					
Total general symptom score	8.4 ± 4.5	11.0 ± 3.5	7.5 ± 4.4	**<0.001**	**0.84**
Highest general symptom score	4.3 ± 1.7	5.0 ± 1.1	4.1 ± 1.8	**<0.001**	**0.55**
G1 sleep disturbance	2.3 ± 1.9	2.8 ± 2.0	2.1 ± 1.8	**0.002**	**0.38**
G2 dysphoric mood	4.0 ± 2.1	4.5 ± 2.3	3.8 ± 2.0	**0.004**	**0.34**
G3 motor disturbance	0.14 ± 0.80	0.17 ± 1.4	0.13 ± 0.52	0.73	0.05
G4 impaired stress tolerance	1.9 ± 2.1	2.9 ± 2.3	1.6 ± 1.9	**<0.001**	**0.63**

Bold values indicate $p < 0.05$ for between-groups analysis.

and impaired stress tolerance (OR = 1.4; 95%CI = 1.1–1.7, $p = 0.002$). The model including these three variables explained 31.5% of the variance ($r^2 = 0.315$, $p < 0.001$) (**Table 5**).

DISCUSSION

To our knowledge, this study is one of the very few and the largest to date to characterize and describe sociodemographic, illness and intervention characteristics in adolescents with APS vs. non-APS. Additionally, this study focused on help-seeking adolescents who had been admitted into an inpatient unit.

According to our results, 26.2% of the adolescents without a psychotic disorder diagnosis fulfilled APS criteria, a somewhat lower prevalence compared to a previous study including mostly adolescent outpatients (33%) (64, 65), but still a clinically significant and higher prevalence than the one found in non-help-seeking adolescents with disruptive behaviors (13%) (33). In the general population, a 7.2% meta-analytical prevalence of psychotic experiences was estimated in children and adults (66). In the Philadelphia Neurodevelopmental Cohort study, 15.5% of the 8–21 year old individuals reported significant psychotic symptoms and another 9.8% reported milder symptoms (67).

APS individuals had a higher number and distribution of comorbid conditions than non-APS individuals (Cohen's d = 0.77), particularly consisting of depressive disorders (5), anxiety disorders (5), and disruptive behavior disorders (68). This finding is clinically relevant because APS status has been associated with hospital treatment for mood and conduct disorders (33). Personality disorder traits, bipolar disorders, disruptive behavior disorders, eating disorders and anxiety disorders, were more frequent in the APS group than the non-APS group, although effect sizes were small. This result supports evidence of the association between APS (21, 22) as well as CHR-P (9, 69) with other comorbid mental disorders.

TABLE 3 | Illness severity, functional level, illness insight and suicidality.

	Total (n = 248)	APS (n = 65)	Non-APS (n = 183)	*P*-value	Effect size
Characteristics					
Illness severity: clinical global impressions-severity scale (CGI-S) mean ± SD[a]					
Overall severity of illness	4.2 ± 1.03	4.8 ± 0.94	3.9 ± 0.9	**<0.001**	**1.0**
Functional level: global assessment of functioning-scale (GAF) mean ± SD[b]					
Current GAF	26.8 ± 16.7	23.0 ± 11.9	28.1 ± 17.9	**0.012**	**0.31**
Highest GAF of past year	57.7 ± 14.7	52.2 ± 16.6	59.7 ± 13.5	**0.002**	**0.52**
Lowest GAF of past year	23.1 ± 15.0	18.9 ± 10.2	24.5 ± 16.0	**0.002**	**0.38**
Global functioning: role scale mean ± SD[c]					
Current role functioning	5.9 ± 1.8	5.7 ± 1.7	6.1 ± 1.9	0.35	0.20
Global functioning: social scale mean ± SD[c]					
Current social functioning	6.5 ± 1.7	5.8 ± 1.5	6.9 ± 1.7	**0.003**	**0.66**
Scale to assess unawareness of mental disorder mean ± SD[d]					
Awareness of mental disorder	2.2 ± 1.7	2.2 ± 1.6	2.2 ± 1.7	0.98	0.006
Awareness of the effect of medication	2.1 ± 1.5	2.2 ± 1.5	2.0 ± 1.5	0.45	0.14
Awareness of the social consequences	1.9 ± 1.5	1.9 ± 1.4	1.9 ± 1.5	0.99	0.0
Suicidality, *n* (%)[e]					
Suicidal ideation	131 (61.8)	38 (73.1)	93 (58.1)	0.29	0.067
Suicide attempts	21 (10.0)	8 (15.3)	13 (8.2)	0.19	0.082

[a] *Data available for 86 patients.*
[b] *Data available for 225 patients.*
[c] *Data available for 88 patients.*
[d] *Data available for 168 patients.*
[e] *Data available for 212 patients.*
Bold values indicate p < 0.05 for between-groups analysis.

TABLE 4 | Correlation between Structured Interview of Prodromal Syndromes (SIPS) symptom domains and functioning as well as severity of illness.

	Current GAF		Lowest GAF past year		Highest GAF past year		Severity of illness CGI-S	
	Pearson's Rho	*p*-value	Pearson's Rho	*p*-value	Pearson's Rho	*p*-value	Pearson's Rho	*p*-value
Total SIPS positive symptom score	−0.034	0.66	−0.045	0.57	0.0005	0.95	0.46	**<0.001**
Total SIPS negative symptom score	−0.17	**0.031**	−0.20	**0.014**	−0.19	**0.022**	0.39	**<0.001**
Total SIPS disorganized symptom score	−0.04	0.58	−0.06	0.46	−0.043	0.61	0.22	**0.04**
Total SIPS general symptom score	0.095	0.21	0.082	0.3	0.017	0.36	0.45	**<0.001**

CGI-S, Clinical Global Impression–Severity scale; GAF, Global Assessment of Functioning; SIPS, Structured Interview for Psychosis-Risk Syndromes.
Bold values indicate p < 0.05 for between-groups analysis.

TABLE 5 | Results of the multivariable, backward elimination logistic regression analysis of variables distinguishing APS vs. non-APS at $p < 0.05$ in univariate analyses.

	B	SE	Wald	Sig	OR	95.0% C.I.	
						Lower	Upper
SIPS P4 perceptual abnormalities/hallucinations	0.69	0.11	38.9	**<0.001**	2.0	1.6	2.5
SIPS G4 impaired stress tolerance	0.31	0.10	9.8	**0.002**	1.4	1.1	1.7
Number of psychiatric diagnoses	0.42	0.14	9.5	**0.002**	1.5	1.2	2.0

($r^2 = 0.315$, $p < 0.001$).
Bold values indicate p < 0.05 for between-groups analysis.

Thus, comorbidity should not rule out APS, but, if anything, increase the diagnostic suspicion. On the other hand, it is also possible for APS status to be a byproduct of overlapping disease processes and expressions of non-psychotic disorders, lowering the true risk for developing a psychotic disorder in the future (22, 28, 70).

Regarding psychopharmacological treatment, as previously reported (22), a high percentage of our non-psychotic APS

sample received atypical antipsychotics (66.1%), which was also high in the non-psychotic non-APS individuals (49.4%). This finding is worrying because no consistent meta-analytical evidence supports the use of atypical antipsychotic drugs in delaying or preventing transition to psychosis over other interventions (71, 72). However, it is also true that rates of antipsychotics were high in other diagnostic groups in this sample, including bipolar-spectrum disorders (49), which supports that atypical antipsychotic use is likely related to the reason for admission to the psychiatric unit and not only to efforts to treat attenuated psychotic symptoms or to prevent full-blown psychosis. Nevertheless, the widespread use of antipsychotics in adolescents for non-psychotic, predominantly depressive disorders is concerning due to the established adverse effects risks that atypical antipsychotics have in youth (73–77).

APS status was associated with a significantly higher severity of attenuated psychotic symptoms according to the SIPS. Effect sizes for these differences were moderate to large (Cohen's $d = 0.51$ to 1.5). Regarding individual items, differences were found in 13/19 items. Effect sizes were large for unusual thought content, suspiciousness and perceptual abnormalities (Cohen's $d = 1.0$ to 1.3), medium for disorganized communication, social anhedonia, avolition, experience of emotions and self, bizarre thinking, trouble with focus and attention and impaired stress tolerance (Cohen's $d = 0.50$ to 0.63), and small for grandiosity, sleep disturbances and dysphoric mood (Cohen's $d = 0.34$ to 0.39).

This greater severity in psychopathology also translated into greater illness severity (Cohen's $d = 1.0$) and poorer functioning (Cohen's $d = 0.31$ to 0.52), as found before (9, 22, 78, 79), including social functioning (Cohen's $d = 0.66$), but not role functioning. However, a previous study using the same instruments found that both social and role functioning were significantly more impaired in CHR-P individuals compared to controls from as early as age 12, which was our lower age limit (80). However, controls in that study were healthy, while in our sample, we compared hospitalized adolescents with vs. without APS who were likely admitted for symptoms related to other psychiatric disorders, which can explain the difficulties in role functioning as well as social and general functioning. The fact that all adolescents (APS and non-APS) reached stringent US criteria for inpatient care resulted in the low functioning scores found in both groups. Nevertheless, our results support previous evidence that APS status is associated with marked functional impairment (21, 81, 82). This finding is particularly relevant because functional impairment can be helpful to differentiate youth meeting CHR-P from other help-seeking individuals (83).

Interestingly, while illness severity was associated with overall psychopathology, including more severe SIPS total positive, negative, disorganized and general symptoms (Pearson $\rho = -0.22$ to -0.46), functioning (current, lowest and highest) was only and weakly (Pearson $\rho = -0.17$ to -0.20) correlated with total negative symptoms, but not with attenuated positive, disorganized and general symptoms. Negative symptoms have been associated with functioning (38–40), not only in schizophrenia, but also in other psychotic individuals, and non-psychotic depressed patients (84). This association was found to be greater with negative than attenuated positive symptoms (85), in line with our results. In contrast, trauma has been found to be correlated with the severity of attenuated positive symptoms but not with negative symptoms in CHR-P individuals (86); yet, CHR-P individuals' negative symptoms may impact the transition to psychosis even more than attenuated positive symptoms (87), although this has not been found consistently (53).

According to our results, perceptual abnormalities (OR=2.0), number of psychiatric diagnoses (OR=1.5), and impaired stress tolerance (OR=1.4) were independently associated with APS status. Among perceptual abnormalities, auditory perceptual abnormalities have been associated with a higher risk of psychosis, while visual perceptual abnormalities have been associated with a lower risk (88). While the number of psychiatric diagnoses was independently associated with APS status in our study, and while APS has previously been associated with comorbid mental disorders, the impact of the different comorbid conditions may vary (21, 22). The most common comorbid conditions in our sample, anxiety and depressive diagnoses, have been associated with impaired global functioning, as well as higher suicidality or self-harm behaviors, but not with transition to psychosis (5). Implications of the presence of other comorbid conditions in APS and their relevance for true risk for conversion to psychosis need further study, particularly in adolescents. Our results further support previous evidence that impaired stress tolerance is a core CHR-P feature, which is associated with more severe psychopathology (89). The presence of impaired stress tolerance has been also suggested to have therapeutic implications in CHR-P (90).

We also found that APS was associated with functioning in univariate analyses, but not in multivariable analyses, supporting that lower functioning is related to other features, including the presence and duration of attenuated positive symptoms (21, 91) and impaired stress tolerance (89). A model including disorganized communication, suspiciousness, verbal memory deficits, and decline in social functioning was found to predict conversion to psychosis (53). Due to having introduced the Global Functioning scales later into the study, they were only available in a subset of patients and could not be entered into the backward elimination logistic regression model. However, APS was associated with significantly lower levels of social functioning. Clinicians should thus monitor functioning, especially social functioning in adolescents with APS.

Finally, our results stress that in adolescent inpatients, DSM-5 APS is associated with higher severity of overall illness, lower functioning and impaired stress tolerance, requiring a higher intensity of clinical care compared to non-APS adolescents admitted into an inpatient unit. This result is supported by prior findings showing that youth with APS have complex medical histories and frequent comorbidities that require therapeutic attention (22, 28, 70). Research about effective treatments for DSM-5-APS has been limited (21), and evidence from studies analyzing CHR-P individuals—from which knowledge could arguably be applied to APS individuals—does not support one treatment over another (72). At the moment, at least needs-based interventions should be offered (9). Perceptual abnormalities and impaired stress tolerance may be targets of needs-based interventions in adolescents aiming to improve quality of life

and aiming to reduce burden for them and their families. Still, prospective studies are needed to inform and develop guidelines regarding youth fulfilling APS criteria.

Strengths and Limitations

The current study has several strengths and limitations that must be taken into consideration when interpreting its results. First, some symptom assessments were based on retrospective recall, which may be prone to recall bias. However, all SIPS symptoms were rated for presence in the last month. Second, the comparison group, including non-psychotic adolescents who fulfilled criteria for inpatient care in the US health care system, was otherwise heterogeneous and functionally impaired. The results should thus be interpreted in the context of help-seeking APS and non-APS samples in need of inpatient care. Third, data were not available to determine to what degree adolescents with APS sought help specifically for APS-related symptomology. Fourth, we did not collect some potentially relevant information, including the reason for the use of psychotropic medications or dosage, which could have relevant implications. Similarly, verbal memory deficits and other cognitive measures, which are relevant according to previous research, were not included in the current analysis. Fifth, we could not retrieve the data for the total number of patients fulfilling our inclusion criteria within our study timeframe outside of this study. Thus, we could not report the participation rate. Sixth, we did not test for interrater reliability of interviewers for all scales used in this study. However, using the same training, certification and ongoing recalibration system via mandatory presence and presentation of all rating scale scores for all interviewers as part of the regular diagnostic consensus conference (led by the study PI CUC) the interrater reliability of the BPSS-FP indices ranged from intraclass-correlations of 0.93–0.98 (92). Seventh, since the Clinical Global Impressions of Severity Scale and social and role function scales were introduced later into the study, data were not available in a sufficiently large number of patients to enter this variable into the multivariable regression analysis; Eighth, the final model obtained from the multivariable regression analysis was not validated, which may have led to overfitting, thus requiring replication and limiting its generalizability and consequently its implementation in clinical practice. Finally, the cross-sectional design precludes any analysis of the predictive value of APS.

Nevertheless, despite these limitations, the study has several strengths. First, this is the largest study to date to comprehensively describe and characterize DSM-5-APS in adolescents. Second, we used structured and validated assessments that were carried out independently and face-to-face for both adolescents and their parents or caregivers to obtain as precise information as possible. These assessments were led by experienced and internally certified Master or MD level clinicians and psychologists. Third, we focused on individuals with a wide variety of psychopathology and treatment characteristics, both in the DSM-5-APS group and in the non-APS comparison group, increasing clinical value vs. comparisons with healthy control subjects. Finally, focusing on APS individuals allowed us to obtain results from a more homogeneous high-risk sample.

CONCLUSIONS

Approximately one in four adolescents hospitalized with non-psychotic disorders meet DSM-5-APS criteria. These help-seeking adolescents have more comorbid psychiatric disorders as well as more severe symptoms, functional impairment and global severity of illness. Thus, they warrant high intensity clinical care. To what degree APS in adolescents with existing and emerging non-psychotic mental disorders is predictive of future transition to a psychotic disorder and what the predictors are for such transition requires further prospective study.

DATA AVAILABILITY STATEMENT

Datasets generated for this study are included in the article. Additional data might be shared upon request from the first or corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board of the North Shore-Long Island Jewish Health System; Ethical Committee of Human Experimentation in the USA. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

GS had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. CC: study concept and design. GS, DG, BC, AA, RC, MC, SJ-F, DV, SW, MG, RS, NL, MB, and CC: acquisition of data. GS and CC: statistical analysis, drafting of the manuscript, administrative, technical, and material support. All authors critical revision of the manuscript for important intellectual content and interpretation of data.

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5.2. PUBLICATION 2

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Demographic and Clinical Characteristics, Including Subsyndromal Symptoms Across Bipolar-Spectrum Disorders in Adolescents

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Abstract

Objectives: Bipolar disorder (BD) is a debilitating illness that often starts at an early age. Prevention of first and subsequent mood episodes, which are usually preceded by a period characterized by subthreshold symptoms is important. We compared demographic and clinical characteristics including severity and duration of subsyndromal symptoms across adolescents with three different bipolar-spectrum disorders.

Methods: Syndromal and subsyndromal psychopathology were assessed in adolescent inpatients (age = 12–18 years) with a clinical mood disorder diagnosis. Assessments included the validated Bipolar Prodrome Symptom Interview and Scale—Prospective (BPSS-P). We compared phenomenology across patients with a research consensus conference-confirmed DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition) diagnoses of BD-I, BD—not otherwise specified (NOS), or mood disorder (MD) NOS.

Results: Seventy-six adolescents (age = 15.6 ± 1.4 years, females = 59.2%) were included (BD-I = 24; BD-NOS = 29; MD-NOS = 23) in this study. Median baseline global assessment of functioning scale score was 21 (interquartile range = 17–40; between-group $p = 0.31$). Comorbidity was frequent, and similar across groups, including disruptive behavior disorders (55.5%, $p = 0.27$), anxiety disorders (40.8%, $p = 0.98$), and personality disorder traits (25.0%, $p = 0.21$). Mania symptoms (most frequent: irritability = 93.4%, $p = 0.82$) and depressive symptoms (most frequent: depressed mood = 81.6%, $p = 0.14$) were common in all three BD-spectrum groups. Manic and depressive symptoms were more severe in both BD-I and BD-NOS versus MD-NOS ($p < 0.0001$). Median duration of subthreshold manic symptoms was shorter in MD-NOS versus BD-NOS (11.7 vs. 20.4 weeks, $p = 0.002$) and substantial in both groups. The most used psychotropics upon discharge were antipsychotics (65.8%; BD-I = 79.2%; BD-NOS = 62.1%; MD-NOS = 56.5%, $p = 0.227$), followed by mood stabilizers (43.4%; BD-I = 66.7%; BD-NOS = 31.0%; MD-NOS = 34.8%, $p = 0.02$) and antidepressants (19.7%; BD-I = 20.8%; BD-NOS = 10.3%; MD-NOS = 30.4%).

Conclusions: Youth with BD-I, BD-NOS, and MD-NOS experience considerable symptomatology and are functionally impaired, with few differences observed in psychiatric comorbidity and clinical severity. Moreover, youth with BD-NOS and

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MD-NOS undergo a period with subthreshold manic symptoms, enabling identification and, possibly, preventive intervention of those at risk for developing BD or other affective episodes requiring hospitalization.

Keywords: bipolar disorder, risk, prevention, subsyndromal, adolescence

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Introduction

Bipolar disorder (BD) is a chronic, recurrent, and often debilitating illness (Skjelstad et al. 2010) characterized by fluctuations in mood, energy, cognition, and behavior (Grande et al. 2016). BD is associated with significant impairments in everyday functioning (Bowie et al. 2010), and is ranked as the illness with the second greatest effect on days out of role functioning (Alonso et al. 2011). However, delay between illness onset and diagnosis has been reported to be as long as 5–10 years (Berk et al. 2007).

Clinical presentation and diagnosis of pediatric BD has been controversial (Moreno et al. 2007; Luby and Navsaria 2010; Van Meter et al. 2016a), especially the decrease in the threshold for diagnosing BD and the concept of the bipolar spectrum (Grande et al. 2016). Nevertheless, 60%–65% of people with BD experience their first symptoms before adulthood (Perlis et al. 2004), and agreement is substantial that the illness trajectory of early-onset BD is more severe than adult-onset BD (Bowie et al. 2010; Arango et al. 2014; Parellada et al. 2017) and is associated with significant impairment (Hunt et al. 2016), and a chronic course and significant treatment resistance (Luby et al. 2010). In addition, childhood onset of bipolar-like symptoms are a good predictor for the development of full BD (Carlson and Pataki 2016; Hafeman et al. 2016).

The longitudinal course of children and adolescents with BD is often manifested by changes in symptom polarity with a fluctuating course, showing a dimensional continuum of bipolar symptom severity from subsyndromal symptoms to mood syndromes meeting full Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria (Birmaher et al. 2006). Nevertheless, bipolar-spectrum pathologies below the level of BD-I (Correll et al. 2007, 2014), and antecedent conditions (Faedda et al. 2014, 2015) also have a significant impact on functionality and quality of life (Luby et al. 2010; Carlson et al. 2016).

BD-I is characterized by the occurrence of at least one manic episode, usually in association with one or more depressive episodes (American Psychiatric Association 2013). As per the Diagnostic and Statistical Manual of Mental Disorders (DSM), one episode of mania without depression is sufficient for a diagnosis of BD-I, as long as there is no other cause that better explains the symptoms (American Psychiatric Association 2013).

BD—not otherwise specified (BD-NOS), renamed ''unspecified BD'' in the fifth edition of the DSM (DSM-5; American Psychiatric Association 2013) is characterized by the presence of symptoms that lack sufficient duration or severity for a BD-I or II diagnosis. This subgroup was defined in the COBY study (Birmaher et al. 2006) and included distinct periods of abnormally elevated or irritable mood with either one less B criterion symptom, or presence of all symptoms, but lasting at least ≥4 hours on ≥4 cumulative instead of ≥4 consecutive days.

Patients with mood disorder NOS (MD-NOS) named ''other specified BD'' in the DSM-5 (American Psychiatric Association 2013), have characteristic symptoms of BD and related disorders that do not meet full criteria for any category previously mentioned and is characterized by subthreshold periods of mania or hypomania that, unlike BD-NOS, last <4 hours per day for <4 cumulative days.

Early signs and symptoms have been detected in BD, including some subthreshold symptoms, which have been reported to precede the initial mood episode in BD and the recurrent mood episodes (Hauser and Correll 2013; Van Meter et al. 2016b). Many of these characteristics have been identified too in youth at genetic risk for BD (Lombardo et al. 2012; Birmaher et al. 2013; Hafeman et al. 2016), including disturbances in mood, cognition, and behavior (Duffy et al. 2007, 2010; Egeland et al. 2012; Mesman et al. 2013, 2016, 2017; McIntyre and Correll 2014; Hafeman et al. 2016). These presentations include nonspecific psychiatric symptoms, like anxiety or irritability (Compton et al. 2010), among other more specific affective symptoms, such as decreased need for sleep or racing thoughts (Correll et al. 2014). These latter ''hallmark'' symptoms could be more specific to BD and are relatively ubiquitous among youth who meet full BD criteria (Van Meter et al., 2016a).

A symptomatic prodrome before the first hypomanic/manic and/or depressive episode in BD has been described (Noto et al. 2015), lasting over 2 years, and a shorter period characterized by subthreshold symptoms that appear before full-blown recurrent episodes (Van Meter et al. 2016a). This has led to increased awareness that recognition and longitudinal assessment of subthreshold symptoms in at-risk populations (either for a first affective episode or for a recurrent mood episode) is important for understanding the illness course (Carlson et al. 2016). Although several risk factors for BD have been identified, including circadian rhythm abnormalities (Lenox et al. 2002), temperamental characteristics (Akiskal et al. 2005; Mendlowicz et al. 2005), neurocognitive deficits (Krabbendam et al. 2005), and adverse life events (Janiri et al. 2015; Pan et al. 2017), specific characteristics and endophenotypes that reliably allow early recognition of BD, remain undiscovered.

Identifying subthreshold symptoms in at-risk individuals might lead to new interventions that could prevent the onset of new affective episodes. Although there is currently little evidence for interventions at these stages (Rios et al. 2015), recent attempts to intervene earlier have led to some positive outcomes (Pfennig et al. 2014; Hunt et al. 2016). For instance, interpersonal and social rhythm therapy (IPSRT) (Goldstein et al. 2018) and family-focused therapy (Miklowitz et al. 2013) have shown promising results.

Rating scales and checklists, which would facilitate the development and identification of early symptoms show great promise (Hunt et al. 2016). Thus, newly developed tools, such as the Bipolar Prodrome Symptom Interview and Scale—Prospective (BPSS-P) (Correll et al. 2014), are relevant.

Unfortunately, subthreshold symptoms are often not correctly identified and addressed, limiting the initiation of preventive interventions. Previous studies have reported and compared different affective symptoms that appear in BD-spectrum disorders (Tijssen et al. 2010; Hafeman et al. 2013, 2016, 2017; Van Meter et al. 2016b; Connor et al. 2017) or have retrospectively characterized the phase preceding the emergence of an episode of mania (Conus et al. 2010; Correll et al. 2014). However, to our knowledge, no study to date has compared these particular BD-spectrum diagnoses with each other regarding mania-like mood states,

using a validated instrument, such as the BPSS-P, and included diagnoses that may be precursor stages for manifest BD, such as BD-NOS and MD-NOS.

Thus, the aim of this study was to characterize and compare patients with different BD-spectrum disorders regarding their clinical characteristics and illness course before hospitalization, including subthreshold symptoms that could lead to a more severe affective episode in the future.

We hypothesized that adolescents with BD-I, BD-NOS, and MD-NOS would report clinical impairment, as defined by low functioning and severe and clinically relevant psychopathology, and relevant threshold and subthreshold symptoms of mania and depression, which would be beyond what could be expected owing to the characteristics of each diagnostic category by their definition (see definitions provided in this section), and which would be most severe and florid in patients with BD-I, followed by those with BD-NOS, and finally, by MD-NOS.

Methods

Setting

Participants were recruited between September 2009 and July 2017 from the adolescent inpatient unit of The Zucker Hillside Hospital, from the ongoing Adolescent Mood and Psychosis Study (AMDPS) (Lo Cascio et al. 2016), an observational study aiming to prospectively characterize the BD prodrome.

This study was registered at ClinicalTrials.gov (NCT01383915).

Participants

Inclusion criteria for AMDPS were as follows: (1) age: 12–18 years; (2) research diagnosis, using the Structured Clinical Interview for DSM-IV Disorders (First et al. 1996), supplemented by pediatric diagnoses from the Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime version (Kaufman et al. 1997) of either (a) BD-1, (b) BD-NOS (renamed ''unspecified BD'' DSM-5; American Psychiatric Association 2013), defined by the COBY study criteria (Birmaher et al. 2006), that is, distinct periods of abnormally elevated or irritable mood with either one less B mania criterion symptom, or presence of all required symptoms for a BD-I or BD-II diagnosis, but lasting at least ≥4 hours on ≥4 cumulative instead of ≥4 consecutive days, or (c) MD-NOS (named ''other specified BD'' in the DSM-5; American Psychiatric Association 2013), defined by presence of symptoms of BD and related disorders that do not meet full criteria for any syndromal mood disorder and that is characterized by subthreshold periods of mania or hypomania that, unlike BD-NOS, last <4 hours per day for <4 cumulative days; (3) currently admitted into a psychiatric hospital; (4) subject and parent (if subject <18 years) willing and able to provide written, informed consent/assent.

Exclusion criteria were as follows: (1) an estimated premorbid IQ <70; (2) fulfilling DSM-IV criteria for pervasive developmental disorder or autism spectrum disorders; and (3) a history of any medical condition known to affect the brain. For the purpose of this study, patients with a DSM-IV diagnosis of BD-I, BD-NOS, or MD-NOS using the Kiddie-Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime version (K-SADS-PL) (Birmaher et al. 2009) and the BPSS-P (Correll et al. 2014) were selected from the overall AMDPS study sample. Psychiatric diagnoses were established according to DSM-IV criteria through research consensus conference (led by CUC) based on the KSADS and BPSS-P in-person interview assessments of the adolescent and the caregiver. Information from the parent and youth interviews was integrated for the diagnostic and psychopathology. When there was a discrepancy, the more severe of the two ratings was accepted, assuming that symptoms are more likely forgotten or hidden than invented or exaggerated.

Written informed consent for this Northwell Health Institutional Review Board-approved study was obtained from all subject's guardians or legal representatives of minors and written assent was obtained from each adolescent subject, unless they were 18 and provided written informed consent.

Clinical and functional assessments

The BPSS-P (Correll et al. 2014) was administered to adolescent inpatients with a clinical diagnosis of affective or psychosis-spectrum disorder. This tool was developed to characterize prodromal and subsyndromal bipolar mania and depression states and to assess the evolution of BD at any stage. The BPSS-P was developed based on an extension downward of DSM criteria for BD and major depressive disorder, and available rating scales for major depressive disorder and BD, a review of the existing literature regarding risk factors and early symptoms and signs of BD, published scales and interviews for the assessment of the psychotic prodrome, input from experts in the area of the schizophrenia prodrome and BD, and open questioning of youth with BD and their caregivers. The BPSS-P is comprised of a 10-item Mania Symptom Index, a 12-item Depression Symptom Index, and a 6-item General Symptom Index.

The BPSS-P was designed to characterize and evaluate the lifetime presence and severity of prodromal/subsyndromal and syndromal manic, depressive, and general symptoms. Symptom severity was rated on an ordinal scale with 0 = absent, 1 = questionably present, 2 = mild, 3 = moderate, 4 = moderately severe, 5 = severe, 6 = extreme, with a rating of ''moderate'' being the lowest subsyndromal rating [rating = 3, i.e., symptoms are ''beginning to be noticed by others'' and are not just ''fully explained by external factors'' that would be a rating = 2, but not yet ''beginning to interfere with functioning'' (rating = 4)]. In addition, the frequency of these symptom episodes is recorded on a Likert scale, as follows: 0 = none, 1 = < once/month, 2 = once/month, 3 = 2–3 times/month, 4 = 4–7 times/month, 5 = 8–27 times/month, 6 = ≥ 28 times/month. Furthermore, duration, onset, and pattern of these symptoms are also recorded.

The BPSS-P has good to excellent psychometric properties including very high internal consistency, inter-rater reliability, and convergent validity (Correll et al. 2014). For the purpose of this study, we analyzed severity as a categorical variable [i.e., presence of symptoms rated at moderate severity (rating = 3) or higher]. For the duration of subthreshold symptoms rated at moderate or higher severity, we restricted the analyses to those individuals who by definition had not (yet) experienced an episode of that polarity, that is, subthreshold symptoms of mania and general symptoms in the BD-NOS and MD-NOS groups and subthreshold symptoms of depression in the MD-NOS group.

Additional rating scales were administered to both adolescents and their caregivers, including the Clinical Global Impression—Severity scale (CGI-S; range = 1–7), which assesses the overall severity of illness (Guy 1976), the Global Assessment of Functioning scale (GAF; range = 0–100) (Piersma and Boes 1997), which assesses functionality, and The Montgomery-Åsberg Depression Rating Scale (MADRS; range = 0–60) (Montgomery and Asberg 1979) and the Young Mania Rating Scale (YMRS; range = 0–60) (Young et al. 1978), which were used to assess affective symptoms.

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Data analysis

We used descriptive statistics to characterize the study population, including demographic variables and clinical characteristics.

After testing normality using Shapiro–Wilk tests and homoscedasticity using the Levene test, between-group comparisons of categorical variables were performed using χ^2 test or Fisher's exact test, whenever ≥1 cell contained ≤5 patients. For comparison of continuous variables, we performed the pertinent analyses using *t*-test for normally distributed variables and Kruskal–Wallis test and Mann–Whitney *U*-tests for non-normally distributed variables, for the 3-group omnibus test, and *post hoc* pairwise comparisons, respectively. Statistical analyses were performed with SPSS 21 for Windows software (IBM). Significance level was set at alpha = 0.05, and all tests were two-tailed.

Results

Demographics and comorbidities

Altogether, 403 help-seeking adolescents and their guardians or legal representatives were consented into AMDPS. Applying the specific inclusion criteria for this report, 76 adolescent inpatients were included (BD-I = 24; BD-NOS = 29; MD-NOS = 23). Table 1 provides the demographic and clinical characteristics of the sample. The average age of participants was 15.6 ± 1.4 years (range = 12–18 years), the average duration of education was 9.7 ± 1.4 years, 59.2% were female, and 51.4% were white, without significant between-group differences. Comorbidities were frequent in all three groups, again, without significant between-group differences, including mainly disruptive behavior disorders (55.3%), anxiety disorders (40.8%), personality disorder traits (25.0%), and substance use disorders (17.1%) according to the KSADS.

Psychopathology at time of admission

The median CGI-S score was 4 or ''moderate'' [interquartile range (IQR) = 3, 4; $p = 0.01$], with greater illness severity for BD-I versus MD-NOS ($p = 0.003$). The median baseline GAF scale score upon admission was low, that is, 21 (IQR = 17, 40), without significant group differences ($p = 0.31$). The median Montgomery–Åsberg Depression Rating Scale (MADRS) score (27, IQR = 18, 35) indicated greater depressive symptom load than the relatively lower median Young Mania Rating Scale (YMRS) score (13, IQR = 7.5, 22) (with each scale having a possible range of 0–60 points). Groups did not differ at the time of assessment as inpatients regarding YMRS scores ($p = 0.65$), whereas MDRS scores differed significantly ($p = 0.006$), with BD-NOS having higher depression ratings than MD-NOS ($p = 0.001$).

Lifetime subsyndromal symptoms assessed with the BPSS-P

Prevalence of symptoms at "moderate" or higher severity. The prevalence of BPSS-P items rated at moderate or higher severity are given in Table 2.

BPSS-P mania index. The most frequent mania-like symptoms rated at moderate or higher severity in the whole sample was irritability (93.4%), followed by distractibility (71.1%). As for BD-I, the most frequent symptoms were irritability (95.8%), mood elevation (95.8%), and racing thoughts/flight of ideas (91.7%). Conversely, patients with BD-NOS presented the highest rates of irritability (93.1%), over talkativeness (89.7%), and distractibility (79.3%) in this sample. As for MD-NOS, the most frequent symptoms were irritability (91.3%), distractibility (52.2%), and increased psychomotor activity (47.8%) (Table 2).

The three groups differed in at least one group comparison on 6 of the 10 BPSS-P mania index items, without differences for irritability ($p = 0.82$), distractibility ($p = 0.057$), increased psychomotor activity ($p = 0.078$), and reckless/dangerous behavior ($p = 0.36$). Specifically, the following symptoms of mania were significantly more frequent in BD-I versus BD-NOS and MD-NOS: mood elevation ($p = 0.013$; $p < 0.0001$), inflated self-esteem/grandiosity ($p = 0.025$; $p < 0.0001$), decreased need for sleep ($p = 0.048$; $p = 0.004$), racing thoughts ($p = 0.024$; $p < 0.0001$), and increased energy/goal directed activity ($p < 0.0001$ each). In addition, the following symptoms of mania were significantly more frequent in BD-NOS versus MD-NOS: mood elevation ($p = 0.002$), inflated self-esteem/grandiosity ($p = 0.011$), overtalkativeness (<0.0001), and racing thoughts/flight of ideas ($p = 0.039$) (Table 2).

BPSS-P depression index. The entire sample reported sub-/syndromal symptoms of depression as well. The following symptoms of depression rated at moderate or higher severity were most frequently reported: depressed mood (81.6%) and suicidality (69.3%). The most frequent symptoms reported in patients with BD-I in this sample were depressed mood (91.7%), anhedonia (75.0%), and worthlessness (75.0%). Similarly, patients with BD-NOS reported high rates of depressed mood (82.8%), but also reported high rates of decreased energy (75.9%). Finally, the most frequent subsyndromal symptoms in MD-NOS were depressed mood (69.6%), suicidality (59.1%), and decreased concentration (40.9%) (Table 2).

The three groups differed in at least one group comparison on 7 of the 12 BPSS-P depression index items, without differences for depressed mood ($p = 0.14$), decreased appetite ($p = 0.067$), increased appetite ($p = 0.12$), insomnia ($p = 0.071$), hypersomnia ($p = 0.058$), indecision ($p = 0.9$), and suicidality ($p = 0.43$).

There were no significant differences between BD-I and BD-NOS on any of the BPSS-P depression items. Conversely, the following symptoms of depression were significantly more frequent in BD-I versus MD-NOS: anhedonia ($p = 0.003$), decreased psychomotor activity ($p = 0.001$), decreased energy ($p = 0.028$), worthlessness/guilt ($p = 0.002$). Furthermore, the following symptoms of depression were significantly more frequent in BD-NOS versus MD-NOS: anhedonia ($p = 0.008$), decreased psychomotor activity ($p = 0.008$), decreased energy ($p = 0.001$), worthlessness/guilt ($p = 0.001$), and decreased concentration ($p = 0.015$) (Table 2).

BPSS-P General Symptom Index. The following general symptoms at moderate or higher severity were the most frequent: mood lability (71.1%) and anger/aggressiveness (69.9%). The three groups only differed regarding 1 of the 6 BPSS-P general symptoms, mood lability ($p = 0.002$). In the BD-I (83.3%) and BD-NOS (82.8%) groups, the proportion of patients with relevant mood lability did not differ significantly, but each BD-I and BD-NOS had significantly higher frequencies of mood lability versus MD-NOS (43.5%; BD-I vs. MD-NOS: $p = 0.004$, BD-NOS vs. MD-NOS: $p = 0.003$) (Table 2).

Severity of symptom ratings. In Table 3 and Figure 1, details regarding the severity ratings of the different affective symptoms are given.

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Table 1. Demographic, Illness and Treatment Variables

	Total (n=*76*), n *(%)*	*BD-I* (n=*24*), n *(%)*	*BD-NOS* (n=*29*), n *(%)*	*MD-NOS* (n=*23*), n *(%)*	p *value*	*Pairwise group comparison*		
						BD-I vs. BD-NOS	*BD-I vs. MD-NOS*	*BD-NOS vs. MD-NOS*
Demographic variables								
Male sex, *n* (%)	31 (40.8)	9 (37.5)	10 (34.5)	12 (52.2)	0.403			
Age (mean ± SD)	15.6 ± 1.4	15.4 ± 1.4	15.9 ± 1.4	15.4 ± 1.4	0.319			
Years of education (mean ± SD)	9.7 ± 1.4	9. 4 ± 1.5	10 ± 1.4	9.7 ± 1.4	0.385			
Race, *n* (%)					0.614			
White	38 (51.4)	11 (47.8)	13 (44.8)	14 (63.6)				
Black or African American	18 (24.3)	7 (30.4)	9 (31.0)	2 (9.1)				
Mixed	14 (18.4)	4 (17.4)	6 (20.7)	4 (18.2)				
Asian or Pacific Islander	4 (5.4)	1 (4.3)	1 (3.4)	2 (9.1)				
Psychopathology, median (Q1, Q3)								
MADRS	27 (18, 35)	24.5 (15.5, 34.8)	31 (27, 36.8)	19 (8, 28)	**0.006**	n.s.	n.s.	0.001
YMRS	13 (7.5, 22)	13 (7, 31)	15 (3.8, 24.3)	11.5 (8.8, 16)	0.64			
GAF	21 (17, 40)	21 (19.3, 28.8)	20 (10, 42)	30 (20, 42)	0.306			
CGI-S	4 (3, 4)	5 (4, 5)	4 (3, 5)	4 (3, 5)	**0.01**	n.s.	0.003	n.s.
Comorbidities, *n* (%)								
Personality disorder traits	*19 (25.0)*	*6 (25.0)*	*10 (34.5)*	*3 (13.0)*	*0.208*			
Borderline personality traits	15 (19.7)	4 (16.7)	9 (31.0)	2 (8.7)	0.119			
Other personality traits	6 (7.9)	2 (8.3)	3 (10.3)	1 (4.4)	0.725			
Anxiety disorders	*31 (40.8)*	*10 (41.7)*	*12 (41.4)*	*9 (39.1)*	*0.981*			
Generalized anxiety disorder	9 (11.8)	4 (16.7)	4 (13.8)	1 (4.4)	0.391			
Obsessive-compulsive disorder	2 (2.6)	0 (0.0)	0 (0.0)	2 (8.7)	0.094			
PTSD	5 (6.6)	2 (8.3)	2 (6.9)	1 (4.4)	0.856			
Panic disorder	17 (22.4)	6 (25.0)	8 (27.6)	3 (13.0)	0.427			
Social phobia	15 (19.7)	4 (16.7)	5 (17.24)	6 (26.1)	0.656			
Disruptive behavior disorders	*42 (55.3)*	*10 (41.7)*	*18 (62.1)*	*14 (60.9)*	*0.268*			
ADHD	27 (35.5)	7 (29.2)	10 (34.5)	10 (43.5)	0.585			
Conduct disorder	10 (13.2)	2 (8.3)	5 (17.2)	3 (13.0)	0.634			
Oppositional defiant disorder	18 (23.7)	5 (20.8)	6 (20.7)	7 (30.4)	0.66			
Disruptive behavior disorder NOS	6 (7.9)	1 (4.2)	2 (6.9)	3 (13.0)	0.512			
Substance use disorders	*13 (17.1)*	*2 (8.3)*	*6 (20.7)*	*5 (21.7)*	*0.384*			
Alcohol use disorder	7 (9.2)	1 (4.2)	3 (10.3)	3 (13.0)	0.555			
Cannabis use disorder	11 (14.5)	1 (4.2)	5 (17.24)	5 (21.7)	0.200			
Eating disorders	10 (13.2)	*5 (20.8)*	*3 (10.3)*	*2 (8.7)*	*0.399*			
Enuresis	7 (9.2)	*2 (8.3)*	*3 (10.3)*	*2 (8.7)*	*0.964*			
Pharmacotherapy: Admission, n (%)								
Antipsychotics	55 (72.4)	20 (83.3)	19 (65.5)	16 (69.6)	*0.331*			
Typical antipsychotics	3 (3.9)	2 (8.3)	0 (0)	1 (4.3)	0.298			
Atypical antipsychotic	52 (68.4)	18 (75.0)	19 (65.5)	15 (65.2)	0.704			
Antidepressants	27 (35.5)	5 (20.8)	11 (37.9)	11 (47.8)	*0.146*			
Selective serotonin reuptake inhibitors	23 (30.3)	5 (20.8)	9 (31)	9 (39.1)	0.391			
Bupropion	3 (3.9)	0 (0)	2 (6.9)	1 (4.3)	0.436			
Others	4 (5.3)	1 (4.2)	1 (3.4)	2 (8.7)	0.673			
Mood stabilizers	23 (30.3)	7 (29.2)	7 (24.1)	9 (39.1)	*0.500*			
Lithium	17 (22.4)	6 (25)	3 (10.3)	8 (34.8)	0.103			
Valproate	7 (9.2)	2 (8.3)	3 (10.3)	2 (8.7)	0.964			
Lamotrigine	4 (5.3)	1 (4.2)	2 (6.9)	1 (4.3)	0.882			
Other mood stabilizers	2 (2.6)	0 (0)	2 (6.9)	0 (0)	0.189			
Anxiolytics	8 (10.5)	4 (16.7)	3 (10.3)	1 (4.3)	0.388			
ADHD medications	9 (11.8)	1 (4.2)	4 (13.8)	4 (17.4)	*0.343*			

(*continued*)

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TABLE 1. (CONTINUED)

	Total (n=*76*), n *(%)*	*BD-I* (n=*24*), n *(%)*	*BD-NOS* (n=*29*), n *(%)*	*MD-NOS* (n=*23*), n *(%)*	p *value*	*Pairwise group comparison*		
						BD-I vs. BD-NOS	*BD-I vs. MD-NOS*	*BD-NOS vs. MD-NOS*
Pharmacotherapy: discharge, *n* (%)								
Antipsychotics	50 (65.8)	19 (79.2)	18 (62.1)	13 (56.5)	*0.227*			
Typical antipsychotics	0 (0)	0 (0)	0 (0)	0 (0)	n.a.			
Atypical antipsychotics	50 (65.8)	19 (79.2)	18 (62.1)	13 (56.5)	0.227			
Antidepressants	*15 (19.7)*	*5 (20.8)*	*3 (10.3)*	*7 (30.4)*	*0.193*			
Selective serotonin reuptake inhibitors	12 (15.8)	4 (16.7)	2 (6.9)	6 (26.1)	0.168			
Bupropion	2 (2.6)	0 (0)	1 (3.4)	1 (4.3)	0.610			
Others	2 (2.6)	1 (4.2)	0 (0)	1 (4.3)	0.530			
Mood stabilizers	*33 (43.4)*	*16 (66.7)*	*9 (31.0)*	*8 (34.8)*	**0.020**	0.010	0.029	n.s.
Lithium	27 (35.5)	14 (58.3)	6 (20.7)	7 (30.4)	**0.014**	0.005	n.s.	n.s.
Valproate	7 (9.2)	2 (8.3)	3 (10.3)	2 (8.7)	0.964			
Lamotrigine	4 (5.3)	3 (12.5)	0 (0)	1 (4.3)	0.124			
Anxiolytics	*6 (7.9)*	*2 (8.3)*	*3 (10.3)*	*1 (4.3)*	0.725			
ADHD medications	*5 (6.6)*	*1 (4.2)*	*2 (6.9)*	*2 (8.7)*	*0.819*			

Bolds values indicate $p < 0.05$ for between-groups analysis. Italic values indicate diagnostic categories that include the subsequent diagnoses.

ADHD, attention deficit hyperactivity disorder; BD-I, bipolar disorder type I; BD-NOS, bipolar disorder not otherwise specified; CGI-S, Clinical Global Impressions Scale; GAF, global assessment of functioning; MADRS, Montgomery Åsberg Depression Rating Scale; MD-NOS, mood disorder not otherwise specified; n.a., not applicable; n.s., not significant; PTSD, posttraumatic stress disorder; YMRS, Young Mania Rating Scale.

TABLE 2. PREVALENCE OF BPSS-P ITEMS RATED AT MODERATE OR HIGHER SEVERITY

	Total (n=*76*), n *(%)*	*BD-I* (n=*24*), n *(%)*	*BD-NOS* (n=*29*), n *(%)*	*MD-NOS* (n=*23*), n *(%)*	p *value*	*Pairwise group comparison*		
						BD-I vs. BD-NOS	*BD-I vs. MD-NOS*	*BD-NOS vs. MD-NOS*
BPSS-P mania symptoms								
1. Mood elevation	49 (64.5)	23 (95.8)	20 (69.0)	6 (26.1)	**<0.0001**	0.013	<0.0001	0.002
2. Irritability	71 (93.4)	23 (95.8)	27 (93.1)	21 (91.3)	0.819			
3. Inflated self-esteem/grandiosity	20 (26.3)	13 (54.2)	7 (24.1)	0 (0)	**<0.0001**	0.025	<0.0001	0.011
4. Decreased need for sleep	38 (50)	18 (75)	14 (48.3)	6 (26.1)	**0.004**	0.048	0.001	n.s.
5. Over-talkativeness	53 (69.7)	19 (79.2)	26 (89.7)	8 (34.8)	**<0.0001**	n.s.	0.002	<0.0001
6. Racing thoughts/flight of ideas	49 (65.3)	22 (91.7)	19 (65.5)	8 (36.4)	**<0.0001**	0.024	<0.0001	0.039
7. Distractibility	54 (71.1)	19 (79.2)	23 (79.3)	12 (52.2)	0.057			
8. Increased energy/goal-directed activity	36 (47.4)	21 (87.5)	11 (37.9)	4 (17.4)	**<0.0001**	<0.0001	<0.0001	n.s.
9. Increased psychomotor activity	47 (61.8)	19 (79.2)	17 (58.6)	11 (47.8)	0.078			
10. Reckless or dangerous behavior	27 (35.5)	8 (33.3)	13 (44.8)	6 (26.1)	0.361			
BPSS-P depression symptoms								
1. Depressed mood	62 (81.6)	22 (91.7)	24 (82.8)	16 (69.6)	0.145			
2. Anhedonia	45 (60.0)	18 (75.0)	20 (69.0)	7 (31.8)	**0.005**	n.s.	0.003	0.008
3. Decreased appetite	19 (25.7)	9 (39.1)	8 (27.6)	2 (9.1)	0.067			
4. Increased appetite	13 (17.3)	7 (30.4)	4 (13.8)	2 (8.7)	0.122			
5. Insomnia	35 (46.1)	13 (54.2)	16 (55.2)	6 (26.1)	0.071			
6. Hypersomnia	17 (22.4)	9 (37.5)	6 (20.7)	2 (8.7)	0.058			
7. Decreased psychomotor activity	22 (29.3)	11 (47.8)	10 (34.5)	1 (4.3)	**0.004**	n.s.	0.001	0.008
8. Decreased energy	44 (57.9)	15 (62.5)	22 (75.9)	7 (30.4)	**0.004**	n.s.	0.028	0.001
9. Worthlessness/guilt	47 (61.8)	18 (75.0)	22 (75.9)	7 (30.4)	**0.001**	n.s.	0.002	0.001
10. Decreased concentration	46 (62.2)	16 (66.7)	21 (75.0)	9 (40.9)	**0.041**	n.s.	n.s.	0.015
11. Indecision	23 (30.7)	8 (33.3)	9 (31.0)	6 (27.3)	0.904			
12. Suicidality	52 (69.3)	17 (70.8)	22 (75.9)	13 (59.1)	0.429			
BPSS-P general symptoms								
1. Mood lability	54 (71.1)	20 (83.3)	24 (82.8)	10 (43.5)	**0.002**	n.s.	0.004	0.003
2. Oppositionality	34 (45.9)	10 (41.7)	12 (44.4)	12 (52.2)	0.756			
3. Anger/aggressiveness	51 (69.9)	15 (62.5)	20 (74.1)	16 (72.7)	0.628			
4. Anxiety	40 (54.8)	16 (66.7)	13 (50.0)	11 (47.8)	0.357			
5. Self-injurious behavior	39 (52.7)	12 (50)	18 (66.7)	9 (39.1)	0.144			
6. Obsessions and compulsions	5 (6.9)	2 (8.7)	1 (3.8)	2 (8.7)	0.739			

Bolds values indicate $p < 0.05$ for between-groups analysis.

BD-I, bipolar disorder type I; BD-NOS, bipolar disorder not otherwise specified; BPSS-P, bipolar prodrome symptom scale—prospective; MD-NOS, mood disorder not otherwise specified; n.s., not significant.

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TABLE 3. SEVERITY OF BPSS-P ITEMS

	Total (n = 76), median (Q1–Q3)	*BD-I (n = 24), median (Q1–Q3)*	*BD-NOS (n = 29), median (Q1–Q3)*	*MD-NOS (n = 23), median (Q1–Q3)*	p *value*	*Pairwise group comparison*		
						BD-I vs. BD-NOS	*BD-I vs. MD-NOS*	*BD-NOS vs. MD-NOS*
BPSS-P mania symptoms	4 (1–5)	5 (4–6)	4 (2–5)	3 (0–4)	**<0.0001**	<0.0001	<0.0001	<0.0001
1. Mood elevation	4 (3–5)	5 (5–6)	4 (3–5)	3 (1–4)	**<0.0001**	<0.0001	<0.0001	0.009
2. Irritability	5 (4.25–6)	5.5 (5–6)	5 (4.5–6)	5 (4–6)	0.081			
3. Inflated self-esteem/ grandiosity	2 (0–4)	4 (1.25–6)	1 (0–3.5)	1 (0–2)	**0.001**	0.004	0.001	n.s.
4. Decreased need for sleep	3.5 (0–6)	5 (3.25–6)	3 (0–6)	0 (0–4)	**0.003**	n.s.	0.001	n.s.
5. Over-talkativeness	5 (3–5)	5 (4–6)	5 (4–5)	3 (1–4)	**<0.0001**	n.s.	0.001	<0.0001
6. Racing thoughts/flight of ideas	4 (2–5)	5 (4.25–6)	4 (2–5)	2.5 (0.75–4)	**<0.0001**	0.024	<0.0001	0.048
7. Distractibility	5 (3–5)	5 (4–6)	5 (4–5)	4 (1–5)	**0.01**	n.s.	0.007	0.012
8. Increased energy/goal-directed activity	3 (2–5)	5 (4–6)	3 (2–4)	1 (0–3)	**<0.0001**	<0.0001	<0.0001	0.004
9. Increased psychomotor activity	4 (3–5)	4 (4–6)	4 (2.5–5)	3 (1–4)	**0.017**	n.s.	0.005	n.s.
10. Reckless or dangerous behavior	1.5 (0–5)	1 (0–4.75)	2 (0–5)	2 (0–4)	0.82			
BPSS-P depression symptoms	3 (0–5)	4 (1–5)	4 (1–5)	2 (0–4)	**<0.0001**	n.s.	<0.0001	<0.0001
1. Depressed mood	5 (4–6)	6 (5–6)	5 (4–6)	4 (3–5)	**0.004**	n.s.	<0.0001	0.022
2. Anhedonia	4 (3–5)	5 (3.25–5)	4 (3–6)	3 (1.5–4)	**0.006**	n.s.	0.002	0.015
3. Decreased appetite	1 (0–4)	1 (0–4)	2 (0–4)	0 (0-I)	**0.026**	n.s.	0.036	0.008
4. Increased appetite	1 (0–3)	2 (0–4)	0 (0–3)	0 (0–2)	**0.047**	0.034	0.033	n.s.
5. Insomnia	3 (0–5)	4 (0–5)	4 (2–5)	1 (0–4)	0.071			
6. Hypersomnia	1 (0–3)	3 (0–5)	1 (0–3)	0 (0–3)	0.092			
7. Decreased psychomotor activity	2 (0–4)	3 (3–5)	1 (0–4)	0 (0–2)	**0.001**	0.03	<0.0001	n.s.
8. Decreased energy	4 (1–5)	4 (1–6)	5 (3.5–6)	2 (0–4)	**0.017**	n.s.	n.s.	0.005
9. Worthlessness/guilt	4 (1–5)	4 (2.5–5)	4 (3.5–5)	3 (0–5)	**0.027**	n.s.	0.031	0.013
10. Decreased concentration	4 (1–5)	4.5 (2.25–5)	4 (3.25–5)	2 (0–4)	**0.014**	n.s.	0.016	0.007
11. Indecision	2 (0–4)	2 (0.25–4.75)	2 (1–4)	1.5 (0–4)	0.350			
12. Suicidality	6 (2–6)	5.5 (3–6)	6 (3–6)	4.5 (0–6)	0.185			
BPSS-P General symptoms	4 (0–5)	4 (0–5)	4 (1–5)	3 (1–5)	**0.038**	n.s.	n.s.	0.011
1. Mood lability	5 (3–6)	5 (4–6)	5 (4–6)	3 (0–5)	**0.001**	n.s.	0.002	0.001
2. Oppositionality	3 (1.75–5)	3 (0–4)	3 (2–5)	4 (2–5)	0.513			
3. Anger/aggressiveness	5 (3–5.5)	5 (3–6)	4 (3–5)	5 (3–5.25)	0.949			
4. Anxiety	4 (2–5)	4.5 (3–5.75)	3.5 (1.75–5)	2 (1–5)	**0.044**	0.031	0.031	n.s.
5. Self-injurious behavior	4 (0–5)	2.5 (0–4.75)	4 (0.5–6)	3 (0–4)	**0.035**	n.s.	n.s.	0.012
6. Obsessions and compulsions	0 (0–1)	0 (0–1)	0 (0–2)	0 (0–1)	0.959			

Bolds values indicate $p < 0.05$ for between-groups analysis.

Severity is rated on an ordinal scale: 0 = absent, 1 = questionably present, 2 = mild, 3 = moderate, 4 = moderately severe, 5 = severe, 6 = extreme.

BD-I, bipolar disorder type I; BD-NOS, bipolar disorder not otherwise specified; BPSS-P, bipolar prodrome symptom scale-prospective; MD-NOS, mood disorder not otherwise specified; n.s., not significant; Q1, first quartile (P25); Q3, third quartile (P75).

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BPSS-P_mania index. Pooled together, the severity of sub-/syndromal symptoms of mania differed significantly across the 3 diagnostic groups ($p < 0.0001$), being higher in patients with BD-I (median 5—severe–worst month lifetime; $p < 0.0001$) versus BD-NOS (median = 4, $p < 0.0001$) and MD-NOS (median = 3, $p < 0.0001$) (Fig. 1). The three groups differed in at least one group comparison on 8 of the 10 mania index items, except for irritability ($p = 0.081$) and reckless/dangerous behavior ($p = 0.82$). Specifically, compared with BD-NOS, BD-I patients scored significantly more severe on 4 of the 10 mania items (mood elevation, inflated self-esteem/grandiosity, racing thoughts/flight of ideas, and increased energy/goal-directed activity). Compared with MD-NOS, BD-I patients scored significantly more severe on 8 of the 10 mania items (mood elevation, inflated self-esteem/grandiosity, decreased need for sleep, over-talkativeness, racing thoughts/flight of ideas, distractibility, increased energy/goal-directed activity, and increased psychomotor activity). Finally, compared with MD-NOS, BD-NOS patients scored significantly more severe on 5 of the 10 mania items (mood elevation, over-talkativeness, racing thoughts/flight of ideas, distractibility, and increased energy/goal-directed activity) (Table 3).

BPSS-P_depression index. Pooled together, the severity of sub-/syndromal symptoms of depression was significantly higher ($p < 0.0001$) in each BD-I and BD-NOS, which had similar median severity scores of 4 (''moderately severe'') versus MD-NOS (median = 2) (Fig. 1). The three groups differed in at least one group comparison on 8 of the 12 depression index items, without differences for insomnia ($p = 0.071$), hypersomnia ($p = 0.092$), indecision ($p = 0.35$), and suicidality ($p = 0.18$). Specifically, compared with BD-NOS, BD-I patients scored significantly more severe on 2

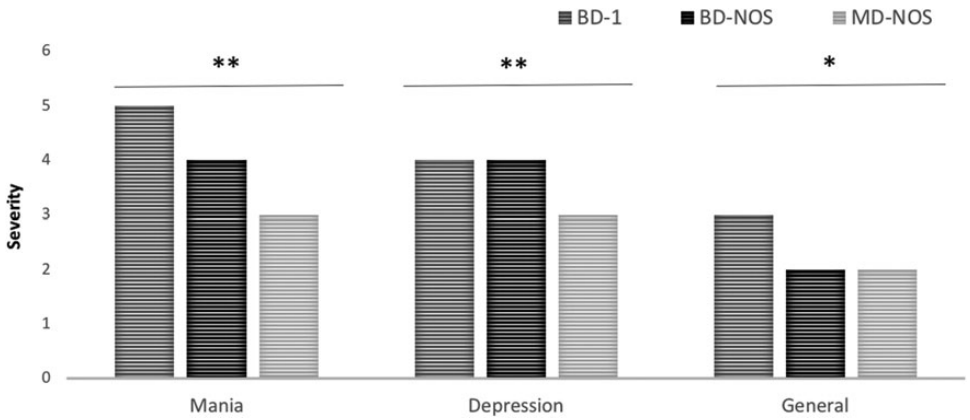

FIG. 1. Severity of BPSS-P mania, depression and general symptom Index subthreshold symptoms. *$p < 0.05$; **$p < 0.0001$. BD-I, bipolar disorder type I; BD-NOS, bipolar disorder not otherwise specified; BPSS-P, bipolar prodrome symptom scale-prospective; MD-NOS, mood disorder not otherwise specified.

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of the 12 depression items (increased appetite and decreased psychomotor activity). Compared with MD-NOS, BD-I patients scored significantly more severe on 7 of the 12 depression items (depressed mood, anhedonia, decreased appetite, increased appetite, decreased psychomotor activity, worthlessness/guilt, and decreased concentration). Finally, compared with MD-NOS, BD-NOS patients scored significantly more severe on 6 of the 12 depression items (depressed mood, anhedonia, decreased appetite, decreased energy, worthlessness/guilt, and decreased concentration) (Table 3).

BPSS-P General Symptom Index. Pooled together, BPSS-P general symptom severity differed across the three diagnostic groups ($p = 0.038$), but in *post hoc* pairwise comparisons only BD-NOS had significantly higher median scores than MD-NOS (4 vs. 3, $p = 0.011$). At least one group comparison was significantly different in three of the six BSS-P general symptom items, including mood lability (BD-I and BD-NOS > MD-NOS), anxiety (BD-I > BD-NOS and MD-NOS), and self-injurious behavior (BD-NOS > MD-NOS) (Table 3).

Duration of symptoms. Subthreshold symptoms of mania and general symptoms in the BD-NOS and MD-NOS groups, and subthreshold symptoms of depression in the MD-NOS group are given in Tables 4 and 5.

The median duration of subthreshold mania symptoms in BD-NOS was 20.4 weeks, with the shortest duration for inflated self-esteem/grandiosity and reckless or dangerous behavior (16.4 weeks, each) and the longest duration for decreased need for sleep (27.4 weeks). As for general symptoms, the median duration was

Table 4. Duration of BPSS-P Mania and General Symptoms Rated at Moderate or Higher Severity Since Onset (Weeks)

	BD-NOS (n = *29*), *median (Q1–Q3)*	*MD-NOS* (n = *23*), *median (Q1–Q3)*
BPSS-P mania symptoms	20.4 (12.1–30.7)	11.7 (6.1–28.4)
1. Mood elevation	20.1 (8.3–31.9)	12 (7.3–40.3)
2. Irritability	20.4 (12.1–30.7)	10.2 (5.3–14.6)
3. Inflated self-esteem/grandiosity	16.4 (0.7–18.2)	4.9 (0.54–43.6)
4. Decreased need for sleep	27.4 (13.7–32.9)	14.57 (11.21–48.07)
5. Over-talkativeness	20.3 (13–30.9)	14.43 (5–34.07)
6. Racing thoughts/flight of ideas	21.4 (15.4–27.7)	12.71 (8.07–37.75)
7. Distractibility	22.4 (12.7–31.1)	8.71 (5.86–12.86)
8. Increased energy/goal-directed activity	23.3 (7.5 33.2)	34.64 (28.43–40.86)
9. Increased psychomotor activity	24.9 (15–31.6)	11.86 (7.86–18.14)
10. Reckless or dangerous behavior	16.4 (7.4–20.9)	8.43 (2.57–14.21)
BPSS-P general symptoms	21.6 (14.9–30.7)	12.0 (7–28.4)
1. Mood lability	20.4 (8.3–30.3)	12 (6.1–28.4)
2. Oppositionality	22 (16.6–30.9)	8.6 (3.7–21)
3. Anger/aggressiveness	21 (8.3–31.2)	10.2 (5.3–18.1)
4. Anxiety	25.5 (18.5–32)	13.2 (8.5–37.7)
5. Self-injurious behavior	21 (15.6–30.1)	24.1 (10.1–46)
6. Obsessions and compulsions	15.4 (1.1–17.9)	11.6 (8.7–14.4)

BD-NOS, bipolar disorder not otherwise specified; BPSS-P, bipolar prodrome symptom scale-prospective; MD-NOS, mood disorder not otherwise specified; Q1, first quartile (P25); Q3, third quartile (P75).

Table 5. Duration of BPSS-P Depressive Symptoms Rated at Moderate or Higher Severity Since Onset (Weeks)

	MD-NOS (n = *23*) *Median (Q1–Q3)*
BPSS-P depression symptoms	21.6 (13.3–29.9)
1. Depressed mood	21.6 (13.3–30.7)
2. Anhedonia	21 (12.4–30.5)
3. Decreased appetite	20.3 (4.2–29.1)
4. Increased appetite	15.7 (8.6–20.7)
5. Insomnia	22.4 (12.1–29.9)
6. Hypersomnia	20.4 (17.1–31.6)
7. Decreased psychomotor activity	24.9 (18.3–32.2)
8. Decreased energy	21.6 (12.7–30.3)
9. Worthlessness/guilt	21.6 (12.1–30.7)
10. Decreased concentration	23.6 (13–30.9)
11. Indecision	20.9 (14.9–27.1)
12. Suicidality	21.6 (14.9–28.4)

BPSS-P, bipolar prodrome symptom scale-prospective; MD-NOS, mood disorder not otherwise specified; Q1, first quartile (P25); Q3, third quartile (P75).

21.6 weeks, with the shortest duration for obsessions and compulsions (15.4 weeks) and the longest duration for anxiety (25.5 weeks) (Table 4).

The median duration of subthreshold symptoms of mania in MD-NOS was 11.7 weeks, with the shortest duration for inflated self-esteem/grandiosity (4.9 weeks) and longest duration for increased energy/goal-directed activity (34.6 weeks). The median duration of depressive symptoms in this group was 21.6 weeks, ranging from 15.7 weeks (increased appetite) to 24.9 weeks (decreased psychomotor activity). The median duration of general symptoms was 12 weeks, with the shortest duration for oppositionality (8.6 weeks) and the longest duration for self-injurious behavior (24.1 weeks) (Tables 4 and 5).

Comparing the durations of subthreshold symptoms, the median duration of subthreshold mania symptoms in BD-NOS was significantly longer than in the MD-NOS group (20.4 vs. 11.7 weeks, $p = 0.002$). The same was true for the general symptom duration (21.6 vs. 12.0 weeks, $p = 0.022$). Within the MD-NOS group, the duration of subthreshold depressive symptoms (21.6 weeks) was significantly longer than the duration of subthreshold mania (11.7 weeks, $p = 0.015$) and general symptoms (12.0 weeks, $p = 0.012$), whose duration was not different from each other ($p = 0.82$).

Pharmacologic treatment

The most used psychotropic medications upon admission were antipsychotics (72.4%, $p = 0.331$), followed by antidepressants (35.5%, $p = 0.146$) and mood stabilizers (30.3%, $p = 0.500$) (Table 1). The most prescribed psychotropic medications upon discharge were antipsychotics (65.8%, $p = 0.227$) and mood stabilizers [43.4%, $p = 0.020$; BD-I (66.7%) vs. BD-NOS (31.0%): $p = 0.01$; BD1 vs. MD-NOS (34.8%): $p = 0.029$], followed by antidepressants (19.7%, $p = 0.193$). Whereas the reduction from admission to discharge in antipsychotic prescribing ($p = 0.38$) and the increase in mood stabilizer prescribing ($p = 0.09$) were not statistically significant at overall group level, the decrease in antidepressant prescribing ($p = 0.029$) was statistically significant. Within individual diagnostic groups, the significant decrease in antidepressant prescribing was apparent only in the BD-NOS group (37.9% to 10.3%, $p = 0.014$), whereas there was a significant increase in mood stabilizer treatment in the BD-I group (29.2% to 66.7%, $p = 0.009$).

Discussion

Psychopathology

This study evaluated a sample of adolescent patients diagnosed with a BD-spectrum disorder who had been admitted to a psychiatric unit. In all three diagnostic groups, psychopathology measures (CGI-S, MADRS) suggested moderate severity of psychopathology, with greater depression than mania scores. These findings are consistent with previous studies, where symptoms in youth with BD-spectrum disorders were considered disabling (Hernandez et al. 2017).

In our sample, patients diagnosed with BD-I and BD-NOS did not differ on depression severity, and BD-NOS scored higher on the MADRS scale compared with MD-NOS, which is consistent with the previous literature, showing important rates of depression in BD-NOS compared with other psychiatric diagnoses including major depression (Towbin et al. 2013). Conversely, overall, YMRS scale scores were only about half as severe as scores on the MADRS (with both scales ranging from 0 to 60 points), and none of the three diagnostic groups differed from each other. In contrast to moderate illness and depressive symptom severity, functional levels, measured with the GAF scale, were severely impaired in all three groups in our sample.

Comorbidity

Comorbidities, as previously described in patients with BD-spectrum disorders (Shain 2012; Muneer 2016), especially in adolescents (Shain 2012), were very highly prevalent in our sample, particularly disruptive behavior disorders and anxiety disorders. With one third, attention-deficit/hyperactivity disorder (ADHD) was the most frequent individual condition comorbid with BD-spectrum disorders. This finding is consistent with some (Wingo and Ghaemi 2007; Torres et al. 2017), but different from other studies conducted in adults where anxiety disorders (particularly panic attacks) were the most common comorbid diagnoses (Merikangas et al. 2011).

Moreover, ADHD was not only the most common comorbidity in BD-I, but also in BD-NOS and, especially, in MD-NOS. Similarly, in the COBY study, ADHD was the most common comorbid condition in BD-NOS, both in nonconverters (63.6%) and in those that converted to BD-I (61.9%) (Axelson et al. 2011). Detecting and managing comorbidities in youth with BD-spectrum disorders is important, as in addition to their own burden, worsening of these conditions could trigger a mood episode recurrence (Yen et al. 2016).

Subsyndromal symptoms

In our sample, using the BPSS-P, we observed important rates (>90%) of mania-like and depression symptoms. This thorough approach enabled the detection of subtle and subthreshold symptoms of different severity and suggests that the BPSS-P can be a useful instrument to detect symptomatology below the threshold of syndromal YMRS ratings and anchors (Correll et al. 2014). Previous studies have suggested that a greater severity of subthreshold mania-like symptoms might imply greater risk of developing a full episode of mania (Tijssen et al. 2010; Mesman et al. 2013; Hafeman et al. 2016; Duffy et al. 2017; Goodday et al. 2017). This risk of BD development might also be increased by comorbid conditions, such as ADHD and anxiety disorders (Mesman et al. 2013) (Hafeman

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et al. 2016) that can also delay symptom remission (Bukh et al. 2016). Unfortunately, the validity of the clinical diagnosis of BD is often suboptimal, especially in youth (Dilsaver and Akiskal 2005) and the presence of syndromal BD is under-recognized, which complicates identification of high-risk youth and timely targeted preventative interventions.

The median duration of subthreshold symptoms of mania was 5 months in the BD-NOS group and 3 months in the MD-NOS group, whereas the median duration of depressive symptoms was 5 months. These are significant amounts of time, especially for adolescents who need to reach relevant social and educational as well as biological milestones and who are at risk of developing BD-I (Birmaher et al. 2006). Early recognition and appropriate intervention of BD-spectrum disorders, and prevention are urgently needed, indicated by data showing that longer delays before first treatment in BD have been associated with longer and more severe depressive phases, more comorbid disorders, and less time free of symptoms in adolescence or early adulthood (Birmaher et al. 2006). Thus, the ability to detect signs and symptoms that could be part of a mania prodrome and to characterize frequencies, severity, and duration of such symptoms is critical for BD prevention and management, as identifying and treating illness early in its time course may be associated with better prognosis (Berk et al. 2007).

Unfortunately, different from schizophrenia, subthreshold symptom detection models for youth at-risk for BD, which would allow earlier intervention and reduction in overall morbidity and mortality, have not been implemented widely (Hunt et al. 2016). Nevertheless, it is hoped that a multidisciplinary approach, including psychoeducation and management of substance misuse and other clinically relevant psychiatric and physical comorbidities (Martin and Smith 2013) could alter the trajectory of mood disorder pathology (Walker et al. 2014) and make early intervention and prevention in BD feasible, including in adolescents (Arango et al. 2018).

However, the field still needs to figure out the specificity of putatively prodromal symptoms for mania in adolescence where many maturational and adaptational processes take place, and mood and affective shifts are observed (Hauser and Correll 2013).

Pharmacologic treatment

Of note, despite the fact that less than one-third of the entire sample had a diagnosis of BD-I, antipsychotics were the most commonly clinically prescribed psychotropic drug class, being prescribed to almost three-quarters of the sample upon admission, without significant differences between the three BD-spectrum groups. Although, at least for pediatric patients, second-generation antipsychotics seem to be more efficacious than conventional mood stabilizers for mania (Correll et al. 2010), this widespread use of antipsychotics even for BD-NOS and MD-NOS is concerning, given the well-known adverse effects, including cardiovascular effects (Geller et al. 2012; Arango et al. 2014). From admission to discharge, the antipsychotic prescribing decreased nonsignificantly to two-thirds, but there was a significant decrease in antidepressant prescribing in the BD-NOS group (37.9% to 10.3%, $p = 0.014$), whereas there was a significant increase in mood stabilizer treatment in the BD-I group (29.2% to 66.7%, $p = 0.009$).

The decrease in antidepressant treatment in the BD-NOS group may have been owing to a recognition of BD-risk and that antidepressants could worsen this risk (Luft et al. 2018); however, we did not collect data on reasons for medication changes during the hospital stay. The significant increase in mood stabilizer treatment in BD-I patients seems to suggest that combination treatments with antipsychotics and mood stabilizers were chosen in this sample in need for hospitalization, likely based on the premise that antipsychotic mood stabilizer cotreatment may be superior to antipsychotic monotherapy. Finally, the decrease in the use of ADHD medication from admission to discharge could indicate that some of the symptoms that patients previously diagnosed with ADHD presented could have been secondary to prodopaminergic treatment.

Limitations

Results of this study must be interpreted within its limitations. First, given the relatively small sample size, power to detect statistical significance was reduced and some of the findings, although not statistically significant, might be clinically relevant. Second, we focused solely on BD-I, BD-NOS, and MD-NOS patients, excluding the 9 patients with BD-II because of the limited number of such adolescents who were part of this consecutively accrued psychiatric adolescent inpatient sample. Future studies containing more youth with BD-II and/or cyclothymia are hoped to shed further light on the cross-sectional differences to other subsyndromal and syndromal mood disorders and their longitudinal outcomes. Third, no nonbipolar-spectrum disorder psychiatric control group was assessed for comparison. Fourth, although the K-SADS-PL is the gold standard tool for diagnosing psychiatric disorders in child and adolescent populations, some symptom collections are based on retrospective data, which may be prone to recall bias. We tried to minimize this potential problem by interviewing caretakers as well. Fifth, many patients received psychotropic medications at the time of the assessment, which could possibly have influenced our results. Sixth, because this is a cross-sectional study, we lack prospective follow-up data at this point, and we cannot conclude if characterized subthreshold symptoms are prodromal or not. Finally, we did not collect information about biological correlates of BD or reasons for medication change.

Nevertheless, despite these limitations, this is one of the few studies that carefully assessed adolescents with BD-I, BD-NOS, and MD-NOS with the same methodology and in the same study. Moreover, the focus on help-seeking individuals with a wide variety of psychopathology and psychotropic treatment is also a strength, as this reflects clinical reality in groups of patients who are at risk of developing a syndromal affective episode and disorder, increasing the generalizability and applicability of these findings. The study has further strengths including the use of structured and validated instruments for the diagnosis and assessment of syndromal and subsyndromal and putatively prodromal psychopathology. Finally, information was obtained from both patients and parents/caregivers and the time delay between symptoms' onset and data collection was still relatively short compared with other retrospective studies (especially in adults), reducing recall bias further.

Conclusions

In conclusion, youth with BD-I, BD-NOS, and MD-NOS present with considerable psychiatric comorbidity and clinical severity as well as functional impairment. Our results suggest that many youths with BD-spectrum diagnoses undergo a long symptomatic period characterized by subthreshold symptoms of the subsequent mood episode. Future studies are necessary to better characterize the BD prodrome, to determine valid and sufficiently specific clinical high-risk criteria, distinguish risk factors, endophenotypes, and comorbidities from prodromal symptomatology, elucidate predictors of conversion to BD across the lifespan, and to develop phase-specific

interventions that titrate the risk of interventions to the risk of transition to mania and to functional impairment or distress.

Clinical Significance

Youth with BD-I, BD-NOS, and MD-NOS experience considerable symptomatology and are functionally impaired, with few differences observed in psychiatric comorbidity and clinical severity. Moreover, youth with BD-NOS and MD-NOS undergo a period with subthreshold manic symptoms, enabling identification and, possibly, preventive intervention of those at risk for developing BD and for suffering a new affective episode that might lead to hospitalization.

Disclosures

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5.3. PUBLICATION 3

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Clinical Review & Education

JAMA Psychiatry | Review

Clinical Validity of *DSM-5* Attenuated Psychosis Syndrome
Advances in Diagnosis, Prognosis, and Treatment

Gonzalo Salazar de Pablo, MD; Ana Catalan, MD, PhD; Paolo Fusar-Poli, MD, PhD, RCPsych

IMPORTANCE Since the release of the *DSM-5* diagnosis of attenuated psychosis syndrome (*DSM-5*–APS) in 2013, several research studies have investigated its clinical validity. Although critical and narrative reviews have reviewed these progresses, no systematic review has comprehensively summarized the available evidence regarding the clinical validity of *DSM-5*–APS.

OBJECTIVE To provide current evidence on the clinical validity of *DSM-5*–APS, focusing on recent advances in diagnosis, prognosis, and treatment.

EVIDENCE REVIEW A multistep literature search using the Web of Science database, Cochrane Central Register of Reviews, Ovid/PsychINFO, conference proceedings, and trial registries from database inception to June 16, 2019, was conducted following PRISMA and MOOSE guidelines and PROSPERO protocol. Studies with original data investigating individuals diagnosed using *DSM-5*–APS or meeting comparable criteria were included. The results of the systematic review were summarized in tables and narratively synthesized against established evidence-based antecedent, concurrent, and prognostic validators. A quantitative meta-analysis was conducted to explore the cumulative risk of psychosis onset at 6, 12, 24, and 36 months in individuals diagnosed using *DSM-5*–APS criteria.

FINDINGS The systematic review included 56 articles, which reported on 124 validators, including 15 antecedent, 55 concurrent, and 54 prognostic validators. The epidemiological prevalence of the general non–help-seeking young population meeting *DSM-5*–APS criteria was 0.3%; the prevalence of individuals meeting *DSM-5*–APS criteria was variable in clinical samples. The interrater reliability for *DSM-5*–APS criteria was comparable with that of other *DSM-5* mental disorders and can be optimized by the use of specific psychometric instruments. *DSM-5*–APS criteria were associated with frequent depressive comorbid disorders, distress, suicidality, and functional impairment. The meta-analysis included 23 prospective cohort studies, including 2376 individuals. The meta-analytical risk of psychosis onset was 11% at 6 months, 15% at 12 months, 20% at 24 months, and 23% at 36 months. Research into predisposing and precipitating epidemiological factors, neurobiological correlates, and effective treatments for *DSM-5*–APS criteria has been limited.

CONCLUSIONS AND RELEVANCE Over recent years, *DSM-5*–APS criteria have received substantial concurrent and prognostic validation, mostly driven by research into the clinical high-risk state for psychosis. Precipitating and predisposing factors, neurobiological correlates, and effective treatments are undetermined to date.

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Supplemental content

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In 2013, the *DSM-5* introduced the diagnosis of attenuated psychosis syndrome (*DSM-5*–APS) in Research Appendix Section III under the heading Conditions for Further Study.[1(p783)] However, *DSM-5*–APS also appears in the main body of the text,[1(p122)] where it is featured with the official codable diagnosis of other specified schizophrenia spectrum disorder and other psychotic disorder (code 298.8) (eTable 1 in the Supplement).

The rationale for introducing *DSM-5*–APS was grounded in clinical research evidence from the clinical high-risk state for psychosis (CHR-P),[2] which has allowed preventive interventions to enter clinical practice.[3] Consequently, the diagnostic structure of *DSM-5*–APS is based on a subset of CHR-P risk criteria (eAppendix 1 in the Supplement), including the attenuated positive symptom syndrome criteria as defined by the Structured Interview for Psychosis-Risk Syndromes (SIPS-APSS)[4] version 2[5,6] (released June 8, 1998) and, to a lesser extent, the Comprehensive Assessment of At-Risk Mental States[7] operationalization of attenuated psychotic symptoms (CAARMS-APS).

Although the SIPS-APSS, CAARMS-APS, and *DSM-5*–APS criteria all measure attenuated psychotic symptoms, there are substantial operationalization differences across them (**Table 1**). The SIPS-APSS and CAARMS-APS operationalization are measured through semistructured interviews (SIPS and CAARMS, respectively) that require specific psychometric training; conversely, *DSM-5*–APS is unstructured and measured clinically, as any other standard psychiatric diagnosis. Consequently, the interrater agreement is very high within SIPS[10] and CAARMS[11] but lower for *DSM-5*–APS.[12] Psychosis onset is also defined psychometrically under the SIPS-APSS and CAARMS-APS criteria but clinically in *DSM-5*–APS. Another key difference is that while *DSM-5*–APS requires symptoms to be sufficiently distressing and disabling for the patient to warrant clinical attention (criterion D), this is not strictly required by the SIPS-APSS or CAARMS-APS criteria. The CAARMS-APS criteria substantially differ from *DSM-5*–APS with respect to frequency (criterion B) and onset (criterion C) of symptoms, requirements for differential diagnosis with other mental disorders (criterion E; the CAARMS-APS is transdiagnostic[13]), substance misuse (symptoms induced by alcohol and cannabis are included in CAARMS-APS), and threshold of psychosis onset (criterion F; because of different operationalizations of Brief Limited Intermittent Psychotic Symptoms[14,15]).

Since the agreement between *DSM-5*–APS and CAARMS-APS in help-seeking individuals is only moderate,[8] these 2 operationalizations are similar but not identical and cannot be interchangeably used, much like the *DSM-5* schizophrenia and schizophreniform disorders share similarities but are distinctive diagnostic categories. The SIPS-APSS and *DSM-5*–APS criteria are more similar; most patients meeting SIPS-APSS criteria also meet *DSM-5*–APS criteria,[16-19] and most—albeit not all—patients clinically diagnosed using *DSM-5*–APS meet psychometric SIPS-APSS criteria.[16] However, disability and distress (criterion D) are not strictly part of the SIPS-APSS criteria (Table 1); to overcome this discrepancy, SIPS version 5.6 (released May 30, 2014) introduced additional questions to specifically rate criteria A to D of *DSM-5*–APS in addition to the APSS criteria (Table 1). Therefore, only SIPS version 5.6 or likely subsequent editions can be used to psychometrically rate *DSM-5*–APS in a strict sense.

To our knowledge, this is the first systematic review, complemented by meta-analyses, that comprehensively assesses the advancements in diagnosis, prognosis, and treatment specifically for *DSM-5*–APS or closely related criteria. This is opposed to loosely focusing on CHR-P findings that are not directly comparable. This work may inform the revision of the *DSM-5* and future research in the field.

Key Points

Question What is the clinical validity of *DSM-5* attenuated psychosis syndrome (*DSM-5*–APS)?

Findings In this systematic review including 56 articles and meta-analysis including 23 cohort studies, the clinical validity of *DSM-5*–APS was tested against evidence-based antecedent, concurrent, and prognostic validators. *DSM-5*–APS has received substantial concurrent and prognostic validation, mostly from psychometric research in the field of the clinical high-risk state for psychosis, while precipitating and predisposing epidemiological factors, neurobiological research, and treatments have been underinvestigated to date.

Meaning Although current evidence supports the potential clinical validity of *DSM-5*–APS, more research should address the epidemiological profile of this diagnostic category as well as predisposing and precipitating risk factors, neurobiological correlates, and effectiveness of treatments.

Methods

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline (eTable 2 in the Supplement)[20] and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guideline (eTable 3 in the Supplement).[21] The study protocol was registered in PROSPERO (CRD42019139330).

Search Strategy and Selection Criteria

A multistep literature search was performed using the following keywords: (*Attenuated Psychosis Syndrome* OR *Attenuated Psychosis Symptoms Syndrome* OR *APS* OR *APSS*). First, the Web of Science database (Clarivate Analytics) was searched, incorporating the Web of Science Core Collection, BIOSIS Citation Index, KCI Korean Journal Database, MEDLINE, Russian Science Citation Index, and SciELO Citation Index, as well as the Cochrane Central Register of Reviews and Ovid/PsychINFO databases from database inception to June 16, 2019, in English. Second, data in relevant conference proceedings (Schizophrenia International Research Society and Early Intervention in Mental Health) and trial registries were searched. Third, the references of systematic reviews or meta-analyses that were retrieved were manually searched.

Abstracts of articles identified that were not relevant were screened out. The remaining full-text articles were then assessed for inclusion eligibility against the inclusion and exclusion criteria.

Condition and Individuals Being Studied

The following inclusion criteria were used: (1) original studies, abstracts, or conference proceedings with no restriction on the topic investigated; (2) conducted in individuals meeting the *DSM-5*–APS,

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Table 1. Diagnostic Criteria of *DSM-5* Attenuated Psychosis Syndrome (*DSM-5*-APS) Compared With the Attenuated Positive Symptom Syndrome Criteria Defined by the Structured Interview for Psychosis-Risk Syndromes (SIPS-APSS) and Attenuated Psychosis Symptoms Criteria Defined by the Comprehensive Assessment of At-Risk Mental States (CAARMS-APS)

Diagnostic Criteria	Criteria; Year of Publication			
	DSM-5-APS[1]; 2013	SIPS-APSS[4-6]; 1998	SIPS Version 5.6 Operationalization of *DSM-5*-APS; 2014	CAARMS-APS[7]; 2006
Severity	Criterion A: at least 1 of the following symptoms is present in attenuated form with relatively intact reality testing and is of sufficient severity or frequency to warrant clinical attention: (1) delusions, (2) hallucinations, and (3) disorganized speech	SIPS positive symptom scales: (P1) unusual thought content, (P2) suspiciousness, (P3) grandiose ideas, (P4) perceptual abnormalities, and (P5) disorganized communication, with at least 1 of these symptoms rated 3, 4, or 5, indicating clinically significant disturbance below a psychotic level of intensity	Same as SIPS-APSS	CAARMS positive symptoms scales rated as 3 to 5 for unusual thought content (P1) and nonbizarre ideas (P2), as 3 to 4 for perceptual abnormalities (P3), and as 4 to 5 for disorganized speech (P4)
Frequency	Criterion B: symptom(s) must have been present at least once per week for the past month	Symptoms ever been present at an average frequency of at least once per week over a month	Same as SIPS-APSS	Symptoms present from once per month to twice per week for >1 h per occasion or 3 to 6 times per week for <1 h per occasion
New onset and worsening	Criterion C: symptom(s) must have begun or worsened in the past year	Symptoms begin within the past year or any symptom currently rated 1 or more scale points higher compared with 12 mo ago; only symptoms that occurred over the past month are rated	Same as SIPS-APSS	Need to be present in the past 12 mo; rated the most severe in the past 12 mo
Distress/disability	Criterion D: symptom(s) is sufficiently distressing and disabling to the individual to warrant clinical attention	Subjective qualifier not used to assign the designation	Attenuated positive symptoms sufficiently distressing and disabling to the patient to warrant clinical attention	Rated on a scale from 0 to 100 but not used to assign the designation
Differential diagnosis	Criterion E: symptom(s) is not better explained by another mental disorder, including a depressive or bipolar disorder with psychotic features, and is not attributable to the physiological effects of a substance or another medical condition	Symptoms ever not been explained better by another *DSM* disorder	Same as SIPS-APSS	No requirement for differential diagnosis with other mental disorders
Lack of lifetime psychotic disorder	Criterion F: criteria for any psychotic disorder have never been met	Severity score of 6 on at least 1 of P1 to P5 and symptoms ever occur for at least 1 h/d at an average frequency of 4 d/wk over 1 mo or symptoms are seriously disorganizing and dangerous (urgency criteria)	Same as SIPS-APSS	Severity score of 6 on at least 1 of P1, P2, and P4 and/or score of 5 to 6 on P3 and frequency of at least 3 to 6 d/wk at >1 h per occasion or daily at <1 h per occasion and symptoms present for longer than 1 week; urgency criteria were not considered
Substance misuse	Assessed within criterion E	Exclude if symptoms are strongly intertwined temporally with substance use episodes	Same as SIPS-APSS	Exclude if symptoms occur only during peak intoxication from hallucinogens, amphetamines, and cocaine; included if due to cannabis or alcohol
Antipsychotic treatments	Not assessed	Usually assessed and considered as an exclusion criterion	Same as SIPS-APSS	Usually assessed and considered as an exclusion criterion
Functional decline	No social/occupational dysfunction decline requirement	No social/occupational dysfunction decline requirement	Same as SIPS-APSS	30% drop in SOFAS score from premorbid level sustained for 1 mo within the past 12 mo or SOFAS score <50 for the past ≥12 mo
Assessment	Unstructured clinical interview	Semistructured psychometric interview	Same as SIPS-APSS	Semistructured psychometric interview
Duration of the assessment	From 20 min[8] to 45 min[9]	Approximately 2 h	Same as SIPS-APSS	Approximately 2 h
Specific psychometric training	Not required	Required	Same as SIPS-APSS	Required

Abbreviation: SOFAS, Social and Occupational Functioning Assessment Scale.

SIPS-APSS, or SIPS version 5.6 operationalization of *DSM-5*-APS criteria (Table 1); and (3) published in English. The following exclusion criteria were used: (1) reviews, editorials, or clinical cases; (2) unpublished data; (3) studies measuring attenuated psychotic symptoms outside the *DSM-5*-APS, SIPS-APSS, or SIPS version 5.6 operationalization of *DSM-5*-APS criteria, such as those using the Basel Screening Instrument for Psychosis[22] or CAARMS-APS,[7] which are prognostically but not diagnostically comparable with *DSM-5*-APS[8]; and (4) studies that do not report specific information on the SIPS-APSS or CAARMS-APS group alone but reported composite

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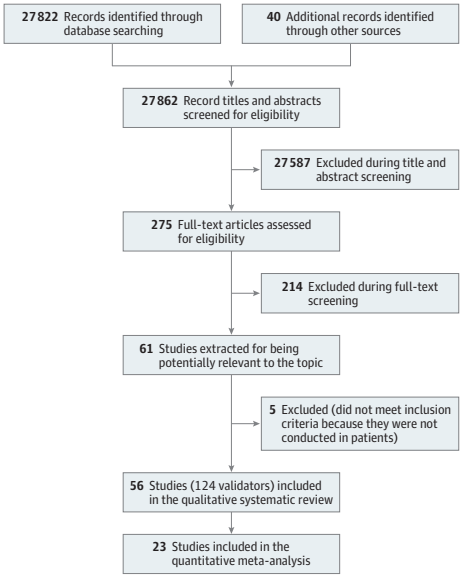
Figure 1. PRISMA Flowchart Outlining Study Selection Process



results, including other CHR-P subgroups (eg, Brief Limited Intermittent Psychotic Symptoms/Brief Intermittent Psychotic Symptoms and Genetic Risk and Deterioration Syndrome).

Outcome Measures and Data Extraction

Data were independently extracted by 2 researchers (G.S.P. and A.C.), and discrepancies were resolved consulting a third senior academic (P.F.-P.). The variables extracted included validator (antecedent, concurrent, or prognostic), author and year of publication, study type (original or abstract), study design (cross-sectional, prospective, retrospective, intervention, or naturalistic), type of diagnostic assessment (clinical or psychometric, including the SIPS version, face-to-face evaluation, medical record review, or telephone), diagnostic criteria (*DSM-5*–APS, SIPS-APSS, or SIPS version 5.6 operationalization of *DSM-5*–APS criteria), sample size, mean age and percentage of women, quality assessment, and key findings.

Quality Assessment

Study quality was assessed in all included studies. A modified version of the Newcastle-Ottawa Scale was used for cross-sectional and cohort studies[23,24] (eTable 4 in the Supplement).

Systematic Review

To systematically assess the validity of *DSM-5*–APS, the available evidence was structured in 3 main classes of potential validators, adapted from Kendler[25]:

1. Antecedent validators, including demographic factors and predisposing and precipitating risk factors.
2. Concurrent validators, including diagnostic factors and diagnostic agreement, comorbidity, neurobiological and neurocognitive factors, symptom measures and functioning, and baseline treatments.
3. Prognostic validators, including overall prognostic accuracy, risk of psychosis onset, predictors of outcomes, and response to treatments.

Meta-analysis

A quantitative meta-analysis was conducted to test the risk of psychosis onset using *DSM-5*–APS, SIPS-APSS, or SIPS version 5.6 operationalization of *DSM-5*–APS criteria (Table 1). The risk of psychosis onset was estimated as the proportion of individuals at risk who developed psychotic disorders (using SIPS, *International Classification of Diseases*, or *DSM*) at 6, 12, 24, and 36 or more months of follow-up, updating a previous publication.[26] A secondary meta-analysis was conducted to address the proportion of individuals meeting the *DSM-5*–APS, SIPS-APSS, or SIPS version 5.6 operationalization of *DSM-5*–APS criteria presenting with comorbid mental disorders (using *International Classification of Diseases* or *DSM*). For these meta-analyses, additional inclusion criterion were nonoverlapping samples and availability of at least 3 independent studies reporting on the same outcome. For pooling proportions in a meta-analysis of multiple studies, the metaprop package 21[27] of Stata statistical software version 14 (StataCorp) was used. The 95% CIs were based on score procedures.[26,28] Since high heterogeneity was expected, random-effects meta-analyses were conducted.[29] Publication biases were assessed with the metafunnel[30] and with the Egger test in metabias[31] functions of Stata[32]; the trim-and-fill method was used to correct the estimates in the case of publication biases.[33] Heterogeneity among study point estimates was assessed using Q statistics. The proportion of the total variability in the effect size estimates was evaluated with the I^2 index.[34] Meta-regressions were planned when there was substantial heterogeneity (>50%) and at least 10 studies per each outcome. All *P* values reported in the meta-analysis were 2-sided, and the level of significance was set at a *P* value less than .05.

Results

Database

The literature search yielded 27 852 citations, which were screened for eligibility; 56 articles reporting on 124 validators, including 15 antecedent validators, 55 concurrent validators, and 54 prognostic validators, were included in the systematic review (**Figure 1**). A total of 21 studies (38%) were used for the risk of psychosis meta-analysis, and 10 studies (18%) were used for the risk of comorbid mental disorders meta-analysis. A total of 46 studies (82%) used SIPS-APSS criteria, 5 (9%) used *DSM-5*–APS diagnosis, 5 (9%) used both *DSM-5*–APS and SIPS-APSS criteria (in 1 study,[18] the sample was mixed, and in 4 studies,[17,25-27] the sample met both criteria), and none used SIPS version 5.6 operationalization of *DSM-5*–APS criteria. The total sample sizes in the included studies ranged from 21 individuals[35] to 2101 individuals[36]; the sample sizes in studies with individuals meeting *DSM-5*–APS and SIPS-APSS criteria ranged from 4 individuals[37] to 689 individuals.[38] The age of participants ranged from 14.6 years[39] to 24.8 years.[8] There were 26 studies from the United States, 16 from Europe, 11 from Australasia, and 3 across different countries.

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Antecedent Validators

Demographic Factors

The epidemiological prevalence of the general non–help-seeking young population meeting *DSM-5*–APS criteria was 0.3% (eTable 5 in the Supplement).[37] The onset/worsening criterion C excluded 2.3% of the general population who felt distressed by attenuated psychotic symptoms.[37] The prevalence of individuals meeting the SIPS-APSS criteria was 1.3%[40] in the general population and 3.5% in college students.[41] The prevalence of individuals meeting SIPS-APSS criteria in clinical samples was highly variable, ranging from 3.1%[36] to 80%[42]; the association of age with the prevalence of help-seeking individuals meeting *DSM-5*–APS and SIPS-APSS criteria was inconsistent.[39,42,43] Retrospectively, 44% of patients diagnosed as having schizophrenia would have met *DSM-5*–APS criteria in the past.[16]

Predisposing and Precipitating Risk Factors

A total 47.8% of individuals meeting SIPS-APSS criteria reported having experienced at least 1 type of trauma (eTable 5 in the Supplement).[44] Younger individuals aged 15 to 18 years meeting SIPS-APSS criteria had better social and role functioning scores and less depressive symptoms than older individuals.[39] Social dysfunction in those meeting SIPS-APSS criteria was associated with symptoms distress.[10]

Concurrent Validators

Diagnostic Factors and Diagnostic Agreement

Assessors agreed with the criterion standard on the presence or absence of *DSM-5*–APS 70% of the time (κ = 0.34) (eTable 6 in the Supplement).[9] Prescreening tools have robust psychometric properties for recognizing individuals meeting SIPS-APSS criteria.[45] The interrater reliability for *DSM-5*–APS (κ = 0.46) is comparable with that of other *DSM-5* mental disorders.[12] The diagnostic agreement between *DSM-5*–APS and CAARMS-APS is only moderate (κ = 0.59).[8]

Comorbidity

Despite criterion E, among individuals meeting *DSM-5*–APS and SIPS-APSS criteria, 49% presented with comorbid depressive disorders, 22% with bipolar disorder, 38% with anxiety disorders, 9% with generalized anxiety disorder, 13% with obsessive-compulsive disorder, 20% with substance use disorders, 13% with cannabis use disorder, 7% with alcohol use disorder, and 22% with social phobia (eTables 7 and 8 in the Supplement). Other comorbid disorders that were not meta-analyzed because there were less than 3 studies included attention-deficit/hyperactivity disorder,[46,47] oppositional defiant disorders,[18] conduct disorders,[18,39] and posttraumatic stress disorder[43] (eTable 6 in the Supplement). Personality disorder traits were also frequent (57.1%),[18] in particular schizotypal personality disorders (rates varied between 17.0%[39] and 67.8%[19]) and borderline personality traits (42.9%[18]). Across help-seeking individuals assessed for *DSM-5*–APS and SIPS-APSS criteria, lifetime suicidality was more frequent in those meeting *DSM-5*–APS and SIPS-APSS criteria than in those not meeting these criteria[42,43]: approximately 26.3%[48] to 38.9%[18] of the population meeting *DSM-5*–APS and SIPS-APSS criteria experienced at least 1 lifetime suicide attempt, and suicidal ideation reached 77.8%.[18] Individuals meeting SIPS-APSS criteria also experienced an increased risk of violence.[49]

Neurobiological and Neurocognitive Factors

Neurocognition[47,50] (particularly vigilance and processing speed[51]), social cognition,[50] and metacognition[47] (which related to self-disturbances[46]) were impaired in individuals meeting SIPS-APSS criteria compared with controls (eTable 6 in the Supplement). Olfactory deficits in individuals meeting SIPS-APSS criteria were associated with the severity of negative symptoms.[35] Individuals meeting SIPS-APSS criteria displayed enhanced frontotemporal functional brain connectivity[52] and reduced mismatch negativity compared with controls.[53]

Symptom Measures and Functioning

Compared with other help-seeking samples, individuals meeting *DSM-5*–APS and SIPS-APSS criteria were more severely ill,[18,42] depressed,[18] and distressed[36] and had poorer functioning[18,42] (eTable 6 in the Supplement). The severity of attenuated psychotic symptoms (positive, negative, disorganized, and general) was significantly higher among help-seeking individuals meeting SIPS-APSS criteria than in those meeting other attenuated psychotic symptom criteria.[42,43] Attenuated psychotic symptoms were also associated with obsessive-compulsive traits, interpersonal sensitivity, and depression.[41] The most frequent unusual thought contents were being perplexed by reality and having overvalued beliefs.[54] The most frequent perceptual abnormalities were simple auditory[44,54] (typically hearing their own voice with a negative content[54]) or simple visual[44]; tactile, olfactory, or complex perceptual abnormalities were more infrequent. The severity of perceptual abnormalities was also lower in male patients compared with female patients[44] and in those with simple compared with complex perceptual abnormalities.[44] The presence of violence content in attenuated psychotic symptoms was associated with increased anxiety, negative beliefs toward self and others, and bullying.[55]

Baseline Treatments

Baseline treatment exposure ranged from 5.5% to 57.1% for antipsychotic medication[17-19,53,56-62] (mostly atypicals[53,56]), 0% to 38.1% for antidepressants,[17-19,58-63] and 4.0% to 20.8% for a combination of both.[17,19,42,60-62,64] Exposure ranged from 4.3% to 33.3% for mood stabilizers[18,58] and 9.8% to 14.3% for anxiolytics[18,58] and was 4.3% for other psychotropic drugs (eg, methylphenidate, antiepileptics)[42] (eTable 6 in the Supplement).

Prognostic Validators

Overall Prognostic Accuracy

There was only 1 study[8] reporting on *DSM-5*–APS prognostic accuracy, which was acceptable at 24 months (area under the curve = 0.76) and comparable with that of CAARMS-APS. Those diagnosed with *DSM-5*–APS had a 5-fold probability of transitioning to psychosis compared with high-risk individuals not diagnosed with *DSM-5*–APS (eTable 9 in the Supplement).[8]

Risk of Psychosis Onset

A total of 23 independent studies (1 using *DSM-5*–APS diagnostic criteria and 22 using SIPS-APSS criteria) reported risk of psychosis onset at follow-up, with an overall sample size of up to 2376 participants. The meta-analytical psychosis risk was 11% at 6 months, 15% at 12 months, 20% at 24 months, and 23% at 36 months follow-up (**Figure 2**) (**Table 2**) (eFigures 1 to 4 in the Supplement). There were

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publication biases at 12 months and 24 months that were corrected with the trim-and-fill method (eAppendices 2 to 5 in the Supplement). Meta-regressions did not show any effect of age, sex, publication year, and study quality (eTable 10 in the Supplement). In the only study using *DSM-5*–APS, there was a 28% risk of psychosis at 21 months.[8]

Predictors of Outcomes

Mean age at the time of psychosis onset was 20.3 years for male individuals and 23.5 years for female individuals,[17] with a transition time of 234 days[65] (eTable 9 in the Supplement). Of those who developed psychosis, 64.8% received a diagnosis of schizophrenia using *DSM-5*.[61] A total of 85.1% of individuals reached psychotic intensity on unusual thought content, 43.3% on suspicious ideas, 13.4% on grandiose ideas, and 46.3% on perceptual abnormalities.[65] Psychosis onset was characterized by the presence of Asian or Pacific Islander race,[17] the emergence of new symptoms[65] along with more severe and persisting positive/negative/general symptoms,[17,19,61] and lower subjective well-being.[56,66] Attenuated odd ideas,[17] thought disorder,[17] unusual thought content,[59,61] and auditory perceptual abnormalities[60] were associated with a higher risk of psychosis, while visual perceptual abnormalities were associated with a lower risk.[60] Speech features,[64] in particular disorganized communication,[58,59] were also associated with an increased risk of psychosis as well as a decline in social functioning.[58,59] Verbal memory deficits,[51,58,59] verbal fluency,[59] processing speed,[51,59] and composite cognitive measures[51] were associated with an increased risk of psychosis. Similarly, abnormalities in emotional processing,[45,67] motor dysfunction,[62] olfactory dysfunction,[35] and mismatch negativity[53] were associated with an increased risk of psychosis. Schizotypal personality disorder was not associated with increased risk of psychosis,[19] but axis II disorders along with familial psychiatric history, tobacco use, number of hospitalizations, and history of trauma were associated with suicide attempts.[48] None of these predictors were externally replicated.

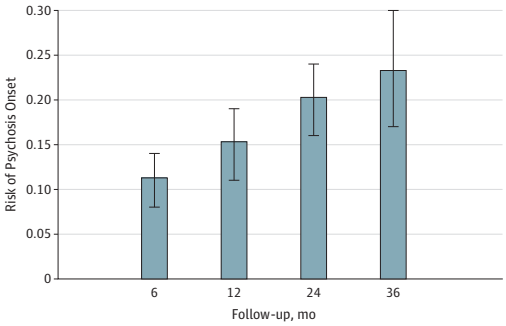
Response to Treatment

Naturalistic studies found that 25.5% of individuals received antidepressants for an average of 3 months with no improvement in negative symptoms or social functioning[63] and that 48% of individuals showed little improvement in their symptoms after 1 year, despite being treated with supportive therapy and/or psychotropic medication[56] (eTable 9 in the Supplement). The only available randomized clinical trial[68] found no significant differences in risk of psychosis onset, improvement of severity of symptoms, or functioning between cognitive behavioral therapy and supportive therapy.

Quality Assessment

The Newcastle-Ottawa Scale scores ranged from 3 to 8. The full results are detailed in eTables 11 and 12 in the Supplement.

Figure 2. Cumulative Risk of Psychosis Onset Using *DSM-5* Attenuated Psychosis Syndrome or Attenuated Positive Symptom Syndrome Criteria Defined by the Structured Interview for Psychosis-Risk Syndromes



The error bars indicate 95% CIs.

Discussion

While there are many meta-analyses on CHR-P in the literature, to our knowledge, this is the first systematic review that specifically addressed the clinical validity of *DSM-5*–APS diagnosis or comparable criteria across 56 studies and 124 validators. Most of the evidence reviewed focused on concurrent and prognostic validators in individuals meeting SIPS-APSS criteria, while antecedent factors were rarely investigated.

The systematic review of antecedent validators identified only a few records. The prevalence of individuals meeting *DSM-5*–APS diagnostic criteria is 0.3% in the general population,[37] 3.5% in college students,[41] and highly variable in clinical samples.[8,42,43] The latter point reflects the significant sampling biases that affect the CHR-P paradigm.[69-73] There is an overall paucity of robust epidemiological research addressing the specific risk or protective factors that may exert a predisposing or precipitating role in individuals meet-

Table 2. Cumulative Risk of Psychosis Onset in Individuals Meeting *DSM-5* Attenuated Psychosis Syndrome (*DSM-5*–APS) and Attenuated Positive Symptom Syndrome Criteria Defined by the Structured Interview for Psychosis-Risk Syndromes (SIPS-APSS) Criteria

Follow-up, mo	No. of Studies[a]	Individuals Meeting *DSM-5*–APS and SIPS-APSS Criteria, No.	Cumulative Risk of Psychosis (95% CI)	Q	*df*	I^2	*P* Value
6	12	824	0.11 (0.08-0.14)	20.77	11	47.04	.04
12	19	1292	0.15 (0.11-0.19)[b]	61.02	18	72.14	<.001
24	18	2212	0.20 (0.16-0.24)[c]	87.22	17	79.36	<.001
36	7	721	0.23 (0.17-0.30)	22.20	6	72.97	<.001

[a] All studies but one[8] refer to SIPS-APSS.

[b] After using the trim-and-fill method, the cumulative risk of psychosis was 0.10 (95% CI, 0.06-0.15).

[c] After using the trim-and-fill method, the cumulative risk of psychosis was 0.14 (95% CI, 0.10-0.18).

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ing *DSM-5*–APS and SIPS-APSS criteria. While recent reviews have indicated that psychosis onset is not largely driven by purely genetic risk factors,[23,74,75] it is not clear how these factors accumulate in individuals meeting *DSM-5*–APS and SIPS-APSS criteria. A further public health limitation is that only half of individuals would report a *DSM-5*–APS–like state preceding their first episode of schizophrenia,[16] calling into question the universality of this syndrome as a prepsychotic stage. Other retrospective cohort studies have confirmed a reasonably large subgroup of patients (30%) after the first episode of psychosis for whom there is no evidence of meeting prior CHR-P criteria for any identifiable length of time.[76,77] The possibility that nonpsychotic risk syndromes could precede the first onset of psychosis was summarized in a 2018 systematic review.[78]

The systematic review identified more concurrent validators. Interrater reliability for *DSM-5*–APS is comparable with that of other *DSM-5* mental disorders, although the confidence intervals of the field test were very large.[12] Noticeably, the reliability of *DSM-5*–APS can be optimized if SIPS version 5.6—or subsequent editions—operationalization of *DSM-5*–APS is being used. Unfortunately, to date, only a few studies have acknowledged using this specific SIPS version. Furthermore, despite criterion E requiring a differential diagnosis, half of the individuals meeting *DSM-5*–APS and SIPS-APSS criteria had comorbid major depressive disorders (eTable 8 in the Supplement). This is in line with phenomenological accounts highlighting the role of mood dysregulation during the phases that precede psychosis onset[79] and supporting the notion that psychosis may arise from multiple psychopathological spectra.[80] Given that psychosis onset can occur from nonpsychotic risk syndromes, the removal of this criterion may improve both its prognostic performance and transdiagnostic value.[8,13,81] Symptomatically, individuals meeting *DSM-5*–APS and SIPS-APSS criteria were more severely ill, more depressed, and had poorer functioning than other help-seeking samples not meeting *DSM-5*–APS and SIPS-APSS criteria, with a duration of untreated attenuated psychotic symptoms around 710 days.[26] Attenuated positive psychotic symptoms more frequently included derealization, overvalued beliefs, and simple auditory abnormalities,[44,54] and the presence of violence content was associated with high distress.[55] This supports the notion that *DSM-5*–APS indexes a clinical syndrome, which is disabling per se and independent from the outcomes.[24,81] In fact, most individuals meeting *DSM-5*–APS and SIPS-APSS criteria had suicidal ideation, and up to one-third of them attempted suicide.[18] At baseline, up to 57% of individuals received antipsychotic medication,[18] 38% received antidepressants,[18] and 33% received mood stabilizers,[18] corroborating the polymorbid distressing nature of this syndrome. Neurocognitive,[47,50,51] social cognitive,[50] and metacognitive[47] dysfunction, although not diagnostically required, are also frequent, while neurobiological research into individuals meeting *DSM-5*–APS and SIPS-APSS criteria is too limited to draw reliable conclusions.

The systematic review of prognostic validators confirmed that the prognostic accuracy of *DSM-5*–APS is acceptable (area under the curve = 0.76) at 24 months and comparable with the CAARMS-APS criteria.[8] Individuals meeting *DSM-5*–APS and SIPS-APSS criteria had a 5-fold probability of transitioning to psychosis compared with high-risk individuals not meeting these criteria, with a 23% risk of psychosis at 36 months' follow-up (Figure 2) (Table 2) (eFigure 4 in the Supplement). The only study using *DSM-5*–APS reported a 28% risk of psychosis onset at 21 months.[8] Of those who converted, around two-thirds received a diagnosis of schizophrenia.[61] These findings indicate a substantial risk of progression to psychosis on top of the baseline distressing clinical profile of the syndrome. However, predicting clinical outcomes in this population is currently hampered by the lack of externally validated prognostic models[82]; available models developed with stepwise approaches[58] did not replicate well in external samples.[59] There was very limited evidence relating to effective treatments for individuals meeting *DSM-5*–APS and SIPS-APSS criteria, in line with the current state of knowledge of the CHR-P field.[83] To our knowledge, only 1 randomized clinical trial compared cognitive behavioral therapy with supportive therapy[68] and did not find differences between them. Some trials are ongoing and are addressing the potential effects of treatments on clinical remission and functional outcomes[81] beyond psychosis onset.[84]

Box. Evidence-Based Reporting Recommendations for Future Clinical Research on *DSM-5* Attenuated Psychosis Syndrome (*DSM-5*–APS)

1. Test the specific *DSM-5*–APS diagnostic criteria A to F upfront in a standard psychiatric clinical assessment
2. Report the exact number of patients meeting the specific *DSM-5*–APS diagnostic criteria A to F
3. If clinical high-risk state for psychosis instruments are being used, indicate their type and version and stratify the findings across SIPS-APSS/CAARMS-APS, Genetic Risk and Deterioration Syndrome, and Brief Limited Intermittent Psychotic Symptoms/Brief Intermittent Psychotic Syndrome subgroups
4. Preferably use SIPS version 5.6—or subsequent editions—operationalization of *DSM-5*–APS for the psychometric assessment of *DSM-5*–APS; ensure an appropriate training
5. If both clinical *DSM-5*–APS and psychometric SIPS-APSS/CAARMS-APS criteria are tested in the same patients, detail their concordance/discordance

Abbreviations: CAARMS-APS, attenuated psychotic symptoms as defined by the Comprehensive Assessment of At-Risk Mental States; SIPS-APSS, attenuated positive symptom syndrome criteria as defined by the Structured Interview for Psychosis-Risk Syndromes.

The potential clinical validity of *DSM-5*–APS is further confirmed by surveys conducted in the general public and health care professionals (eTable 13 in the Supplement). Most practitioners consider *DSM-5*–APS to constitute a mental disorder[85] in which medication, family involvement, and cognitive coping skills can be helpful.[86] Importantly, in these surveys involving the general public, health care professionals,[87] undergraduates,[88] and college students,[89] the levels of stigma associated with the *DSM-5*–APS and SIPS-APSS criteria were not perceived to be higher than other mental disorders or than other psychoticlike experiences.[87,88]

Limitations

The main limitation of this review is the scarce amount of evidence on precipitating and predisposing factors, neurobiology, and preventive treatments. A further important limitation is that most studies used the SIPS-APSS designation, which does not exactly match *DSM-5*–APS. For example, some studies measured SIPS-APSS criteria and considered them as *DSM-5*–APS diagnostic criteria without clarifying the SIPS version used[18,35,38-47,49,51-60,62-64,66-68,90-101] or

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whether the symptoms were distressing and disabling to the patient to warrant clinical attention.[43,102] Therefore, this review supports the clinical utility of SIPS-APSS criteria; since *DSM-5*–APS is most similar, it also supports the clinical utility of *DSM-5*–APS diagnosis. Future studies are required to carefully avoid confusing CHR-P operationalizations with *DSM-5*–APS by testing criteria A to F (Table 1) upfront, either clinically or using SIPS version 5.6—or subsequent editions—operationalization of *DSM-5*–APS (**Box**). Accordingly, the text describing *DSM-5*–APS should be revised for accuracy and consistency with the specific evidence presented here. Most importantly, the revision of *DSM-5*–APS should carefully overcome the current misleading availability of different specifications across the main text and research appendix (eTable 1 in the Supplement). Because of such inconsistency, individuals at risk of psychosis may be mislabeled under the Other Specified Schizophrenia Spectrum and Other Psychotic Disorder code.[43] Furthermore, with few exceptions,[44,54,55] most studies were carried out in relatively small samples.

Conclusions

Current evidence supports the potential clinical validity of *DSM-5*–APS. However, more research is required to clarify the epidemiological profile of this diagnosis, its predisposing and precipitating risk factors, and neurobiological correlates and to identify effective treatments.

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DISCUSSION

6. DISCUSSION

Summary of findings/ State of the art

The work presented in this thesis intends to advance knowledge on the characterization, prognosis, and therapeutic factors in individuals with clinical syndromes which put them at high risk of developing psychotic disorders, with a particular focus on adolescents. Figure 5 below displays the different sections of the dissertation and the main publications and complementary publications included.

The main findings of the studies included in this doctoral dissertation can be summarized as follows:

Substantial advances in the detection and prognosis of CHR-P individuals have been made being indicated prevention for individuals at CHR-P one of the most established approaches of primary prevention in psychiatry. Stratified evidence by CHR-P designation -including DSM-5–APS and BLIPS- and research about individuals at risk of developing bipolar disorder has been more limited, in adolescents in particular.

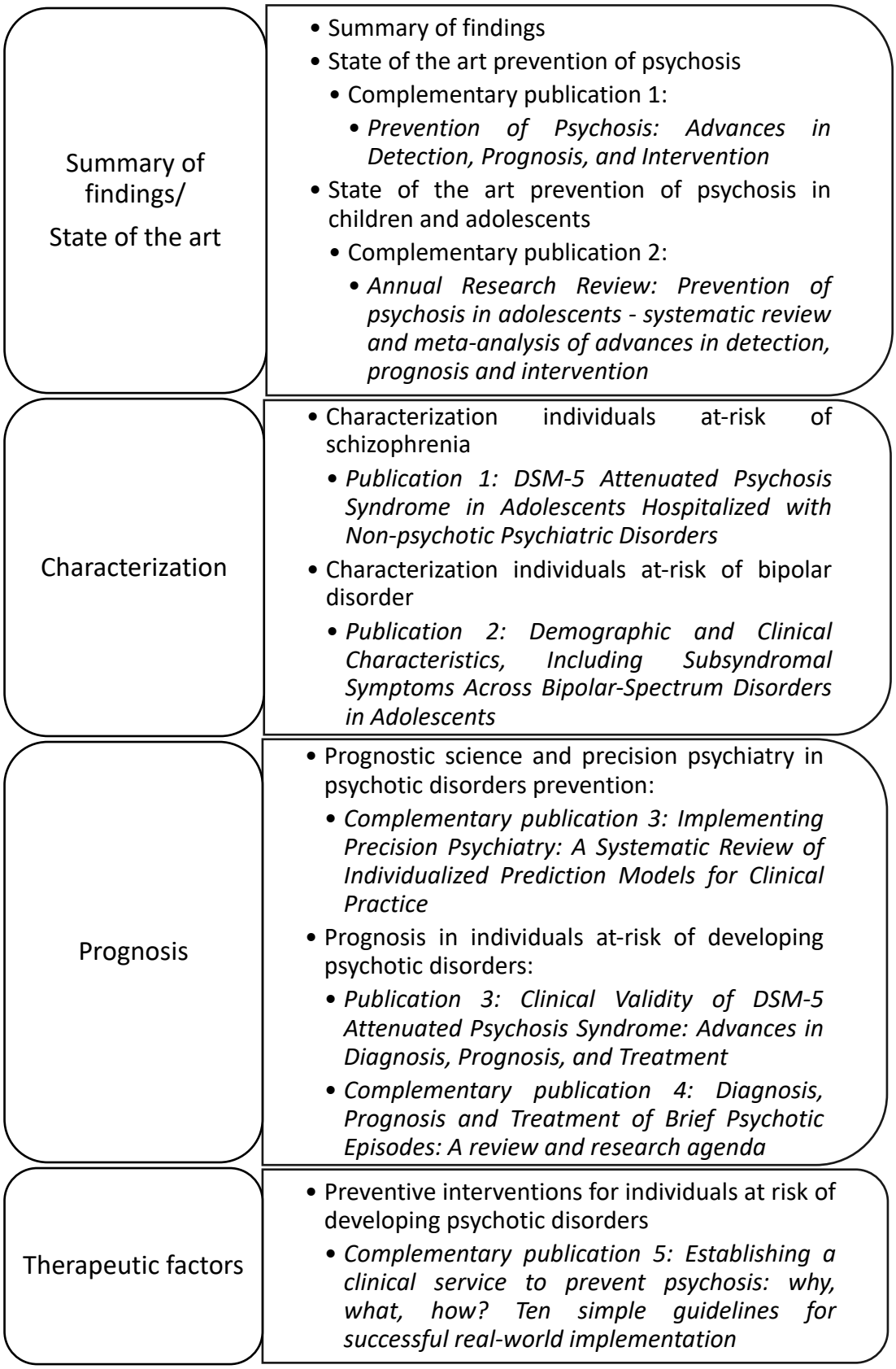
The prevalence of individuals meeting DSM-5–APS criteria is variable in clinical samples. In our sample of inpatient adolescents with non-psychotic psychiatric disorders, 26.2% fulfilled DSM-5–APS criteria. Mood and anxiety disorders were highly prevalent, and their functioning and cognition were impaired. They were frequently prescribed antipsychotic medication.

Comorbidity was frequent in individuals at risk of developing bipolar affective psychosis (BD-NOS and MD-NOS), particularly disruptive behavior disorders and anxiety disorders. They also had significant symptomatology; subthreshold manic symptoms were common; their median duration was longer in adolescents with BD-NOS than in adolescents with MD-NOS; the duration was substantial in both groups.

The meta-analytical risk of psychosis for DSM-5–APS was 15% at 12 months, 20% at 24 months, and 23% at ≥36 months; for CHR-P adolescents, transition risk was 20% at 12 months and 23% at 24 and ≥36 months; for BLIPS, the transition rates were even higher, reaching 39% at 24 months and 38% at ≥36 months. Psychosis was the most frequently investigated condition in validated prediction models in psychiatry, particularly CHR-P. Models were most frequently prognostic, and predictors were most frequently clinical.

Current evidence suggests a need for specialized services to detect CHR-P individuals in primary and secondary care settings. It further suggests the need to formulate a prognosis with validated psychometric instruments and to offer needs-based and psychological interventions to these individuals. At the moment, there is great diversity in how clinical services have been implemented.

Figure 5: Thesis Discussion Outline



Characterization

This dissertation characterized adolescents at-risk of developing psychotic disorders meeting DSM-5 Attenuated Psychosis Syndrome criteria and adolescents at risk of developing bipolar affective disorder meeting BD-NOS and MD-NOS criteria. We found that 26.2% of non-psychotic adolescents admitted into an inpatient unit fulfilled DSM-5–APS criteria. This prevalence appeared to be slightly lower but comparable to previous studies including adolescents under psychiatric clinical care (33%) (Lindgren et al., 2010, Lindgren et al., 2014). The prevalence was higher than the one found in adolescents with disruptive behaviors who were not seeking help (13%) (Manninen et al., 2014).

Comorbidity was frequent in DSM-5–APS individuals (80% for depressive disorders, 55.4% for anxiety disorders, 52.3% for disruptive, impulse-control and conduct disorders, 36.9% for bipolar disorders, 36.9% for personality disorder traits, 20% for substance use disorders, see annex 10 for complete comorbidity results), which sustains previous studies suggesting there is an association between DSM-5–APS (Gerstenberg et al., 2015) as well as CHR-P (Addington et al., 2017c, Fusar-Poli et al., 2020b) and other comorbid mental disorders. Thus, comorbidity should not rule out DSM-5–APS but increase the diagnostic suspicion.

Total positive symptom ($p<0.001$; Cohen's $d=1.5$), negative symptom ($p<0.001$; Cohen's $d=0.55$), disorganized symptom ($p<0.001$; Cohen's $d=0.51$), and general symptom ($p<0.001$; Cohen's $d=0.84$) scores were significantly higher in APS individuals compared to non-APS hospitalized adolescents (for an itemized

description see annex 11). Overall, illness severity (CGI-S) was higher in the APS group ($p<0.001$). Current functioning ($p=0.0012$), highest and lowest functioning in the past year (both $p=0.002$) were worse in the CHR-P group (illness severity, functional level, illness insight, and suicidality results in DSM-5–APS vs. non-APS individuals are fully presented in annex 12). Our results support previous evidence that APS status is also associated with marked functional impairment (Gaudiano and Zimmerman, 2013, Kelleher et al., 2012b). This finding is relevant because functional impairment may help differentiate young people meeting CHR-P criteria from other help-seeking individuals (Lo Cascio et al., 2017).

The use of psychotropic medication in APS adolescents admitted into a psychiatric unit was high (66.1% were on antipsychotics, 42.9% on antidepressants, and 25% on mood stabilizers, see annex 10 for complete treatment results in APS and non-APS adolescents). No consistent meta-analytical evidence supports the use of antipsychotic drugs over other interventions in delaying or preventing transition to psychosis (Davies et al., 2018a, Stafford et al., 2013). Thus, the use of antipsychotics for non-psychotic disorders in adolescents is concerning because of the adverse effects of atypical antipsychotics in young people (Galling et al., 2016, Al-Dhaher et al., 2016, Carbon et al., 2015). However, most antipsychotics in pediatric populations are used for other reasons, including irritability and conduct problems. This affirmation is supported by the high rates of antipsychotics in other diagnostic groups, including bipolar-spectrum disorders.

Perceptual abnormalities (OR=2.0), number of comorbid conditions (OR=1.5), and impaired stress tolerance (OR=1.4) were associated with the DSM-5–APS status. Auditory perceptual abnormalities might be associated with a particularly high risk compared to visual perceptual abnormalities (Lehembre-Shiah et al., 2017), which are typically found in individuals with physical conditions. APS has been associated with comorbid mental disorders, but the impact of these conditions seems to vary (Gerstenberg et al., 2015). Implications of the presence of other comorbid conditions in DSM-5–APS and their influence on the transition to psychosis need further study in adolescents. Finally, impaired stress tolerance seems to be a core CHR-P feature, associated with more severe psychopathology (Devylder et al., 2013).

We also found that comorbidities were frequent in inpatient adolescents with bipolar spectrum disorders, particularly disruptive behavior disorders (55.3%), anxiety disorders (40.8%), and personality disorder traits (25.0%) (see annex 13 for comorbidity results). The predominance of disruptive behavior disorders is consistent with some (Wingo and Ghaemi 2007, Torres et al., 2017), but different from other studies conducted in adults where anxiety disorders (particularly panic attacks) were the most common comorbid diagnoses (Merikangas et al., 2011). ADHD has been previously reported as the most common comorbid condition in BD-NOS (Axelson et al., 2011). In any case, detecting and managing comorbidities in youth with bipolar spectrum disorders is essential, as in addition to their own burden, worsening of these conditions could trigger a mood episode recurrence (Yen et al., 2016).

Adolescents with BD-NOS scored higher on the MADRS scale measuring depression than adolescents with MD-NOS (p=0.001), which is consistent with the previous literature, showing important rates of depression in BD-NOS compared to other psychiatric diagnoses (Towbin et al., 2013). BD-NOS presented the highest rates of irritability (93.1%), over talkativeness (89.7%), and distractibility (79.3%) within bipolar spectrum disorders. As for MD-NOS, the most frequent symptoms were irritability (91.3%), distractibility (52.2%), and increased psychomotor activity (47.8%). Mood elevation (p=0.002), inflated self-esteem/grandiosity (p=0.011), over talkativeness (p<0.001), and racing thoughts/flight of ideas (p=0.039) were significantly more frequent in BD-NOS versus MD-NOS (see annex 14 for the prevalence of BPSS-P items rated at moderate or higher severity). Previous research also found clinical severity to be significant in pediatric bipolar spectrum disorders (Hernandez et al., 2017).

BPSS-P can be a valuable instrument to detect symptomatology below the threshold of syndromal YMRS ratings and anchors (Correll et al., 2014). It may enable the detection of subtle and subthreshold symptoms. Studying individuals with subthreshold manic symptoms is essential due to their risk of developing a full episode of mania, particularly the ones with the most severe symptoms (Mesman et al., 2013, Hafeman et al., 2016, Goodday et al., 2017, Duffy et al., 2017, Tijssen et al., 2010). This risk of developing BD might also be increased by comorbid conditions, such as ADHD and anxiety disorders (Mesman et al., 2013, Hafeman et al., 2016), which can also delay remission (Bukh et al., 2016).

The median duration of subthreshold symptoms of mania was five months in the BD-NOS group and three months in the MD-NOS group. These are significant amounts of time for adolescents, who need to reach relevant socio-educational and biological milestones. Our results suggest that many youths with bipolar spectrum disorders undergo a long symptomatic period characterized by subthreshold symptoms of the subsequent mood episode.

62.1% BD-NOS and 56.5% MD-NOS were on second-generation antipsychotics (see annex 13 for treatment characteristics in bipolar spectrum disorders). For pediatric patients, second-generation antipsychotics seem to be superior to mood stabilizers for mania (Correll et al., 2010). Furthermore, lithium was found to be less effective than risperidone for treating manic/mixed episodes in children (Duffy et al., 2018).

However, this widespread use of antipsychotics, even for BD-NOS and MD-NOS, is also concerning, given the well-known adverse effects, including cardiovascular effects (Geller et al., 2012, Arango et al., 2014).

Characterization findings derived from the third study of this dissertation are of particular relevance as they provide evidence about the potential clinical utility of DSM-5–APS. DSM-5–APS has received substantial concurrent and prognostic validation, fundamentally from psychometric research in the field of the clinical high-risk state for psychosis. In contrast, other factors, including precipitating and predisposing epidemiological factors, neurobiological research, and treatments, have been under-investigated to date. The smallest number of studies in this meta-analysis was found for antecedent factors, which were rarely investigated.

The prevalence of DSM-5–APS appears to be variable in clinical samples, reflecting the significant sampling biases that affect the CHR-P paradigm (Salazar de Pablo et al., 2020a). It seems around half of the individuals report a DSM-5–APS–like state before their first episode of psychosis. Although this number is significant, it implies that the presence of a period of time fulfilling DSM-5–APS criteria should not be universally assumed for all the patients.

As an alternative, non-psychotic risk syndromes may precede the first onset of psychosis in some patients (Lee et al., 2018). According to our meta-analytical results, half of the individuals meeting DSM-5–APS and equivalent criteria had comorbid depressive disorders. Additionally, 38% presented with anxiety disorders and 22% with bipolar disorders. Both samples of adolescent inpatients at risk of developing psychotic disorders shared a significant proportion of comorbid conditions. These high comorbidity proportions, particularly comorbid depressive disorders, support that psychosis may emerge from non-psychotic syndromes (Fusar-Poli et al., 2017c). Both theories are not excluding necessarily.

Findings derived from the studies in this dissertation support that individuals at high risk of developing psychotic disorders can be characterized with the currently available psychometric instruments to detect individuals at risk of developing psychotic disorders, including the SIPS/SOPS and the BPSS-P. Furthermore, evaluation of their functioning with psychometric tools as the GAF is recommended.

Prognosis

A prognostic evaluation of individuals at risk of developing psychotic disorders is essential for preventive approaches. One of the main goals of this doctoral dissertation is to contribute to the development of prognostic science, including precision psychiatry, in the field of psychotic disorders' prevention. We have verified that precision psychiatry has become a consolidated clinical research area in this discipline, with a substantial number of individualized risk prediction models developed or validated in about four million participants (Salazar de Pablo et al., 2020d).

According to the results of this doctoral dissertation, 65.8% of the individualized risk prediction models were prognostic. They employed most frequently clinical predictors (69.5%). Risk prediction models most commonly focused on psychotic disorders (35.8%), with CHR-P studies representing a substantial area of research (18.3%) (Salazar de Pablo et al., 2020d), and highlighting the importance of promptly detecting prodromal or subthreshold symptoms in individuals at risk of developing psychotic disorders. These results confirm the close link between precision psychiatry and preventive approaches (Fusar-Poli et al., 2020b), since the detection of these prodromal/subsyndromal symptoms, accompanied by decreased functioning and severity of illness, is a necessary step for the implementation of preventive approaches in risk enriched populations in which these interventions have proven to be most helpful (Fusar-Poli et al., 2020b). These results highlight the relevance of precision psychiatry in

individuals at risk of developing psychotic disorders and the importance of a comprehensive evaluation of clinical factors.

Methodologically speaking, only a third of the validated prediction models are currently externally validated, and the implementation of risk prediction models in psychiatry has not yet been possible (Salazar de Pablo et al., 2020d). Advances are currently limited by the scarce replication of existing models and the challenges of implementation research in real-world clinical practice. The next generation of precision psychiatry research is required to address this translational gap.

This doctoral dissertation has evaluated the meta-analytical transition risk of a) individuals fulfilling DSM-5 Attenuated Psychosis Syndrome and equivalent criteria, b) individuals fulfilling BLIPS criteria, and c) adolescents at CHR-P. Transition to psychosis is a clinically meaningful endpoint for individuals at risk of developing psychotic disorders, as it translates into real-world morbidity (Fusar-Poli et al., 2020a, Yoviene Sykes et al., 2020).

The transition risk was estimated as 11% (95%CI: 8-14%) at 6 months follow up, 15% (95%CI: 11-19%) at 12 months follow up, 20% (95%CI: 16-24%) at 24 months follow up, and 23% (95%CI: 17-30%) at ≥36 months follow up for DSM-5–APS individuals (Salazar de Pablo et al., 2020a) (see annex 15). Of those who transition to psychosis, around two-thirds receive a diagnosis of schizophrenia (Crump et al., 2018). These rates suppose a 5-fold probability of transitioning to psychosis compared to high-risk individuals not meeting any CHR-P criteria

(Fusar-Poli et al., 2018a), which indicates a substantial risk of progression to psychosis on top of the baseline distressing clinical profile of this syndrome.

Among the positive symptoms evaluated by psychometric instruments as the SIPS/SOPS, increases in the severity of unusual thought content (85%) and perceptual abnormalities (46%) appear to be the most likely to result in a transition to psychosis for DSM-5–APS individuals (Marshall et al., 2019). Other studies have found an association between attenuated odd ideas (Brucato et al., 2017), thought disorders (Brucato et al., 2017), unusual thought content (Crump et al., 2018, Addington et al., 2017b), and auditory perceptual abnormalities (Lehembre-Shiah et al., 2017) with transition to psychosis. Speech features (Bedi et al., 2015) and disorganized communication (Cornblatt et al., 2015, Addington et al., 2017b) were also associated with an increased risk of transition. Cognitive features, including verbal memory deficits (Cornblatt et al., 2015), verbal fluency (Addington et al., 2017b), and processing speed (Addington et al., 2017b, Keefe et al., 2006), have also been associated with an increased risk of psychosis. However, schizotypal personality disorder alone has not been associated with an increased risk of psychosis (Zoghbi et al., 2019). Axis II comorbidity, family psychiatric history, tobacco use, number of hospitalizations, and history of trauma were associated with suicide attempts in DSM-5–APS individuals (Zuschlag et al., 2018).

The meta-analytical risk of transition to psychosis for BLIPS was 20.1% (95%CI: 14.6-27.0%) at 6 months, 33.7% (95%CI: 25.2%-43.5%) at 12 months, 39.1% (95%CI: 28.7%-50.6%) at 24 months, and 38.3% (95%CI: 30.5%-46.7%) at ≥36

months follow-up (see annex 16). Despite these high rates, it has not yet been possible to identify prognostic factors associated with a consistently high risk of psychotic recurrence for BLIPS or any other brief psychotic episode denomination, including ATPD and BPD (see prognostic factors of psychotic recurrence in brief psychotic episodes in annex 17). Frequency of episodes over follow-up (Fusar-Poli et al., 2017a) and seriously disorganizing or dangerous BLIPS features (Fusar-Poli et al., 2017a, Fusar-Poli et al., 2019b) have been associated with higher transitions to psychosis in individual studies.

Finally, the meta-analytical risk of psychosis was 10.4% (95%CI: 5.8%-18.1%) at 6 months follow up, 19.8% (95%CI: 14.6%-26.3%) at 12 months follow up, 23.0% (95%CI: 18.0%-29.0%) at 24 months follow up, and 23.3% (95%CI: 17.3%-30.7%) at ≥36 months follow-up in CHR-P adolescents, which appears to be similar to the risk in CHR-P adults (Fusar-Poli et al., 2020b, Catalan et al., 2020) (see annex 18). However, it has been suggested that inpatient samples as the ones described in this doctoral dissertation, may be associated with a particularly high level of risk enrichment (Fusar-Poli et al., 2016d, Fusar-Poli et al., 2016e). Besides, the transition to psychosis may increase in the long-term in adolescents, as they experience larger periods of time at risk of developing psychotic disorders than adult populations (Dominguez et al., 2013). In line with this significant long-term impact, 60% of CHR-P adolescents do not recover and may remain with symptoms after six years (de Wit et al., 2014).

Within CHR-P adolescents, the CHR-P individuals who transitioned to psychosis had higher baseline severity of attenuated psychotic symptoms than those who

did not transition to psychosis (Simeonova et al., 2011). Neurocognitive impairments were more severe in CHR-P individuals who transitioned to psychosis than in CHR-P individuals who did not transition (Woodberry et al., 2013), with a significant impairment in olfactory identification (Woodberry et al., 2010). The social and role functioning remained stable in those who developed psychosis but improved in those not developing psychosis (Velthorst et al., 2018). Cannabis use was not associated with poorer functioning (Auther et al., 2012). Positive remarks and warmth within families predicted clinical improvements for adolescents at CHR-P, while conflictual communications were related to an increase in attenuated psychotic symptoms (O'Brien et al., 2009).

All these studies and findings confirm that, although several factors have been associated with psychosis, the risk factor with the most robust evidence is the CHR-P status (OR=9.32, class I-convincing evidence) (Radua et al., 2018). However, which factors discriminate individuals who transition from individuals who do not transition to psychosis is unclear, and findings are conflicting. Recent meta-analytical results suggest that only two factors are associated with class II-highly suggestive evidence: increased attenuated psychotic symptoms (SMD=0.348) and decreased global functioning (SMD=-0.291) (Oliver et al., 2019b).

The evidence on the predictors of transition in individuals at risk of developing bipolar disorder or AFP is limited. However, lower levels of mood symptoms appear to be associated with increased recovery rates among CHR-P individuals

(Schlosser et al., 2012), suggesting they may be important therapeutic targets for both individuals at risk of developing non-affective and affective psychosis.

The evidence presented in this doctoral dissertation highlights the importance of detecting attenuated symptoms and monitoring functioning in young people with these symptoms. Doing so is one of the primary goals of the instruments employed in this dissertation and described in the psychometric instruments section (SIPS/SOPS, BPSS-P, and GAF). These may also help refine clinical prediction models and promote the implementation of precision psychiatry, which in turn shall act as a catalyst for improving preventive interventions and outcomes in individuals at risk of developing psychotic disorders.

Therapeutic factors

According to the actual meta-analytical evidence, no specific intervention is more effective than the others for the prevention of transition to psychosis (Davies et al., 2018a) in CHR-P individuals. There is also no intervention superior to the control conditions for achieving improvements in attenuated psychotic symptoms (Davies et al., 2018b), negative symptoms (Devoe et al., 2018), functioning (Devoe et al., 2019, Schmidt et al., 2015) or depressive symptoms (Stafford et al., 2013).

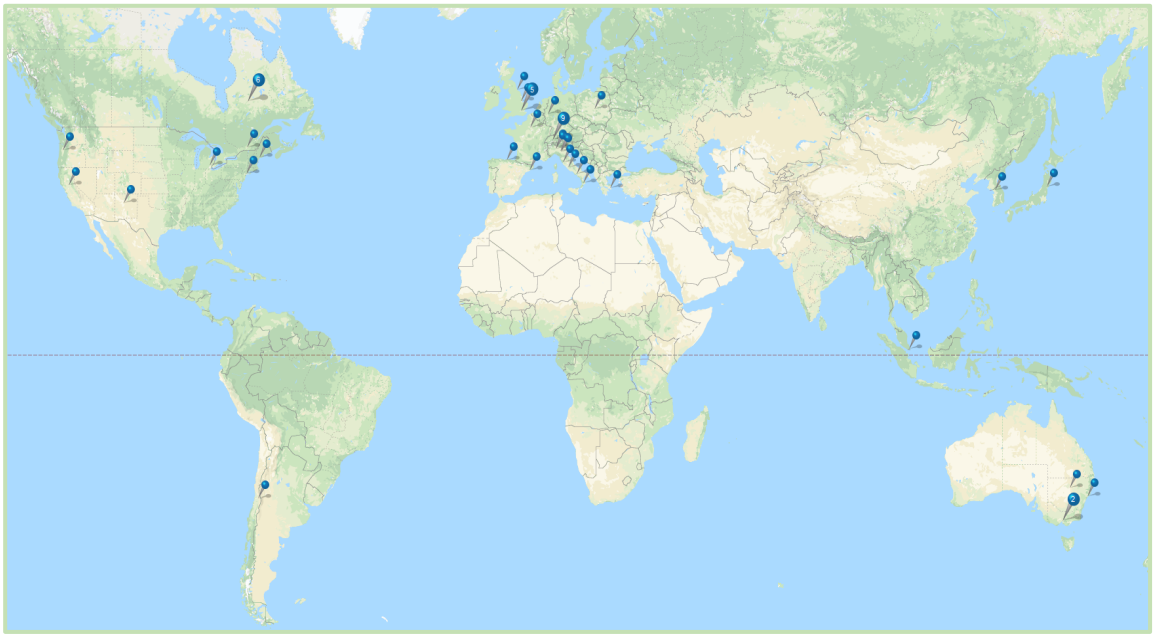
A need for specialized services to detect individuals at CHR-P, to formulate a prognosis with validated psychometric instruments, and to offer needs-based and psychological interventions has been identified in the manuscripts of this

dissertation. The “National Institute for Health and Care Excellence” (NICE) guidelines recommend CBT, with or without family intervention, for these patients (NICE, 2014). However, providing family intervention may be particularly relevant in adolescents and underage patients (Miklowitz et al., 2014). Low-dose, second-generation antipsychotic medication could be considered a second-line treatment for those patients whose symptoms are particularly impairing.

Specialized clinical services to prevent psychosis have been established worldwide (see distribution in Figure 6). They are the best places to provide these interventions to adolescents and young adults at risk (Fusar-Poli et al., 2020b). NICE and EPA guidelines highlight the importance of monitoring the symptoms and treating comorbidities- particularly depression and anxiety- (NICE, 2014, Schultze-Lutter et al., 2015).

Stratified interventions targeting the differential level of risk for psychosis and the values of the individuals at risk of developing psychotic disorders should be specifically considered (Salazar de Pablo et al., 2020d).

Figure 6. Geographical distribution of clinical services to prevent psychosis in CHR-P individuals



adapted from (Salazar de Pablo et al., 2021a)

Although the risk of developing bipolar disorder is significant, also in clinical services for CHR-P individuals (Tay et al., 2015, Carr et al., 2000, Leuci et al., 2019), the evidence about the implementation of clinical services for individuals at risk of developing bipolar psychotic disorders is particularly limited. At the moment, subthreshold symptom detection models for youth at-risk for BD, which would allow earlier intervention and a reduction in overall morbidity and mortality, have not been implemented widely (Hunt et al., 2016). According to a systematic review, only five studies have evaluated pharmacological interventions for individuals at risk of developing bipolar disorder. Ten have evaluated psychotherapeutic interventions, with 755 participants at risk of developing

bipolar disorder in total (Saraf et al., 2020), none of them as part of a clinical service to prevent affective psychotic disorders. Besides, the inclusion criteria for individuals at risk of developing bipolar disorder were remarkably heterogeneous. Further harmonized research is critical in this area.

RECOMMENDATIONS FOR FUTURE RESEARCH AND CLINICAL CARE

The results of this doctoral dissertation have several diagnostic, prognostic, and therapeutic implications.

Established and validated psychometric instruments should be used to characterize individuals at risk of developing psychotic disorders. For instance, the SIPS/SOPS and the CAARMS allow identifying individuals who are clinically and functionally impaired but also facilitate the interaction with patients and the detection of comorbid conditions, which are common in individuals at risk of developing psychotic disorders, including depressive disorders, anxiety disorders and suicidality (Fusar-Poli et al., 2014b, Fusar-Poli et al., 2020b, Salazar de Pablo et al., 2020a). Instruments to detect individuals at risk of developing bipolar disorders have also shown promising results, particularly the BPSS-P (Correll et al., 2014, Salazar de Pablo et al., 2020c). These instruments are recommended to characterize individuals at risk of developing psychotic disorders and establishing which particular criteria they fulfill. However, they require appropriate training (Salazar de Pablo et al., 2020a). Both instruments may have therapeutic

implications, allowing the monitoring of symptoms after the treatments are provided.

It is recommended for the findings across APS, BLIPS, and GRD to be stratified (Salazar de Pablo et al., 2020a). In the APS field, it is important to report the number of patients meeting DSM-5–APS criteria, including, if possible, which diagnostic criteria (A to F) are not met (if any). In line with this, the concordance and discordance between instruments may provide additional valuable information.

Our results support that the BLIPS stage represents the most severe clinical stage preceding the psychosis onset (Fusar-Poli et al., 2017a). It is key for symptoms not to be better explained in the context of a schizoaffective disorder, manic or depressive episodes with psychotic features, another medical condition, or the effects of a substance (Fusar-Poli et al., 2021). Also, related to specifiers within BLIPS, it is essential to know if a) it is the first episode or multiple episodes have occurred; b) if the onset is acute or not; c) if the episode is associated with stress and d) if polymorphic symptoms (several types of hallucination or delusion, changing in both type and intensity from day to day or within the same day) (Ritsner, 2011) appear. The presence of seriously disorganizing or dangerous behaviors appears to be particularly important (Fusar-Poli et al., 2017a, Fusar-Poli et al., 2019b).

Regarding AFP, the bipolar prodrome needs to be better characterized through clinical high-risk criteria and subsyndromal symptoms. The ability to detect signs and symptoms that could be part of a mania prodrome and the ability to describe

such symptoms (their frequencies, severity, and duration) is critical for BD prevention and management, as identifying and treating the illness early in its time course may be associated with a better prognosis (Berk et al., 2007). However, at the moment, subthreshold symptom detection models for youth at-risk for BD, which would allow earlier intervention and reduction in overall morbidity and mortality, have not been implemented widely (Hunt et al., 2016).

At the moment, delays before the first treatment in BD have been associated with more prolonged and more severe depressive phases, more comorbid disorders, and less time free of symptoms in adolescence and early adulthood (Birmaher et al., 2006). A multidisciplinary approach, including psychoeducation and management of comorbidities, could alter the trajectory and improve the prognosis of these patients (Martin and Smith, 2013). Therefore, individuals with risk factors and subthreshold symptoms would benefit from preventive efforts and close observation (Ratheesh et al., 2017), particularly those in which an exceptionally high risk of developing psychotic disorders is suspected.

Further recommendations apply to adolescents due to the sensible stage of life in which they are immersed. Overall, this dissertation describes the core clinical characteristics of adolescents at risk of developing psychotic disorders and describes some of the instruments that clinicians can use to detect them. Furthermore, it highlights the core outcomes presented by this population, as well as the evidence on the effectiveness of the interventions. The evidence appraised here should be used as a benchmark to conduct future research on children and

adolescents at risk of psychosis due to the negative consequences that have been observed in terms of functioning and comorbidities (Catalan et al., 2020).

Many maturational and adaptational processes occur during adolescence, and mood and affective shifts are observed (Hauser and Correll, 2013). In this context, further work is needed for the evaluation of the specificity of these symptoms. Family interventions seem to be important in pediatric populations, also in adolescents at risk of developing psychotic disorders (Miklowitz et al., 2014). Also, poor adherence is not uncommon and is associated with illness severity and substance use, among others (Edgcomb and Zima, 2018). Specific approaches to improve insight and adherence to interventions are particularly important for adolescents. With its challenges, early intervention and prevention are feasible in adolescents, also in the bipolar disorder field, in which efforts so far have been more limited (Arango et al., 2018).

As for the implementation of preventive interventions, the articles included in this doctoral dissertation highlight that preventive interventions provided at the moment may not be enough to support the needs of individuals at risk of developing psychotic disorders in the long term. In line with this, extending the clinical monitoring of outcomes for at least three years has been proposed since there is an increased risk of psychotic recurrence and of developing persistent psychotic disorders for at least three years after the initial assessment (Fusar-Poli et al., 2017a). This dissertation has further highlighted that transitional and transdiagnostic strategies across adolescents and young adults, offering needs-based interventions and psychological interventions, have the most substantial

evidence for the implementation of clinical services. Multidisciplinary services in the community with psychiatrists, psychologists, case managers, and nurses are recommended (Salazar de Pablo et al., 2021a).

One of the challenges in this field is that healthcare resources are typically diverted towards more severe psychotic patients (Fusar-Poli et al., 2019c). Standalone services would probably guarantee that professionals focus on individuals at risk of developing psychotic disorders, especially those with particularly distressing symptoms and special needs. Physically locating these services outside general psychiatric services may reduce stigmatization (Kotlicka-Antczak et al., 2015, Kotlicka-Antczak et al., 2018). It is essential to personalize the interventions according to the characteristics, risk profiles, and preferences of the individuals (Salazar de Pablo et al., 2020d) (see annex 19 for recommendations for real-world implementation of CHR-P services).

Finally, and methodologically speaking, facilitating the external validation of individualized risk prediction models, including clinical predictors as subthreshold and prodromal symptoms, is probably the most robust approach to address the real-world implementation of this knowledge. The next generation of risk prediction models in psychiatry should replicate existing algorithms through collaborative data sharing efforts and establish international clinical research infrastructures, which may maximize the efficiency of the research carried out (Fusar-Poli et al., 2018c). More international clinical research infrastructures may stimulate, in turn, a global network of CHR-P services.

This doctoral dissertation has several limitations that must be taken into consideration when interpreting its results. The most relevant are summarized here:

The individual studies included in this doctoral dissertation share some limitations. First, the instruments used to evaluate subthreshold/subsyndromal symptoms (including the SIPS/SOPS and the BPSS-P), require specific training in its use and spending an extended amount of time interviewing patients before the specific designation individuals fulfill can be established. However, the extensive amount of time invested translates into comprehensive and detailed evidence. Second, the original studies included in this dissertation share the limitation relative to the sample size, which may condition the power to detect statistical significance. We were able to observe differences between the groups in a significant proportion of the outcomes evaluated. Third, other syndromes with a high risk of developing psychotic and affective disorders have been described in the literature, but they were not characterized in the current doctoral dissertation. We evaluated some of the most relevant and most established clinical syndromes at high risk of developing psychotic disorders in the literature. Forth, the cross-sectional design difficulties the establishment of the psychopathology described as definitely prodromal.

The evidence summarized in the reviews included in the doctoral dissertation has some additional limitations. The studies included were in general heterogeneous in their design, methodology, and quality. Meta-regressions evaluated their influence on the results. Most studies were conducted in specific clinical services,

including help-seeking individuals fulfilling most frequently APS criteria, followed by BLIPS and GRD criteria. Individuals with other designations (e.g., basic symptoms) were hardly mentioned. We have tried to focus on the most common designations that put individuals at higher risk of developing psychotic disorders.

Nevertheless, despite these limitations, both the individual studies and the reviews have several strengths. The first individual study is the most extensive study to describe and characterize DSM-5–APS in adolescents comprehensively. The second individual study is one of the few carefully evaluating adolescents fulfilling BD-NOS and MD-NOS criteria. To our knowledge, it is the first study to do so in a sample of adolescents admitted into an inpatient unit. Both studies used structured and validated assessments that were carried out independently and face-to-face. Assessments were led by experienced and certified Master or MD level clinicians and psychologists. Information was obtained from both patients and parents/caregivers. The time delay between symptoms onset and data collection was still relatively short compared with other retrospective studies, reducing recall bias further. We focused on help-seeking individuals with a wide variety of psychopathology and psychotropic treatment characteristics, reflecting the clinical reality in these groups of patients and increasing the generalizability and applicability of the findings. Finally, focusing on subgroups allowed us to obtain more precise results from more homogeneous samples.

All the reviews are in accordance with the PRISMA reporting guidelines (Moher et al., 2009) (see annex 20); the meta-analyses are in accordance with MOOSE reporting guidelines (Stroup et al., 2000) (see annex 21). In all the systematic

reviews, a multistep literature search was carried out by independent researchers. Independent researchers also carried out data extraction. All the studies included quality assessments, which were appropriate for the study design. Finally, the databases were large and sufficiently powered to answer the research questions.

CONCLUSIONS

7. CONCLUSIONS

1. The prevalence of individuals meeting DSM-5–APS criteria in inpatient adolescents with non-psychotic psychiatric disorders was 26.2%. Adolescents with APS had significantly more comorbid psychiatric disorders than non-APS adolescents (3.5 vs. 2.4, $p<0.001$), particularly disruptive behavior disorders, personality disorder traits, anxiety disorders, and eating disorders. Clinically they presented more positive symptoms, negative symptoms, disorganized symptoms, and general symptoms (all $p<0.001$) than inpatient adolescents without this syndrome and were more functionally impaired ($p=0.012$) and more severely ill ($p<0.001$) than adolescents not meeting DSM-5–APS criteria. 66.1% were on antipsychotics.

2. Comorbidity was frequent in individuals at risk of developing bipolar affective psychosis (BD-NOS and MD-NOS), particularly disruptive behavior disorders (62.1% in BD-NOS, 60.9% in MD-NOS) and anxiety disorders (41.4% in BD-NOS, 39.1% in MD-NOS). They also had significant symptomatology, and subthreshold manic symptoms were common. The most frequent manic symptom was irritability (93.1% in BD-NOS, 91.3% in MD-NOS), and the most frequent depression symptom was depressed mood (82.8% in BD-NOS, 69.6% in MD-NOS). The median duration of subthreshold manic symptoms was substantial in both groups: 20.4 weeks in BD-NOS and 11.7 weeks in MD-NOS. The most used psychotropics upon discharge were antipsychotics (62.1% in BD-NOS, 56.5% in MD-NOS) and mood stabilizers (31.0% in BD-NOS, 34.8% in MD-NOS).

3. Current evidence supports the potential clinical validity of DSM-5–APS. DSM-5–APS has received substantial concurrent validation, with significant comorbidity rates (49% depressive disorders, 38% anxiety disorders, 22% bipolar disorders, 20% substance use disorders) and prognostic validation with significant transition rates (20% at 24 months, 23% at ≥36 months). Evidence came mainly from the psychometric research in the CHR-P field.

4. Meta-analytical transition rates were significant for DSM-5–APS (15% at 12 months, 20% at 24 months, and 23% at ≥36 months) and CHR-P adolescents (20% at 12 months and 23% at 24 and ≥36 months). For BLIPS, the transition rates were even higher (33.7% at 12 months, 39.1% at 24 months, and 38.3% at ≥36 months follow-up).

5. Validated psychometric instruments are commonly used across adolescents and young adults to detect CHR-P individuals. Therapeutic advances have been limited, and there is great diversity in how clinical services have been implemented. Standalone multidisciplinary transitional and transdiagnostic services in the community across adolescents and young adults, offering needs-based interventions and psychological interventions, have the most substantial evidence.

SUMMARY

8. SUMMARY

8.1. INTRODUCTION

Psychotic disorders and psychotic experiences are common in the general population (McGorry et al., 1995). Psychotic disorders have a significant impact on individual's personal life but also on the society. In the last decades, interest in the prevention of mental disorders has increased through the characterization, the prognostic evaluation, and the establishment of preventive interventions in individuals at risk of developing psychotic disorders (Fusar-Poli et al., 2020b). In these individuals, a prodromal period may present, during which they are found to be at high risk of developing psychotic disorders. Several descriptions of this prodromal period according to their characteristics and the features found have been piloted. While in some patients the risk of developing non-affective psychotic disorders as schizophrenia prevails, in others, the features they present put them at high risk of developing affective psychotic disorders such as bipolar disorder.

Around 85% of the clinical high risk for psychosis (CHR-P) individuals meet attenuated psychotic symptoms criteria. Meanwhile, 10% meet "Brief Limited Intermittent Psychotic Symptoms" (BLIPS) criteria, and 5% meet "Genetic Risk and Deterioration" (GRD) syndrome criteria (Fusar-Poli et al., 2016b). The most common CHR-P designation (attenuated psychotic symptoms) and the clinical research conducted in these patients has led to the introduction of Attenuated Psychosis Syndrome in the DSM-5 (DSM-5–APS).

These are the criteria for DSM-5–APS (American Psychiatric Association, 2013):

A. At least one of the following symptoms is present in an attenuated form, with relatively intact reality testing, and is of sufficient severity or frequency to warrant clinical attention:
    1. Delusions.
    2. Hallucinations.
    3. Disorganized speech.
B. Symptom(s) have been present at least once per week for the past month.
C. Symptom(s) have begun or worsened in the past year.
D. Symptom(s) is/are sufficiently distressing and disabling for the individual to warrant clinical attention.
E. Symptom(s) is/are not better explained by another mental disorder, including a depressive or bipolar disorder with psychotic features, and is not attributable to a substance or another medical condition's physiological effects.
F. Criteria for any psychotic disorder have never been met.

No systematic review has summarized the available evidence regarding the clinical validity of DSM-5–APS. Besides, the evidence on DSM-5–APS and CHR-P is even more limited in children and adolescents. Few efforts have been made to characterize and describe DSM-5–APS, excluding other CHR-P criteria, and advance the knowledge on this designation specifically in adolescents (Gerstenberg et al., 2015).

The “Structured Interview for Psychosis-Risk Syndromes” (SIPS) (Miller et al., 1999, Miller et al., 2003) is a semi-structured interview used to diagnose psychosis-risk syndromes in the last month. It includes four sections according to the symptoms evaluated: positive symptoms, negative symptoms, disorganized symptoms, and general symptoms (Cornblatt et al., 2015). The severity of the symptoms is rated using an ordinal scale from 0=absent to 6=extreme. As part of the SIPS, the Scale of Prodromal Symptoms (SOPS) is used to determine whether participants meet the research criteria for “Attenuated Psychotic Symptoms Syndrome” (APSS), considered equivalent to DSM-5–APS. The SIPS/SOPS also records symptoms onset, frequency, and past year history.

In the field of the prevention of affective psychotic disorders, BD-not otherwise specified (BD-NOS) criteria include periods of abnormally elevated or irritable mood (American Psychiatric Association, 2013). Mood disorder NOS (MD-NOS) is characterized by subthreshold periods of mania or hypomania (Salazar de Pablo et al., 2020b). Meeting either of these two criteria puts these people at high clinical risk of developing bipolar disorder type I (BD-I). Therefore, it puts them at increased risk of developing psychotic disorders too, as BD-I is an affective psychosis. The efforts to characterize prodromal and subsyndromal bipolar mania and depression states and ultimately the prevention of psychotic affective disorders as BD-I have been even more limited, particularly in underage individuals.

The “Bipolar Prodrome Symptom Interview and Scale-Prospective” (BPSS-P) (Correll et al., 2014) has a similar structure to the SIPS. It intends to characterize

prodromal and subsyndromal bipolar mania and depression states and assess the evolution of BD at any stage. It is designed to evaluate the lifetime presence and severity of prodromal/subsyndromal and syndromal manic, depressive, and general symptoms. Symptom severity is rated using an ordinal scale from 0=absent to 6=extreme, with a rating of 3=moderate being the lowest subsyndromal rating. Furthermore, the duration, frequency, onset, and pattern of these symptoms are also recorded.

A good assessment of the prognosis and risk of developing psychotic disorders has the potential to maximize the benefits of early intervention in psychosis (Fusar-Poli et al., 2018c). Although the risk appears to be significant for all the CHR-P individuals, several characteristics may affect this risk, which may also be different in children and adolescents. Besides, although updated meta-analytical evidence does not exist, previous evidence shows that individuals with BLIPS may be at exceptionally high risk compared to other subgroups (Fusar-Poli et al., 2017a, Fusar-Poli et al., 2016a). It is essential to assess the risk of transition to psychosis in individuals at high clinical risk as a way to prevent psychotic disorders (Fusar-Poli et al., 2012).

It has been estimated that the prevalence of mental conditions is higher than 13% among children and adolescents (Polanczyk et al., 2015). Furthermore, once established, mental disorders have negative effects on the functioning and quality of life of young people (Catalan et al., 2020). Additionally, they result in a substantial economic burden on our society (Fatori et al., 2018). One-third of psychotic disorders see an onset before the age of 18 (Madaan et al., 2008).

Besides, the prevalence of psychotic symptoms is also high: around 7.5% in adolescents (Kelleher et al., 2012a). However, most evidence in the field of the prevention of psychotic disorders in individuals at risk has been developed either in adult populations or in populations with a limited % of adolescents.

Interventions in individuals with clinical syndromes that put them at high clinical risk of developing psychotic disorders aim to prevent or delay the onset of psychosis (Fusar-Poli et al., 2013a). They also intend to reduce comorbidity, reduce the duration of untreated psychosis, and improve the functioning of these patients (Schultze-Lutter et al., 2015, Addington et al., 2017a, Fusar-Poli et al., 2017a). These interventions are usually carried out in specialized prevention services, which are expanding globally (Kotlicka-Antczak et al., 2020). Knowledge generated about those preventive services for individuals at high risk of developing psychotic disorders has been limited, and guidelines for the translational implementation of these services scarce.

8.2. OBJECTIVES

A. Provide state-of-the-art evidence on the CHR-P paradigm and the field of psychotic disorders' prevention, by reviewing the advances in the characterization, prognosis and therapeutic factors, both in adult populations and adolescents.

B. Evaluate with prodromal symptom scales the proportion of non-psychotic adolescents admitted into an inpatient unit who meet Attenuated Psychosis Syndrome criteria. Compare their sociodemographic, illness, and intervention peculiarities with other adolescents admitted into the same inpatient unit without that designation.

C. Evaluate a clinical sample of adolescents with bipolar spectrum disorders, including adolescents at risk of developing BD-I, with scales designed to characterize the bipolar prodrome. Describe their sociodemographic, illness, and intervention peculiarities and compare them with adolescents with BD-I.

D. Provide current evidence on the clinical validity of DSM-5 Attenuated Psychosis Syndrome, recently introduced into the DSM-5. Assess the most recent advances in diagnosis, prognosis, and treatment in individuals with DSM-5 Attenuated Psychosis Syndrome and closely related criteria.

E. Evaluate the prognosis of individuals at risk of developing psychotic disorders, providing the transition to psychosis rates for individuals with DSM-5 Attenuated Psychosis Syndrome, individuals with Brief Limited Intermittent Psychotic Symptoms, and adolescents at CHR-P.

8.3. HYPOTHESIS

A. Advances in the characterization and prognostic factors in CHR-P individuals will be substantial, while therapeutic advances will be limited. Some of the clinical characteristics including comorbidity rates and the prognosis including transition rates will be similar in adult populations and adolescents. Families will have a particularly important role in adolescents.

B. Adolescents with Attenuated Psychosis Syndrome will represent a significant proportion of the adolescents with non-psychotic psychiatric disorders admitted into an inpatient unit. They will have more comorbid conditions and will be more clinically and functionally impaired than adolescents not fulfilling these criteria.

C. Adolescents at risk of developing BD-I (fulfilling BD-NOS or MD-NOS criteria), admitted into an inpatient unit, will report relevant threshold and subthreshold affective and psychotic symptoms as well as clinical and functional impairment. Some of these symptoms will be less severe compared to adolescents with BD-I.

D. We expect to confirm the potential clinical validity of DSM-5 Attenuated Psychosis Syndrome by summarizing the evidence on antecedent, concurrent, and prognostic validators. We expect concurrent and prognostic validation from the psychosis prevention research field to be substantial for this syndrome.

E. The meta-analytical risk of transition to psychosis will be significant in CHR-P individuals, including those meeting DSM-5 Attenuated Psychosis Syndrome criteria. The risk will be particularly high in individuals with Brief Limited Intermittent Psychotic Symptoms and equivalent in CHR-P adolescents.

8.4. METHODS

This thesis incorporates several manuscripts authored by the doctoral student. A summary of the methodology of the main articles of the doctoral dissertation can be found below:

PUBLICATION 1

Salazar de Pablo G, Guinart D, Cornblatt BA, Auther AM, Carrión RE, Carbon M, Jiménez-Fernández S, Vernal DL, Walitza S, Gerstenberg M, Saba R, Lo Cascio N, Brandizzi M, Arango C, Moreno C, Van Meter D, Fusar-Poli P, Correll CU. DSM-5 Attenuated Psychosis Syndrome in Adolescents Hospitalized With Non-psychotic Psychiatric Disorders Front. Psychiatry Oct 21;11:568982.

This study interviewed help-seeking, hospitalized adolescents aged 12–18 years and their caregivers with established research instruments. First, it evaluated the presence of APS among non-psychotic adolescents admitted into an inpatient unit. Second, it characterized and compared adolescents fulfilling the APS criteria

and adolescents not fulfilling the APS criteria regarding sociodemographic, illness, and intervention characteristics. Third, it correlated psychopathology with levels of functioning and severity of illness. Finally, it investigated the influence of individual clinical, functional, and comorbidity variables on the likelihood of participants to be diagnosed with APS. Diagnoses were established in research consensus conferences. DSM criteria and SIPS/SOPS, a semi-structured interview to diagnose psychosis-risk syndromes, were used.

PUBLICATION 2

Salazar de Pablo G, Guinart D, Cornblatt BA, Auther AM, Carrión RE, Carbon M, Jiménez-Fernández S, Vernal DL, Walitza S, Gerstenberg M, Saba R, Lo Cascio N, Brandizzi M, Arango C, Moreno C, Van Meter A, Correll CU. Demographic and Clinical Characteristics, Including Subsyndromal Symptoms Across Bipolar-Spectrum Disorders in Adolescents. J Child Adolesc Psychopharmacol. 2020 May;30(4):222-234.

This cross-sectional study included adolescents (age: 12–18 years) with Bipolar-Spectrum Disorder, recruited from the adolescent inpatient unit at the “Zucker Hillside Hospital,” from the “Adolescent Mood and Psychosis Study” (AMDPS), an observational study aiming to characterize the BD prodrome prospectively. Assessments included the validated BPSS-P to evaluate syndromal and subsyndromal psychopathology. Additional rating scales were administered to adolescents and their caregivers. They included the CGI-S for overall severity of

illness, the GAF for functioning, the MADRS for symptoms of depression, and the YMRS for symptoms of mania. We compared phenomenology across patients with research consensus conference-confirmed DSM-IV diagnoses of BD-I, BD-NOS, or MD-NOS.

PUBLICATION 3

Salazar de Pablo G, Catalan A, Fusar-Poli P. Clinical Validity of DSM-5 Attenuated Psychosis Syndrome: Advances in Diagnosis, Prognosis, and Treatment. JAMA Psychiatry. 2020 Mar 1;77(3):311-320.

This systematic review and meta-analysis followed PRISMA and MOOSE guidelines. A literature search of multiple databases, conference proceedings, and trial registries from inception until June 2019 was conducted. Studies investigating individuals diagnosed using DSM-5–APS or meeting other comparable criteria (APSS according to the SIPS) were included. The results of the systematic review were summarized in tables and narratively synthesized against evidence-based antecedent, concurrent, and prognostic validators. A quantitative meta-analysis exploring the cumulative risk of psychosis onset at 6, 12, 24, and ≥36 months in individuals diagnosed using DSM-5–APS or equivalent criteria was carried out. Heterogeneity among study point estimates and publication bias were assessed.

8.5. RESULTS

PUBLICATION 1

Salazar de Pablo G, Guinart D, Cornblatt BA, Auther AM, Carrión RE, Carbon M, Jiménez-Fernández S, Vernal DL, Walitza S, Gerstenberg M, Saba R, Lo Cascio N, Brandizzi M, Arango C, Moreno C, Van Meter D, Fusar-Poli P, Correll CU. DSM-5 Attenuated Psychosis Syndrome in Adolescents Hospitalized With Non-psychotic Psychiatric Disorders Front. Psychiatry Oct 21;11:568982.

Of 248 consecutively recruited adolescents with non-psychotic psychiatric disorders, 26.2% fulfilled APS criteria. Adolescents fulfilling the APS criteria had more psychiatric disorders than those not fulfilling them (3.5 vs. 2.4, $p<0.001$; Cohen's d=0.77). Disruptive behavior disorders (Cramer's V=0.16), anxiety disorders (Cramer's V=0.15), personality disorder traits (Cramer's V=0.26), and eating disorders (Cramer's V= 0.16) were more common in APS individuals than in non-APS individuals. Adolescents with APS had more severe positive symptoms (Cohen's d=1.5), negative symptoms (Cohen's d=0.55), disorganized symptoms (Cohen's d=0.51), and general symptoms (Cohen's d=0.84), and were also more functionally impaired (Cohen's d=0.31) and severely ill (Cohen's d=1.0). Perceptual abnormalities (OR=2.0), the number of psychiatric diagnoses (OR=1.5), and impaired stress tolerance (OR=1.4) were associated with the APS status independently. 66.1% of APS adolescents were prescribed antipsychotics and 42.9% antidepressants.

PUBLICATION 2

Salazar de Pablo G, Guinart D, Cornblatt BA, Auther AM, Carrión RE, Carbon M, Jiménez-Fernández S, Vernal DL, Walitza S, Gerstenberg M, Saba R, Lo Cascio N, Brandizzi M, Arango C, Moreno C, Van Meter A, Correll CU. Demographic and Clinical Characteristics, Including Subsyndromal Symptoms Across Bipolar-Spectrum Disorders in Adolescents. J Child Adolesc Psychopharmacol. 2020 May;30(4):222-234.

Seventy-six adolescents (age=15.6±1.4 years, females=59.2%) with bipolar spectrum disorders were included. Functioning was low in individuals with bipolar spectrum disorders (median GAF=21, IQR=17-40). Comorbidity included disruptive behavior disorders (55.5%), anxiety disorders (40.8%), and personality disorder traits (25.0%). Manic symptoms, particularly irritability (93.4%), were common in adolescents with bipolar spectrum disorders. Depressive symptoms, particularly depressed mood (81.6%), were also common in adolescents with bipolar spectrum disorders. Manic and depressive symptoms were more severe in adolescents with BD-I and BD-NOS compared to adolescents with MD-NOS ($p<0.001$). The median duration of subthreshold symptoms of mania was shorter in MD-NOS versus BD-NOS (11.7 vs. 20.4 weeks, $p=0.002$) and substantial in both groups. The most used psychotropics upon discharge were antipsychotics (62.1% in BD-NOS, 56.5% in MD-NOS) and mood stabilizers (31.0% in BD-NOS, 34.8% in MD-NOS).

PUBLICATION 3

Salazar de Pablo G, Catalan A, Fusar-Poli P. Clinical Validity of DSM-5 Attenuated Psychosis Syndrome: Advances in Diagnosis, Prognosis, and Treatment. JAMA Psychiatry. 2020 Mar 1;77(3):311-320.

The systematic review included 56 articles, which reported on 124 validators. The interrater reliability for DSM-5–APS criteria was comparable with that of other DSM-5 mental disorders. DSM-5–APS criteria were associated with frequent depressive comorbid disorders, distress, functional impairment and suicidality. The meta-analysis included 23 prospective cohort studies, including 2376 individuals. The meta-analytical risk of psychosis onset was 11% at 6 months, 15% at 12 months, 20% at 24 months, and 23% at ≥36 months. 49% DSM-5–APS individuals had depressive disorders, 38% anxiety disorders, 22% bipolar disorders, and 20% substance use disorders. Research into effective treatments for DSM-5–APS has been limited.

8.6. DISCUSSION

This doctoral thesis presents advances in the knowledge on the characterization, prognosis, and therapeutic factors in individuals with clinical syndromes which put them at high risk of developing psychotic disorders. It has a particular focus on adolescents. It characterizes clinically adolescents with DSM-5 Attenuated

Psychosis Syndrome and adolescents with bipolar spectrum disorders in a sample of adolescents hospitalized.

The prevalence of individuals meeting DSM-5–APS criteria is variable in clinical samples. In our sample of inpatient adolescents with non-psychotic psychiatric disorders, 26.2% fulfilled DSM-5–APS criteria. Comorbidity was frequent in DSM-5–APS individuals (80% for depressive disorders, 55.4% for anxiety disorders, 52.3% for disruptive, impulse-control and conduct disorders, 36.9% for bipolar disorders, 36.9% for personality disorder traits, 20% for substance use disorders). Total positive, negative, disorganized, and general symptom scores were significantly higher in APS individuals vs. non-APS hospitalized adolescents. Illness severity (CGI-S) was higher in the APS group and functioning was worse. The use of psychotropic medication in APS adolescents admitted into a psychiatric unit was high (66.1% were on antipsychotics, 42.9% on antidepressants, and 25% on mood stabilizers).

Comorbidities were also frequent in inpatient adolescents with bipolar spectrum disorders, particularly disruptive behavior disorders (55.3%), anxiety disorders (40.8%), and personality disorder traits (25.0%). Adolescents with BD-NOS presented the highest rates of irritability (93.1%) and over talkativeness (89.7%) within bipolar spectrum disorders. As for adolescents with MD-NOS, the most frequent symptoms were irritability (91.3%) and distractibility (52.2%). The median duration of subthreshold symptoms of mania was five months in the BD-NOS group and three months in the MD-NOS group. 62.1% BD-NOS and 56.5% MD-NOS were on second-generation antipsychotics.

The meta-analytical risk of psychosis for DSM-5–APS was 15% at 12 months, 20% at 24 months, and 23% at ≥36 months; in CHR-P adolescents, transition risk was 20% at 12 months and 23% at 24 and ≥36 months; for BLIPS, the transition rates were even higher. Psychosis was the most frequently investigated condition in validated prediction modeling studies in psychiatry, particularly clinical high risk of psychosis. There is great diversity in how clinical services have been implemented.

The results of this doctoral dissertation have several diagnostic, prognostic, and therapeutic implications:

- Established and validated psychometric instruments should be used to characterize individuals at risk of developing psychotic disorders.
- Evidence from the different at-risk syndromes should be stratified.
- The bipolar prodrome needs to be better characterized through the homogeneous application of consistent clinical high-risk criteria and evaluation of subsyndromal symptoms.
- Negative consequences observed in terms of functioning and comorbidities highlight the importance of high-intensity clinical care in at-risk adolescents with risk factors and subthreshold symptoms.
- A multidisciplinary approach, including psychoeducation and management of comorbidities, could alter the trajectory and improve the prognosis.
- The consideration of maturational and adaptational processes in adolescents and the importance of family interventions should be valued.

- Preventive interventions provided at the moment may not be enough to support the needs of individuals at risk of developing psychotic disorders in the long term.
- Transitional and transdiagnostic services across adolescents and young adults offering needs-based interventions and psychological interventions have the most substantial evidence.

This doctoral dissertation has several strengths. Structured and validated assessments from both patients and parents/ caregivers were carried out independently, and the time delay between the onset of symptoms and the data collection was short. We focused on help-seeking individuals with a wide variety of characteristics and psychopathology, reflecting the clinical reality in these groups of patients and increasing the generalizability and applicability of the findings. All the reviews, including the complementary publications, are in accordance with established reporting guidelines. In all the systematic reviews, a multistep literature search was carried out by independent researchers. Independent researchers also carried out data extraction. All the studies included quality assessments, which were appropriate for the study design. Finally, the databases were large and sufficiently powered to answer the research questions.

8.7. CONCLUSIONS

1. The prevalence of individuals meeting DSM-5–APS criteria in inpatient adolescents with non-psychotic psychiatric disorders was 26.2%. Adolescents

with APS had significantly more comorbid psychiatric disorders than non-APS adolescents (3.5 vs. 2.4, $p<0.001$), particularly disruptive behavior disorders, personality disorder traits, anxiety disorders, and eating disorders. Clinically they presented more positive symptoms, negative symptoms, disorganized symptoms, and general symptoms (all $p<0.001$) than inpatient adolescents without this syndrome and were more functionally impaired ($p=0.012$) and more severely ill ($p<0.001$) than adolescents not meeting DSM-5–APS criteria. 66.1% were on antipsychotics.

2. Comorbidity was frequent in individuals at risk of developing bipolar affective psychosis (BD-NOS and MD-NOS), particularly disruptive behavior disorders (62.1% in BD-NOS, 60.9% in MD-NOS) and anxiety disorders (41.4% in BD-NOS, 39.1% in MD-NOS). They also had significant symptomatology, and subthreshold manic symptoms were common. The most frequent manic symptom was irritability (93.1% in BD-NOS, 91.3% in MD-NOS), and the most frequent depression symptom was depressed mood (82.8% in BD-NOS, 69.6% in MD-NOS). The most used psychotropics upon discharge were antipsychotics (62.1% in BD-NOS, 56.5% in MD-NOS) and mood stabilizers (31.0% in BD-NOS, 34.8% in MD-NOS).

3. Current evidence supports the potential clinical validity of DSM-5–APS. DSM-5–APS has received substantial concurrent validation, with significant comorbidity rates (49% depressive disorders, 38% anxiety disorders, 22% bipolar disorders, 20% substance use disorders) and prognostic validation with

significant transition rates. Evidence came mostly from psychometric research in the field of the clinical high-risk state for psychosis.

4. Meta-analytical transition rates were significant for DSM-5–APS (15% at 12 months, 20% at 24 months, and 23% at ≥36 months) and CHR-P adolescents (20% at 12 months and 23% at 24 and ≥36 months). For BLIPS, the transition rates were even higher (33.7% at 12 months, 39.1% at 24 months, and 38.3% at ≥36 months follow-up).

5. Validated psychometric instruments are commonly used across adolescents and young adults to detect CHR-P individuals. Therapeutic advances have been limited, and there is great diversity in how clinical services have been implemented.

RESUMEN

9. RESUMEN

9.1. INTRODUCCIÓN

Los trastornos psicóticos y las experiencias psicóticas son frecuentes en la población general (McGorry et al., 1995) y tienen una gran carga personal, clínica y social. En los últimos años, ha aumentado el interés por la prevención de los trastornos psicóticos mediante la caracterización, la evaluación pronóstica y el establecimiento de intervenciones preventivas en pacientes con alto riesgo clínico de psicosis (Fusar-Poli et al., 2020b). Las personas con trastornos psicóticos presentan frecuentemente un periodo prodrómico en el que se encuentran en alto riesgo clínico, y en el que estaría justificado intervenir preventivamente. En este paradigma, se han descrito pacientes en alto riesgo de desarrollar trastornos psicóticos no afectivos como la esquizofrenia y pacientes en alto riesgo de desarrollar trastornos psicóticos afectivos como el trastorno bipolar.

El 85% de los pacientes en estados mentales de alto riesgo o “Clinical High Risk for Psychosis” (CHR-P) de acuerdo con el paradigma del riesgo ultra alto o “ultra-high risk,”- particularmente en riesgo de desarrollar trastornos no psicóticos como la esquizofrenia-, cumplen criterios de síntomas psicóticos atenuados. Mientras tanto, el 10% de los individuos cumplen criterios de síntomas psicóticos breves intermitentes y limitados o “Brief Limited Intermittent Psychotic Symptoms” (BLIPS) y el 5% cumplen criterios de riesgo genético y deterioro o “Genetic Risk and Deterioration” (GRD) (Fusar-Poli et al., 2016b). La designación más común, los pacientes con síntomas psicóticos atenuados, y la investigación

clínica realizada en estos pacientes, han llevado a la introducción del Síndrome de Psicosis Atenuada [“Attenuated Psychosis Syndrome” (APS)] en el DSM-5.

Estos son los criterios del DSM-5–APS (American Psychiatric Association, 2013):

A. Al menos uno de los siguientes síntomas debe estar presente en forma atenuada, con juicio de realidad relativamente intacto y con suficiente gravedad o frecuencia para justificar atención clínica:
    a. Delirios.
    b. Alucinaciones.
    c. Lenguaje desorganizado.
B. Los síntomas deben haber estado presentes al menos una vez por semana en el último mes.
C. Los síntomas deben haber empezado o empeorado en el último año.
D. Los síntomas deben ser suficientemente angustiantes e incapacitantes para que el individuo pida ayuda clínica.
E. Los síntomas no deben ser explicados mejor por otro trastorno mental, incluyendo trastornos depresivos o trastornos bipolares con síntomas psicóticos y no deben ser atribuibles a los efectos fisiológicos de una sustancia o condición médica.
F. No deben cumplirse criterios para ningún otro trastorno psicótico.

Ninguna revisión sistemática ha resumido la evidencia disponible sobre la validez clínica de este síndrome. Además, la evidencia sobre este tema es aún más limitada en adolescentes, y se han realizado pocos esfuerzos para caracterizar y describir el DSM-5–APS, excluyendo otros criterios clínicos dentro de los CHR-

P, y avanzar en el conocimiento sobre los adolescentes con esta condición que han sido ingresados en unidades de psiquiatría (Gerstenberg et al., 2015).

La “Structured Interview for Psychosis-Risk Syndromes” (SIPS) (Miller et al., 1999, Miller et al., 2003) es una entrevista semiestructurada que se utiliza para diagnosticar los síndromes que componen los CHR-P. Incluye cuatro secciones principales según los síntomas evaluados: síntomas positivos, síntomas negativos, síntomas de desorganización y síntomas generales (Cornblatt et al., 2015). Como parte de la SIPS, la “Scale of Prodromal Symptoms” (SOPS) se utiliza para determinar si los participantes cumplen con los criterios de investigación para el síndrome de síntomas psicóticos atenuados o “Attenuated Psychotic Symptoms Síndrome” (APSS), considerados equivalentes a los criterios DSM-5–APS. La SIPS/SOPS permite registrar el inicio de los síntomas, así como la frecuencia de estos en el año previo.

En el ámbito de la prevención de los trastornos psicóticos afectivos, el trastorno bipolar no especificado o “bipolar disorder-not otherwise specified” (BD-NOS) incluye periodos de humor anormalmente elevado o irritable (American Psychiatric Association, 2013). El trastorno afectivo no especificado o “mood disorder-not otherwise specified” (MD-NOS) incluye periodos subumbrales de manía o hipomanía (Salazar de Pablo et al., 2020b). Cumplir cualquiera de estos dos criterios pone a estas personas en alto riesgo clínico de desarrollar trastorno bipolar tipo I, y, por tanto, en alto riesgo clínico de desarrollar trastornos psicóticos, al ser el trastorno bipolar tipo I una psicosis afectiva. Los esfuerzos para caracterizar la sintomatología subsindrómica y prodrómica, tanto depresiva

como maníaca y, en última instancia, la prevención de trastornos psicóticos afectivos como el trastorno bipolar tipo I han sido limitados, particularmente en menores de edad ingresados en unidades de psiquiatría.

La “Bipolar Prodrome Symptom Interview and Scale-Prospective” (BPSS-P) (Correll et al., 2014) tiene una estructura similar a la SIPS. Pretende caracterizar estados prodrómicos y subsindrómicos de depresión y manía en el trastorno bipolar y evaluar la evolución del trastorno bipolar en cualquier etapa. Está diseñada para evaluar la presencia a lo largo de la vida y la gravedad de los síntomas maníacos, depresivos y generales, tanto prodrómicos/ subsindrómicos, como sindrómicos. La gravedad de los síntomas se califica en una escala ordinal desde 0=ausente a 6=extremo, siendo una calificación de 3=moderada, la calificación subsindrómica más baja. Además, se registra la duración, frecuencia, aparición y patrón de dichos síntomas.

Una buena evaluación pronóstica y una evaluación del riesgo de desarrollar trastornos psicóticos en pacientes en alto riesgo clínico tiene el potencial de maximizar los beneficios de las intervenciones preventivas (Fusar-Poli et al., 2018c). Aunque el riesgo es significativo para todos los individuos en estados mentales de alto riesgo, varias características pueden influir en este riesgo, que también puede ser diferente en adolescentes. Además, aunque no existe evidencia meta-analítica actualizada al respecto, la evidencia previa sugiere que las personas con BLIPS pueden tener un riesgo particularmente alto en comparación con otros subgrupos de pacientes en alto riesgo clínico de desarrollar psicosis (Fusar-Poli et al., 2017a, Fusar-Poli et al., 2016a). En este

sentido, es necesario evaluar el riesgo de transición a psicosis en personas en alto riesgo clínico como forma de prevenir la aparición de trastornos psicóticos (Fusar-Poli et al., 2012).

Se ha estimado que la prevalencia de trastornos mentales en niños y adolescentes está por encima del 13% (Polanczyk et al., 2015). Una vez establecidos, éstos tienen efectos negativos en la funcionalidad y en la calidad de vida (Catalan et al., 2020). Además, tienen una gran carga económica para la sociedad (Fatori et al., 2018). Un tercio de los trastornos psicóticos empiezan antes de los 18 años (Madaan et al., 2008). Además, la prevalencia de síntomas psicóticos es alta en la población general: alrededor de un 7.5% en adolescentes (Kelleher et al., 2012a). Sin embargo, la mayor parte de la evidencia en el campo de la prevención de trastornos psicóticos en individuos en alto riesgo clínico se ha desarrollado en poblaciones adultas o en poblaciones con un porcentaje bajo de adolescentes.

Las intervenciones en individuos con un síndrome de alto riesgo clínico de desarrollar trastornos psicóticos tienen como objetivo prevenir o retrasar la aparición de psicosis (Fusar-Poli et al., 2013a), así como reducir la comorbilidad, disminuir la duración de psicosis no tratada y mejorar la funcionalidad de estos pacientes (Schultze-Lutter et al., 2015, Addington et al., 2017a, Fusar-Poli et al., 2017a). Estas intervenciones se realizan habitualmente en servicios especializados de prevención de psicosis, los cuales se están expandiendo globalmente (Kotlicka-Antczak et al., 2020). El conocimiento sobre dichos

servicios preventivos ha sido limitado y las directrices para su implementación translacional han sido escasas.

9.2. OBJETIVOS:

A. Aportar evidencia actualizada sobre el paradigma del síndrome de alto riesgo clínico de psicosis y sobre el campo de la prevención de los trastornos psicóticos, revisando los avances en la caracterización, factores pronósticos y factores terapéuticos, tanto en población adulta como en adolescentes.

B. Evaluar con escalas para síntomas prodrómicos la proporción de adolescentes con trastornos no psicóticos que cumplen criterios de DSM-5–APS en una unidad de internamiento. Comparar sus características sociodemográficas, clínicas y terapéuticas con las de otros adolescentes ingresados en la misma unidad que no cumplen dichos criterios.

C. Evaluar una muestra clínica de adolescentes en riesgo de desarrollar trastorno bipolar tipo I (adolescentes que cumplen criterios de BD-NOS y MD-NOS), utilizando escalas diseñadas para caracterizar sintomatología prodrómica y subsindrómica en el trastorno bipolar. Describir las peculiaridades sociodemográficas, clínicas y de intervención de estos pacientes, comparándolos con adolescentes con trastorno bipolar tipo I.

D. Proporcionar evidencia actualizada sobre la validez clínica del Síndrome de Psicosis Atenuada, introducido recientemente en el DSM-5. Evaluar los avances más recientes en el diagnóstico, pronóstico y tratamiento en personas con un Síndrome de Psicosis Atenuada según el DSM-5 o que cumplen criterios equivalentes.

E. Evaluar la transición a psicosis en pacientes con un Síndrome de Psicosis Atenuada (según criterios DSM-5), pacientes con síntomas psicóticos breves, intermitentes y limitados, y adolescentes en alto riesgo clínico de desarrollar psicosis.

9.3. HIPÓTESIS:

A. Los avances en la caracterización y factores pronósticos en los pacientes en CHR-P serán sustanciales, mientras que los avances terapéuticos serán limitados. Algunas de las características clínicas y el pronóstico serán similares en poblaciones adultas y en adolescentes.

B. Los adolescentes con Síndrome de Psicosis Atenuada representarán una proporción significativa de los adolescentes con trastornos psiquiátricos no psicóticos ingresados en una unidad de internamiento para adolescentes. Tendrán más comorbilidad y estarán más deteriorados clínica y funcionalmente que los adolescentes que no cumplen criterios para dicho diagnóstico.

C. Los adolescentes en alto riesgo clínico de desarrollar un trastorno psicótico bipolar (que cumplen criterios de BD-NOS o MD-NOS), ingresados en una unidad de hospitalización, reportarán síntomas psicóticos y afectivos significativos, tanto sindrómicos como subsindrómicos, así como deterioro clínico y funcional. Algunos de estos síntomas serán menos graves en comparación con los que sufren los adolescentes con BD-I.

D. La evidencia actual respaldará la potencial validez clínica del Síndrome de Psicosis Atenuada según criterios DSM-5. Esta designación habrá recibido una validación concurrente y pronóstica sustancial, principalmente gracias a la investigación en el campo de la prevención de psicosis.

E. El riesgo meta-analítico de transición a psicosis será significativo en los individuos con un alto riesgo clínico de desarrollar psicosis, incluidos los que cumplen los criterios del Síndrome de Psicosis Atenuada según el DSM-5. El riesgo será particularmente alto en personas con síntomas psicóticos breves, intermitentes y limitados. El riesgo será similar en adolescentes y en personas con Síndrome de Psicosis Atenuada según el DSM-5.

9.4. MÉTODOS

Esta tesis incorpora varios artículos del doctorando. A continuación, se muestra un resumen de la metodología de los principales artículos de la tesis doctoral:

PUBLICACIÓN 1

Salazar de Pablo G, Guinart D, Cornblatt BA, Auther AM, Carrión RE, Carbon M, Jiménez-Fernández S, Vernal DL, Walitza S, Gerstenberg M, Saba R, Lo Cascio N, Brandizzi M, Arango C, Moreno C, Van Meter D, Fusar-Poli P, Correll CU. DSM-5 Attenuated Psychosis Syndrome in Adolescents Hospitalized With Non-psychotic Psychiatric Disorders Front. Psychiatry Oct 21;11:568982.

En este estudio, se entrevistó a adolescentes de entre 12 y 18 años hospitalizados en unidad de psiquiatría, así como a sus cuidadores. Primero, se evaluó la presencia de DSM-5–APS entre los adolescentes no psicóticos ingresados. En segundo lugar, se caracterizaron y se compararon las características sociodemográficas, clínicas y de intervención entre aquellos adolescentes que cumplían con criterios de APS y los que no cumplían dichos criterios. En tercer lugar, se correlacionó la psicopatología con los niveles de funcionamiento y la gravedad de la enfermedad. Finalmente, se investigó la influencia de las variables clínicas, funcionales y de comorbilidad individuales sobre la probabilidad de que los participantes cumplieran criterios de APS. El diagnóstico se estableció en conferencias de consenso con el investigador principal del estudio. Se utilizaron criterios DSM y el instrumento SIPS/SOPS,

que es una entrevista semiestructurada para diagnosticar síndromes de alto riesgo clínico de psicosis.

PUBLICACIÓN 2

Salazar de Pablo G, Guinart D, Cornblatt BA, Auther AM, Carrión RE, Carbon M, Jiménez-Fernández S, Vernal DL, Walitza S, Gerstenberg M, Saba R, Lo Cascio N, Brandizzi M, Arango C, Moreno C, Van Meter A, Correll CU. Demographic and Clinical Characteristics, Including Subsyndromal Symptoms Across Bipolar-Spectrum Disorders in Adolescents. J Child Adolesc Psychopharmacol. 2020 May;30(4):222-234.

El “Adolescent Mood and Psychosis Study” (AMDPS) es un estudio observacional que tiene como objetivo caracterizar prospectivamente la sintomatología prodrómica en el trastorno bipolar. Este es un estudio transversal que incluye adolescentes (edad: 12-18 años) con un trastorno del espectro bipolar, reclutados en la unidad de hospitalización para adolescentes del “Zucker Hillside Hospital.” Las evaluaciones incluyeron la “Bipolar Prodrome Symptom Interview and Scale- Prospective” (BPSS-P) para evaluar psicopatología sindrómica y subsindrómica, la CGI-S para evaluar severidad de la enfermedad, la GAF para evaluar funcionalidad, la MADRS para evaluar síntomas de depresión y la YMRS para evaluar síntomas de manía. Comparamos la fenomenología entre pacientes con BD-I, BD-NOS y MD-NOS.

PUBLICACIÓN 3

Salazar de Pablo G, Catalan A, Fusar-Poli P. Clinical Validity of DSM-5 Attenuated Psychosis Syndrome: Advances in Diagnosis, Prognosis, and Treatment. JAMA Psychiatry. 2020 Mar 1;77(3):311-320.

Este artículo incluye una revisión sistemática y un meta-análisis, que siguieron las guías PRISMA y MOOSE. Se realizó una búsqueda bibliográfica en múltiples bases de datos, actas de congresos y registros de ensayos clínicos hasta junio de 2019. Se incluyeron estudios que investigaron a individuos con un diagnóstico de DSM-5–APS o que cumplían criterios equivalentes (APSS según la SIPS). Los resultados de la revisión sistemática se resumieron en tablas y se sintetizaron narrativamente según si hacían referencia a validadores antecedentes, concurrentes o pronósticos. Se llevó a cabo un meta-análisis cuantitativo, explorando el riesgo acumulativo de aparición de psicosis a los 6, 12, 24 y ≥36 meses en personas con un diagnóstico de APS según el DSM-5 o que cumplían criterios equivalentes. Se evaluó a su vez la heterogeneidad y la posible presencia de sesgo de publicación.

9.5. RESULTADOS

PUBLICACIÓN 1

Salazar de Pablo G, Guinart D, Cornblatt BA, Auther AM, Carrión RE, Carbon M, Jiménez-Fernández S, Vernal DL, Walitza S, Gerstenberg M, Saba R, Lo

Cascio N, Brandizzi M, Arango C, Moreno C, Van Meter D, Fusar-Poli P, Correll CU. DSM-5 Attenuated Psychosis Syndrome in Adolescents Hospitalized With Non-psychotic Psychiatric Disorders Front. Psychiatry Oct 21;11:568982.

De 248 adolescentes con trastornos psiquiátricos no psicóticos reclutados consecutivamente, 26.2% cumplieron criterios de APS. Los adolescentes que cumplieron con dichos criterios tuvieron más trastornos psiquiátricos que los que no los cumplieron (3.5 frente a 2.4, $p<0.001$; d de Cohen=0.77). En particular, los trastornos de conducta disruptiva (V de Cramer=0.16), los rasgos disfuncionales de personalidad (V de Cramer=0.26), los trastornos de ansiedad (V de Cramer= 0.15) y los trastornos alimentarios (V de Cramer=0.16) fueron más comunes en los individuos con APS. Los adolescentes con DSM-5–APS tuvieron una mayor gravedad en cuanto a síntomas positivos (d de Cohen=1.5), negativos (d de Cohen=0.55), de desorganización (d de Cohen=0.51) y generales (d de Cohen=0.84). También estaban más deteriorados funcionalmente (d de Cohen=0.31) y puntuaron por encima en cuanto a gravedad de la enfermedad (d de Cohen=1.0). Las anomalías perceptivas (OR=2.0), el número de diagnósticos psiquiátricos (OR=1.5) y la tolerancia alterada al estrés (OR=1.4) se asociaron de forma independiente con cumplir criterios de APS. El uso de psicofármacos en adolescentes con APS fue elevado (66.1% tomaba antipsicóticos y 42.9% antidepresivos).

PUBLICACIÓN 2

Salazar de Pablo G, Guinart D, Cornblatt BA, Auther AM, Carrión RE, Carbon M, Jiménez-Fernández S, Vernal DL, Walitza S, Gerstenberg M, Saba R, Lo Cascio N, Brandizzi M, Arango C, Moreno C, Van Meter A, Correll CU. Demographic and Clinical Characteristics, Including Subsyndromal Symptoms Across Bipolar-Spectrum Disorders in Adolescents. J Child Adolesc Psychopharmacol. 2020 May;30(4):222-234.

Se incluyeron 76 adolescentes (edad 15.6±1.4 años, 59.2% mujeres). El funcionamiento en estos pacientes fue bajo (mediana GAF=21, IQR=7-40). La comorbilidad fue frecuente en estos pacientes, incluyendo trastornos de conducta disruptiva (55.5%), trastornos de ansiedad (40.8%) y rasgos disfuncionales de personalidad (25.0%).

Los síntomas maníacos, en particular la irritabilidad (93,4%), fueron frecuentes en los adolescentes con trastornos del espectro bipolar. Los síntomas depresivos, en particular el ánimo bajo (81,6%), también fueron frecuentes en los adolescentes con trastornos del espectro bipolar. Los síntomas de manía y síntomas depresivos fueron más graves en los adolescentes con BD-I y BD-NOS en comparación con los de los adolescentes con MD-NOS ($p<0.001$). La mediana de duración de los síntomas subumbrales de mania fue más corta en el MD-NOS que en el BD-NOS (11.7 semanas en lugar de 20.4 semanas, $p=0.002$), aunque fue sustancial en ambos grupos. El 62.1% de los adolescentes con BD-NOS y el 56.5% de los adolescentes con MD-NOS recibieron

antipsicóticos de segunda generación. El 31% de los BD-NOS y el 34.8% de los MD-NOS recibieron fármacos eutimizantes.

PUBLICACIÓN 3

Salazar de Pablo G, Catalan A, Fusar-Poli P. Clinical Validity of DSM-5 Attenuated Psychosis Syndrome: Advances in Diagnosis, Prognosis, and Treatment. JAMA Psychiatry. 2020 Mar 1;77(3):311-320.

La revisión sistemática incluyó 56 artículos, que informaron sobre 124 validadores. La fiabilidad entre evaluadores para los criterios DSM-5-APS fue comparable con la de otros trastornos mentales del DSM-5. Los criterios DSM-5-APS se asociaron frecuentemente con trastornos depresivos, trastornos de ansiedad, comportamiento suicida y deterioro funcional. Se meta-analizaron 23 cohortes independientes, incluyendo 2376 personas con este síndrome. El riesgo meta-analítico de aparición de psicosis fue del 11% a los 6 meses, del 15% a los 12 meses, del 20% a los 24 meses y del 23% a los ≥36 meses. 49% de los pacientes con DSM-5–APS presentaron trastornos depresivos comórbidos. El 38% presentaron trastornos de ansiedad y el 22% trastornos del espectro bipolar. La investigación sobre tratamientos efectivos para personas que cumplen criterios DSM-5–APS ha sido limitada.

9.6. DISCUSIÓN

Esta tesis doctoral presenta avances en el conocimiento sobre la caracterización, el pronóstico y los factores terapéuticos de distintos síndromes clínicos que confieren un alto riesgo de desarrollar trastornos psicóticos, con el foco de atención en pacientes jóvenes y adolescentes. A su vez, se caracterizan síndromes de alto riesgo clínico de psicosis, considerando tanto a personas en riesgo de desarrollar trastornos psicóticos no afectivos como la esquizofrenia, como a personas en riesgo de desarrollar trastornos psicóticos afectivos como el trastorno bipolar.

En una muestra de adolescentes hospitalizados, se caracterizó tanto a adolescentes con un Síndrome de Psicosis Atenuada según criterios DSM-5, como a adolescentes en alto riesgo clínico de desarrollar psicosis afectivas, poniendo especial énfasis en los síntomas atenuados/subsindrómicos y prodrómicos. La prevalencia de individuos que cumplen criterios DSM-5–APS es variable en las muestras clínicas. En nuestra muestra de adolescentes hospitalizados con trastornos psiquiátricos no psicóticos, el 26.2% cumplía criterios DSM-5–APS.

La comorbilidad fue frecuente en los adolescentes con DSM-5–APS (80% presentaron trastornos depresivos, 55.4% trastornos de ansiedad, 52.3% trastornos disruptivos, de control de impulsos y de conducta, 36.9% trastornos del espectro bipolar, 36.9% rasgos disfuncionales de personalidad, 20% trastornos por uso de sustancias). Los síntomas psicóticos positivos, negativos, generales y de desorganización fueron mayores en adolescentes con APS que

en los adolescentes hospitalizados sin dicha denominación. La gravedad de la enfermedad fue mayor en los pacientes con APS y el funcionamiento peor. Se prescribió tratamiento antipsicótico en un 66.1%, tratamiento antidepresivo en un 42.9% y estabilizadores del estado de ánimo en un 25% de los adolescentes hospitalizados.

La presencia de trastornos comórbidos también fue frecuente en adolescentes hospitalizados con trastornos del espectro bipolar, en particular los trastornos de conducta disruptiva (55.3%), trastornos de ansiedad (40.8%) y rasgos disfuncionales de personalidad (25.0%). Los adolescentes con BD-NOS presentaron las tasas más altas de irritabilidad (93.1%) y verborrea (89.7%) dentro de los distintos trastornos del espectro bipolar. En cuanto a los adolescentes con MD-NOS, los síntomas más frecuentes fueron irritabilidad (91.3%) y distraibilidad (52.2%). La mediana de duración de los síntomas subumbrales de manía fue de cinco meses en el grupo con BD-NOS y de tres meses en el grupo con MD-NOS. El 62.1% de los adolescentes con BD-NOS y el 56.5% de los adolescentes con MD-NOS recibieron antipsicóticos de segunda generación.

El riesgo meta-analítico de psicosis en el DSM-5–APS fue del 15% a los 12 meses, del 20% a los 24 meses y del 23% a los ≥36 meses; en adolescentes con CHR-P, el riesgo de transición fue del 20% a los 12 meses y del 23% a los 24 y ≥36 meses; en el BLIPS, las tasas de transición fueron aún más altas; para pacientes adolescentes las tasas de transición fueron similares a las encontradas en el DSM-5–APS. La psicosis fue la condición investigada con mayor frecuencia

en los estudios de modelos de predicción, sobre todo el estudio pronóstico de los pacientes en alto riesgo clínico de psicosis. Existe una gran diversidad en la forma en que se han implementado los servicios clínicos de prevención de psicosis.

Los resultados de esta tesis doctoral tienen varias implicaciones diagnósticas, pronósticas y terapéuticas.

- Se deben utilizar instrumentos psicométricos validados para caracterizar a las personas en riesgo de desarrollar trastornos psicóticos.
- Es recomendable estratificar la evidencia en función de los distintos síndromes clínicos siempre que sea posible.
- Es necesario seguir avanzando en la caracterización de los pródromos del trastorno bipolar y en la evaluación de los síntomas subsindrómicos mediante la aplicación de criterios clínicos de manera consistente.
- Las consecuencias negativas observadas en términos de funcionamiento y comorbilidad en estos pacientes resaltan la importancia de una atención clínica especializada y de alta intensidad en aquellos adolescentes con factores de riesgo y síntomas subumbrales.
- Un enfoque multidisciplinario que incluya psicoeducación y manejo de las comorbilidades podría alterar la trayectoria y mejorar el pronóstico de estos pacientes.
- Se deben considerar los procesos de maduración y adaptación y la importancia de las intervenciones familiares en los pacientes adolescentes.

- Las intervenciones preventivas proporcionadas en este momento pueden no ser suficientes a largo plazo para satisfacer las necesidades de las personas en riesgo de desarrollar trastornos psicóticos.
- Los servicios de transición y transdiagnósticos para adolescentes y adultos jóvenes que ofrecen intervenciones basadas en las necesidades e intervenciones psicológicas tienen la evidencia más sustancial.

Esta tesis doctoral tiene fortalezas importantes. En los estudios individuales se obtuvo información tanto de los pacientes como de los padres/cuidadores utilizando evaluaciones estructuradas y validadas, y el tiempo entre la aparición de los síntomas y la recogida de datos fue corto. Nos centramos en personas que buscaban ayuda y con una amplia variedad de características y de psicopatología, lo que refleja la realidad clínica de estos pacientes y aumenta la generalización y aplicabilidad de los hallazgos. Todas las revisiones, incluidas las publicaciones complementarias, se ajustaron a las guías clínicas y directrices de presentación establecidas. En todas las revisiones sistemáticas, investigadores independientes llevaron a cabo una búsqueda bibliográfica en varios pasos. La extracción de datos también fue llevada a cabo por investigadores independientes. Todos los estudios incluyeron evaluaciones de la calidad, que fueron apropiadas para el diseño de los estudios. Finalmente, las bases de datos fueron grandes y tuvieron suficiente potencia estadística para responder a las preguntas de investigación planteadas.

9.7. CONCLUSIONES

- La prevalencia del DSM-5–APS en adolescentes hospitalizados con trastornos psiquiátricos no psicóticos fue del 26.2%. Los adolescentes con DSM-5–APS tuvieron más trastornos psiquiátricos comórbidos que los adolescentes que no cumplieron dichos criterios (3.5 vs. 2.4, $p<0.001$), particularmente trastornos de conducta disruptiva, rasgos disfuncionales de personalidad, trastornos de ansiedad y trastornos de la alimentación. Clínicamente presentaron más síntomas positivos, síntomas negativos, síntomas de desorganización y síntomas generales (todos $p<0.001$) que los adolescentes hospitalizados sin dicho síndrome. Estaban más afectados funcionalmente ($p=0.012$) y la gravedad de la enfermedad fue mayor ($p<0.001$) que en los adolescentes que no cumplían dichos criterios. A un 66.1% de ellos se les prescribió medicación antipsicótica.

- La comorbilidad fue frecuente en adolescentes en riesgo de desarrollar una psicosis afectiva bipolar (BD-NOS y MD-NOS), particularmente trastornos de conducta disruptiva (62.1% en BD-NOS, 60.9% en MD-NOS) y trastornos de ansiedad (41.4% en BD-NOS, 39.1% en MD-NOS). También presentaron afectación clínica significativa y los síntomas de manía subumbrales fueron frecuentes. El síntoma más prevalente fue la irritabilidad (93.1% en BD-NOS, 91.3% en MD-NOS). Los psicotrópicos más utilizados al alta fueron los antipsicóticos (62.1% en BD-NOS, 56.% en MD-NOS) y los estabilizadores del estado de ánimo (31.0% en BD-NOS, 34.8% en MD-NOS).

- La evidencia actual respalda la validez clínica del DSM-5–APS. Este síndrome ha recibido una validación concurrente sustancial, con tasas de comorbilidad significativas (49% presentaron trastornos depresivos, 38% trastornos de ansiedad, 22% trastornos del espectro bipolar, 20% trastornos por uso de sustancias) y validación pronóstica, con tasas de transición significativas. La evidencia viene principalmente de la investigación en el ámbito de la prevención de psicosis.

- Las tasas meta-analíticas de transición fueron significativas para el DSM-5–APS (15% a los 12 meses, 20% a los 24 meses y 23% a los ≥36 meses) y para los adolescentes con CHR-P (20% a los 12 meses y 23% a los 24 y ≥36 meses). En los pacientes con BLIPS, las tasas de transición fueron más altas (33.7% a los 12 meses, 39.1% a los 24 meses y 38.3% tras 36 o más meses de seguimiento).

- Los instrumentos psicométricos validados se han utilizado frecuentemente en adolescentes y adultos jóvenes para detectar individuos en CHR-P. Los avances terapéuticos han sido limitados y ha habido una gran diversidad respecto a la implementación de servicios clínicos de prevención de psicosis.

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ANNEXES

11. Annex 1. SIPS-APSS and CAARMS-APS criteria

	APSS SIPS (from 1998 onwards) (McGlashan T, 2010, Miller et al., 1999, Miller et al., 2003)	**CAARMS-APS** (12/2006) (Yung et al., 2005)
Diagnostic criteria		
Severity	SOPS-positive symptom scales P1. unusual thought content, P2. suspiciousness, P3. grandiose ideas, P4. perceptual abnormalities, P5. disorganized communication, with at least one of these symptoms rated 3, 4, or 5 indicating clinically significant disturbance below a psychotic level of intensity.	CAARMS-positive symptoms scales rated 3-5 (P1. unusual thought content, P2. non-bizarre ideas), 3-4 (P3. perceptual abnormalities), 4-5 (P4. disorganized speech).
Frequency	Symptoms ever been present at an average frequency of at least once/week over a month.	Symptoms present from 1/month to 2/week, >1 hour per occasion, OR 3 to 6/week, <1 hour per occasion.
New onset and worsening	Begin within the past year, or any currently rate one or more scale points higher compared to 12 months ago; rated only symptoms that occurred over the past month.	Need to be present in the past 12 months; rated the most severe in the past 12 months.
Distress/ disability	Subjective qualifier not used to assign the designation.	Rated on a scale 0-100 but not used to assign the designation.
Differential diagnosis	Symptoms ever not been explained better by another DSM disorder.	No requirement for differential diagnosis with other mental disorders.
Lack of lifetime psychotic disorder	Severity score of 6 on at least one of P1–P5 AND symptoms ever occur for at least 1h/day at an average frequency of four days/week over one month OR symptoms are seriously	Severity score of 6 on at least one of P1, P2, P4 and/or 5–6 on P3 AND frequency of at least 3 to 6/week, > 1 hour per occasion, or daily, <1 hour per occasion AND symptoms present for longer than

	disorganizing and dangerous (urgency criteria)	one week. Urgency criteria not considered.
Substance misuse	Exclude if symptoms are strongly intertwined temporally with substance use episodes.	Exclude if symptoms occur only during peak intoxication from hallucinogens, amphetamines and cocaine; included if due to cannabis or alcohol.
Antipsychotic treatments	Usually assessed and considered as an exclusion criterion	Usually assessed and considered as an exclusion criterion
Functional decline	No social/occupational dysfunction decline requirement	30% drop in SOFAS score from premorbid level, sustained for a month, within the past 12mo OR SOFAS score <50 for the past 12 month or more.
Assessment	Semi-structured psychometric interview, 2 hours, training required	Semi-structured psychometric interview, 2 hours, training required

* SIPSv.5.6-DSM-5–APS Attenuated positive symptoms sufficiently distressing and disabling to the patient to warrant clinical attention.

Annex 2. Proposals of Criteria to Characterize the Bipolar Prodrome

Correll et al., (Correll et al., 2007)	**McNamara et al., (McNamara et al., 2010)**	**Bechdolf et al., (Bechdolf et al., 2010)**	**Pavuluri et al., (Pavuluri, 2010)**	**Brietzke et al., (Brietzke et al., 2012)**	**Fusar-Poli et al., (Fusar-Poli et al., 2018b)**
-**Early prodromal phase:** sub-clinical and non-specific symptoms, attenuated manic symptoms. -**Late prodromal phase**: bipolar disorder NOS. -**Subsyndromal stage:** cyclothymia, hypomania. -**Syndromal stage:** bipolar disorder-I and II.	-**Putative risk factors:** first-degree relative with bipolar disorder, sexual/ physical abuse, psychosocial stress, substance use/abuse, antidepressant/ stimulant medication exposure, n-3 fatty acid deficiency. **-Prodromal clinical features:** ADHD, unipolar depression, hypomania, anger/ irritability, anxiety.	**-Sub-threshold mania:** presence of an A criterion plus at least two B criteria, duration of 2–4 days. -**Depression plus cyclothymic features:** *depression: depressed mood or loss of interest plus 2 depression criteria, duration ≥1 week. *cyclothymic features: numerous episodes with sub-threshold mania as in group I	**-Family history.** **-Prodromal symptom complex:** symptoms of mania, comorbid ADHD and/or ODD, and temperamental features. -**Neurobiological markers.** **-Endophenotypic marker.** **-Temperament.**	**-Genetic risk** **-Environmental risk**: childhood trauma, sexual/ physical abuse, neglect or parental loss. **-Profile of risk biomarkers.**	**-Sub-threshold mania:** as per (Bechdolf et al., 2010). -**Depression plus cyclothymic features:** as per (Bechdolf et al., 2010). -**Depression plus genetic risk group:** as per (Bechdolf et al., 2010). **-Cyclothymic features and Genetic risk.** **-Sub-threshold mixed episode:** Sub-threshold mania and depressed mood nearly every day

	-Mania/bipolar-I disorder onset.	and depression, duration of subthreshold mania 4hrs/day for ≥4 days. -**Depression plus genetic risk group:** depression as in group II and first degree relative with BD.			but <5 consecutive days. **-Mood swings:** Recent onset mood instability.

Adapted from (Hauser and Correll, 2013)

Annex 3. Criteria for BD-NOS and MD-NOS

A) Criteria for BD-NOS in the COBY Study (Towbin et al., 2013) renamed "unspecified BD" in the DSM-5 (American Psychiatric Association, 2013)

Unspecified BD category (296.80 (F31.9)) applies to presentations in which symptoms characteristic of a bipolar and related disorder cause clinically significant distress or impairment in social, occupational, or other important areas of functioning predominate, but, do not meet the full criteria for any of the disorders in the bipolar and related disorders diagnostic class. It includes presentations in which there is insufficient information to make a more specific diagnosis (e.g., in emergency room settings) (American Psychiatric Association, 2013).

BD-not otherwise specified (BD-NOS) criteria (Towbin et al., 2013)
A) A distinct period of abnormally elevated, expansive, or irritable mood plus the following: 1. At least 2 DSM-IV-TR "B" manic symptoms (3 if the mood is irritability only) that are clearly associated with the onset of abnormal mood 2. A clear change in functioning. 3. The presence of the elated and/or irritable mood and manic symptoms for a significant part of the day (a minimum of 4 hours, though this did not necessarily need to be expressed consecutively). 4. A minimum of 4 days (not necessarily consecutive) meeting the previous criteria over the subject's lifetime.
B) Mood and affective symptoms must be abnormal for the child's level of development and environment.

C) Symptoms or mood changes that occur during substance use or antidepressant treatment do not count toward a bipolar diagnosis.
D) Exclusion criteria: 1. Current or lifetime DSM-IV diagnosis of schizophrenia, mental retardation, autism, or severe autism spectrum disorders 2. Mood disorders due to substance abuse, a medical condition, or secondary to use of medications (e.g., corticosteroids).
E) Subjects determined to have the onset of BP before comorbid substance use disorders are included.
F) Subjects with mild comorbid Asperger disorder or pervasive developmental disorder–not otherwise specified (PDD-NOS) are included if their mood symptomatology was clearly episodic and best accounted for by the bipolar diagnosis.
G) Child does not meet the DSM-IV criteria for BP-I or BP-II.

B) Criteria for MD-NOS, "other specified BD" in the DSM-5

Patients with mood disorder NOS (MD-NOS) named "other specified BD" in the DSM-5 296.89 (F31.89) (American Psychiatric Association, 2013) have characteristic symptoms of BD and related disorders that do not meet full criteria for any category previously mentioned and is characterized by subthreshold periods of mania or hypomania that, unlike BD-NOS, last <4 hours per day for <4 cumulative days (Salazar de Pablo et al., 2020b).

This category applies to presentations in which symptoms characteristic of a bipolar and related disorder cause clinically significant distress or impairment in social, occupational, or other important areas of functioning predominate but do not meet the full criteria for any of the disorders in the bipolar and related disorders diagnostic class. The other specified bipolar and related disorder

category is used in situations in which the clinician chooses to communicate the specific reason that the presentation does not meet the criteria for any specific bipolar and related disorder. This is done by recording “other specified bipolar and related disorder” followed by the specific reason (e.g., “short-duration cyclothymia”).

Individuals with other specified designations include:

1. Short-duration hypomanic episodes (2-3 days) and major depressive episodes: A lifetime history of one or more major depressive episodes in individuals whose presentation has never met the full criteria for a manic or hypomanic episode, but who have experienced two or more episodes of short-duration hypomania that meet the full symptomatic criteria for a hypomanic episode that last 2-3 days. The episodes of hypomanic symptoms do not overlap in time with the major depressive episodes, so the disturbance does not meet criteria for major depressive episode, with mixed features.

2. Hypomanic episodes with insufficient symptoms and major depressive episodes: A lifetime history of one or more major depressive episodes in individuals whose presentation has never met the full criteria for a manic or hypomanic episode, but who have experienced one or more episodes of hypomania that do not meet full symptomatic criteria (i.e., at least 4 consecutive days of elevated mood and one or two of the other symptoms of a hypomanic episode, or irritable mood and two or three of the other symptoms of a hypomanic episode). The episodes of hypomanic symptoms do not overlap in time with the major depressive episodes, so the disturbance does not meet criteria for major depressive episode, with mixed features.

3. Hypomanic episode without prior major depressive episode: One or more hypomanic episodes in an individual whose presentation has never met full criteria for a major depressive episode or a manic episode. If this occurs in an individual with an established diagnosis of persistent depressive disorder (dysthymia), both diagnoses can be concurrently applied during the periods when the full criteria for a hypomanic episode are met.

4. Short-duration cyclothymia (less than 24 months): Multiple episodes of hypomanic symptoms that do not meet the criteria for a hypomanic episode and multiple episodes of depressive symptoms that do not meet the criteria for a major depressive episode that persist over a period of less than 24 months (less than 12 months for children or adolescents), in an individual whose presentation has never met full criteria for a major depressive, manic, or hypomanic episode and does not meet criteria for any psychotic disorder. During the course of the disorder, the hypomanic or depressive symptoms are present for more days than not, the individual has not been without symptoms for more than 2 months at a time, and the symptoms cause clinically significant distress or impairment.

Annex 4. Established CHR-P instruments (modified from (Fusar-Poli et al., 2020b))

The CHR-P state comprises the ultra-high risk state and/or the Basic Symptoms (Fusar-Poli et al., 2020b).

- The following instruments were considered to define the UHR state: “Comprehensive Assessment of At-Risk Mental States” (CAARMS) (Yung et al., 2005) and “Structured Interview for Psychosis-risk Syndromes” (SIPS) (Fusar-Poli et al., 2016c, McGlashan T, 2010) and “Early Recognition Inventory” (ERIraos) (Haefner et al., 2011). Furthermore, before the development of these instruments, the CHR-P state was defined through the “Positive and Negative Syndrome Scale” (PANSS) (Kay et al., 1987), “Brief Psychiatric Rating Scale” (BPRS) (Overall and Gorham, 1988).
- The following instruments were considered to define the BS (Fusar-Poli et al., 2020b): “Bonn Scale for the Assessment of Basic Symptoms” (BSABS) (Vollmer-Larsen et al., 2007), “Basel Screening Instrument for Psychosis” (BSIP) (Riecher-Rössler et al., 2008), and “Schizophrenia Proneness Instrument” (Fux et al., 2013) - Adult (SPI-A) and Child and Youth (SPI-CY) version -.

Annex 5. Complementary Publication 1

Fusar-Poli P, **Salazar de Pablo G**, Correll CU, Meyer-Lindenberg A, Millan MJ, Borgwardt S, Galderisi S, Bechdolf A, Pfennig A, Kessing LV, van Amelsvoort T, Nieman DH, Domschke K, Krebs MO, Koutsouleris N, McGuire P, Do KQ, Arango C. Prevention of Psychosis: Advances in Detection, Prognosis, and Intervention.JAMA Psychiatry. 2020 Jul 1;77(7):755-765. doi: 10.1001/jamapsychiatry.2019.4779.

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Prevention of Psychosis
Advances in Detection, Prognosis, and Intervention

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IMPORTANCE Detection, prognosis, and indicated interventions in individuals at clinical high risk for psychosis (CHR-P) are key components of preventive psychiatry.

OBJECTIVE To provide a comprehensive, evidence-based systematic appraisal of the advancements and limitations of detection, prognosis, and interventions for CHR-P individuals and to formulate updated recommendations.

EVIDENCE REVIEW Web of Science, Cochrane Central Register of Reviews, and Ovid/PsychINFO were searched for articles published from January 1, 2013, to June 30, 2019, to identify meta-analyses conducted in CHR-P individuals. MEDLINE was used to search the reference lists of retrieved articles. Data obtained from each article included first author, year of publication, topic investigated, type of publication, study design and number, sample size of CHR-P population and comparison group, type of comparison group, age and sex of CHR-P individuals, type of prognostic assessment, interventions, quality assessment (using AMSTAR [Assessing the Methodological Quality of Systematic Reviews]), and key findings with their effect sizes.

FINDINGS In total, 42 meta-analyses published in the past 6 years and encompassing 81 outcomes were included. For the detection component, CHR-P individuals were young (mean [SD] age, 20.6 [3.2] years), were more frequently male (58%), and predominantly presented with attenuated psychotic symptoms lasting for more than 1 year before their presentation at specialized services. CHR-P individuals accumulated several sociodemographic risk factors compared with control participants. Substance use (33% tobacco use and 27% cannabis use), comorbid mental disorders (41% with depressive disorders and 15% with anxiety disorders), suicidal ideation (66%), and self-harm (49%) were also frequently seen in CHR-P individuals. CHR-P individuals showed impairments in work (Cohen *d* = 0.57) or educational functioning (Cohen *d* = 0.21), social functioning (Cohen *d* = 1.25), and quality of life (Cohen *d* = 1.75). Several neurobiological and neurocognitive alterations were confirmed in this study. For the prognosis component, the prognostic accuracy of CHR-P instruments was good, provided they were used in clinical samples. Overall, risk of psychosis was 22% at 3 years, and the risk was the highest in the brief and limited intermittent psychotic symptoms subgroup (38%). Baseline severity of attenuated psychotic (Cohen *d* = 0.35) and negative symptoms (Cohen *d* = 0.39) as well as low functioning (Cohen *d* = 0.29) were associated with an increased risk of psychosis. Controlling risk enrichment and implementing sequential risk assessments can optimize prognostic accuracy. For the intervention component, no robust evidence yet exists to favor any indicated intervention over another (including needs-based interventions and control conditions) for preventing psychosis or ameliorating any other outcome in CHR-P individuals. However, because the uncertainty of this evidence is high, needs-based and psychological interventions should still be offered.

CONCLUSIONS AND RELEVANCE This review confirmed recent substantial advancements in the detection and prognosis of CHR-P individuals while suggesting that effective indicated interventions need to be identified. This evidence suggests a need for specialized services to detect CHR-P individuals in primary and secondary care settings, to formulate a prognosis with validated psychometric instruments, and to offer needs-based and psychological interventions.

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Annex 6. Complementary Publication 2

Catalan A*, **Salazar de Pablo G***, Vaquerizo Serrano J, Mosillo P, Baldwin H, Fernández-Rivas A, Moreno C, Arango C, Correll CU, Bonoldi I, Fusar-Poli P. Annual Research Review: Prevention of psychosis in adolescents - systematic review and meta-analysis of advances in detection, prognosis and intervention. J Child Psychol Psychiatry. 2020 Sep 14. doi: 10.1111/jcpp.13322.

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Annual Research Review: Prevention of psychosis in adolescents – systematic review and meta-analysis of advances in detection, prognosis and intervention

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Background: The clinical high-risk state for psychosis (CHR-P) paradigm has facilitated the implementation of psychosis prevention into clinical practice; however, advancements in adolescent CHR-P populations are less established. **Methods:** We performed a PRISMA/MOOSE-compliant systematic review of the Web of Science database, from inception until 7 October 2019, to identify original studies conducted in CHR-P children and adolescents (mean age <18 years). Findings were systematically appraised around core themes: detection, prognosis and intervention. We performed meta-analyses (employing Q statistics and I^2 test) regarding the proportion of CHR-P subgroups, the prevalence of baseline comorbid mental disorders, the risk of psychosis onset and the type of interventions received at baseline. Quality assessment and publication bias were also analysed. **Results:** Eighty-seven articles were included (n = 4,667 CHR-P individuals). Quality of studies ranged from 3.5 to 8 (median 5.5) on a modified Newcastle–Ottawa scale. *Detection*: Individuals were aged 15.6 ± 1.2 years (51.5% males), mostly (83%) presenting with attenuated positive psychotic symptoms. CHR-P psychometric accuracy improved when caregivers served as additional informants. Comorbid mood (46.4%) and anxiety (31.4%) disorders were highly prevalent. Functioning and cognition were impaired. Neurobiological studies were inconclusive. *Prognosis*: Risk for psychosis was 10.4% (95%CI: 5.8%–18.1%) at 6 months, 20% (95% CI: 15%–26%) at 12 months, 23% (95%CI: 18%–29%) at 24 months and 23.3% (95%CI: 17.3%–30.7%) at ≥36 months. *Interventions*: There was not enough evidence to recommend one specific treatment (including cognitive behavioural therapy) over the others (including control conditions) to prevent the transition to psychosis in this population. Randomised controlled trials suggested that family interventions, cognitive remediation and fish oil supplementation may improve cognition, symptoms and functioning. At baseline, 30% of CHR-P adolescents were prescribed antipsychotics and 60% received psychotherapy. **Conclusions:** It is possible to detect and formulate a group-level prognosis in adolescents at risk for psychosis. Future interventional research is required. **Keywords:** Psychosis; schizophrenia; clinical high-risk state for psychosis; psychosis risk; prevention; evidence; prediction; first-episode; meta-analysis; childhood; adolescence.

Introduction

Psychotic disorders typically onset in adolescence and early adulthood, with the peak of risk occurring between the ages of 12 and 25 years (Radua et al., 2018). Once the disorder onsets, the opportunities to improve its course are limited (Millan et al., 2016). Therefore, early intervention and particularly preventive approaches in young people with subtle signs and symptoms of the disorder (termed 'primary indicated prevention' Arango et al., 2018; Fusar-Poli, Bauer, et al., 2019) have the potential to benefit the lives of many young people. Primary indicated prevention in individuals at clinical high-risk state for psychosis (CHR-P) has grown exponentially over the past two decades and has become one of the most established preventive approaches in psychiatry (Correll et al., 2018; Fusar-Poli, McGorry, & Kane,

Ana Catalan and Gonzalo Salazar de Pablo have contributed equally and shared the first position authorship.
Ilaria Bonoldi and Paolo Fusar-Poli have contributed equally and shared the senior position authorship.
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Annex 7. Complementary Publication 3

Salazar de Pablo G, Studerus E, Vaquerizo-Serrano J, Irving J, Catalan A, Oliver D, Baldwin H, Danese A, Fazel S, Steyerberg EW, Stahl D, Fusar-Poli P. Implementing Precision Psychiatry: A Systematic Review of Individualized Prediction Models for Clinical Practice. Schizophr Bull. 2020 Sep 11:sbaa120. doi: 10.1093/schbul/sbaa120.

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MAJOR REVIEW

Implementing Precision Psychiatry: A Systematic Review of Individualized Prediction Models for Clinical Practice

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Background: **The impact of precision psychiatry for clinical practice has not been systematically appraised. This study aims to provide a comprehensive review of validated prediction models to estimate the individual risk of being affected with a condition (diagnostic), developing outcomes (prognostic), or responding to treatments (predictive) in mental disorders.** ***Methods:*** **PRISMA/RIGHT/CHARMS-compliant systematic review of the Web of Science, Cochrane Central Register of Reviews, and Ovid/PsycINFO databases from inception until July 21, 2019 (PROSPERO CRD42019155713) to identify diagnostic/prognostic/predictive prediction studies that reported individualized estimates in psychiatry and that were internally or externally validated or implemented. Random effect meta-regression analyses addressed the impact of several factors on the accuracy of prediction models.** ***Findings:*** **Literature search identified 584 prediction modeling studies, of which 89 were included. 10.4% of the total studies included prediction models internally validated (n = 61), 4.6% models externally validated (n = 27), and 0.2% (n = 1) models considered for implementation. Across validated prediction modeling studies (n = 88), 18.2% were diagnostic, 68.2% prognostic, and 13.6% predictive. The most frequently investigated condition was psychosis (36.4%), and the most frequently employed predictors clinical (69.5%). Unimodal compared to multimodal models (β = .29, P = .03) and diagnostic compared to prognostic (β = .84, p < .0001) and predictive (β = .87, P = .002) models were associated with increased accuracy.** ***Interpretation:*** **To date, several validated prediction models are available to support the diagnosis and prognosis of psychiatric conditions, in particular, psychosis, or to predict treatment response. Advancements of knowledge are limited by the lack of implementation research in real-world clinical practice. A new generation of implementation research is required to address this translational gap.**

Key words: risk/prognosis/prediction/individualized/prevention/evidence/implementation/validation

Introduction

Precision medicine is an emerging approach for disease prevention, diagnosis, and treatment that considers individual variability in patient and disease characteristics, genes, environment, and lifestyle of each person.[1,2] The

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Annex 8. Complementary Publication 4

Fusar-Poli P, **Salazar de Pablo G**, Rajkumar RP, López-Díaz A, Malhotra S, Heckers S, Lawrie S, Pillmann F. Diagnosis, Prognosis and Treatment of Brief Psychotic Episodes: A Review and Research Agenda. Lancet Psychatry. 2021.

Doctopic: Review and Opinion

Diagnosis, prognosis, and treatment of brief psychotic episodes: a review and research agenda

Paolo Fusar-Poli, Gonzalo Salazar De Pablo, Ravi Philip Rajkumar, Álvaro López-Díaz, Savita Malhotra, Stephan Heckers, Stephen M Lawrie, Frank Pillmann

Brief psychotic episodes represent an intriguing paradox in clinical psychiatry because they elude the standard *Lancet Psychiatry* 2021

Annex 9. Complementary Publication 5

Salazar de Pablo G, Estradé Vaz A, Cutroni M, Andlauer O, Fusar-Poli. Establishing a clinical service to prevent psychosis: what, how and when? Transl psychiatry. 2021 Jan 13;11(1):43. doi: 10.1038/s41398-020-01165-x.

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Translational Psychiatry

REVIEW ARTICLE Open Access

Establishing a clinical service to prevent psychosis: What, how and when? Systematic review

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Abstract

The first rate-limiting step to successfully translate prevention of psychosis in to clinical practice is to establish specialised Clinical High Risk for Psychosis (CHR-P) services. This study systematises the knowledge regarding CHR-P services and provides guidelines for translational implementation. We conducted a PRISMA/MOOSE-compliant (PROSPERO-CRD42020163640) systematic review of Web of Science to identify studies until 4/05/2020 reporting on CHR-P service configuration, outreach strategy and referrals, service user characteristics, interventions, and outcomes. Fifty-six studies (1998–2020) were included, encompassing 51 distinct CHR-P services across 15 countries and a catchment area of 17,252,666 people. Most services (80.4%) consisted of integrated multidisciplinary teams taking care of CHR-P and other patients. Outreach encompassed active (up to 97.6%) or passive (up to 63.4%) approaches: referrals came mostly (90%) from healthcare agencies. CHR-P individuals were more frequently males (57.2%). Most (70.6%) services accepted individuals aged 12–35 years, typically assessed with the CAARMS/SIPS (83.7%). Baseline comorbid mental conditions were reported in two-third (69.5%) of cases, and unemployment in one third (36.6%). Most services provided up to 2-years (72.4%), of clinical monitoring (100%), psychoeducation (81.1%), psychosocial support (73%), family interventions (73%), individual (67.6%) and group (18.9%) psychotherapy, physical health interventions (37.8%), antipsychotics (87.1%), antidepressants (74.2%), anxiolytics (51.6%), and mood stabilisers (38.7%). Outcomes were more frequently ascertained clinically (93.0%) and included: persistence of symptoms/comorbidities (67.4%), transition to psychosis (53.5%), and functional status (48.8%). We provide ten practical recommendations for implementation of CHR-P services. Health service knowledge summarised by the current study will facilitate translational efforts for implementation of CHR-P services worldwide.

Introduction

The clinical high risk for psychosis (CHR-P) paradigm[1] represents one of the most established preventive approaches in clinical psychiatry[2]. It originated in Australia around 25 years ago[3] and since then, it has progressively gained importance[4]. CHR-P individuals are young and accumulate risk factors for the disorders[5–7], that lead to functional impairments[8] and attenuated psychotic symptoms[9]. Because of these features, these individuals seek help[10] at specialised CHR-P mental health services. The detection[11], prognostic assessment[12] and preventive treatment[13–16] in CHR-P individuals[15] have the potential to maximize the benefits of early interventions in psychosis[17,18]. A recent evidence-based summary by the European College of Neuropsychopharmacology Network for the Prevention of Mental Disorders and Mental Health Promotion[19] indicated that the first rate-limiting step to prevent psychosis is to establish specialised CHR-P services[20]. Accordingly, several CHR-P services have been implemented worldwide, as recently mapped by the

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Endnote reference file: CHR-P clinical services.enl

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Annex 10. Comorbidity and Treatment characteristics in DSM-5–APS vs. non-APS individuals

	Total (n=248)	APS (n=65)	Non-APS (n=183)	P value	Effect size
Lifetime Consensus Diagnoses, n (%)					
Number of psychiatric diagnoses	2.6±1.5	3.5±1.5	2.4±1.4	**<0.001**	**0.77**
Depressive Disorders	191 (77.0)	52 (80.0)	139 (76.0)	0.51	0.042
Major Depressive Disorder	137 (55.2)	42 (64.6)	95 (51.9)	0.077	0.11
Other Specified Depressive Disorder	53 (21.4)	10 (15.4)	43 (23.5)	0.170	0.09
Persistent Depressive Disorder	18 (7.3)	5 (7.7)	13 (7.1)	0.87	0.01
Disruptive, Impulse-Control and Conduct Disorders	97 (39.1)	34 (52.3)	63 (34.4)	**0.011**	**0.16**
ADHD	58 (23.4)	13 (20.0)	45 (24.6)	0.45	0.05
Oppositional Defiant Disorder	40 (16.1)	16 (24.6)	24 (13.1)	**0.03**	**0.14**
Conduct Disorder	26 (10.5)	11 (16.9)	15 (8.2)	**0.049**	**0.12**
Disruptive Behavior Disorder not otherwise specified	11 (4.4)	4 (6.2)	7 (3.8)	0.43	0.05
Bipolar Disorders	57 (23.0)	24 (36.9)	33 (18.0)	**0.002**	**0.20**
Other Specified Bipolar and Related Disorder	41 (16.5)	18 (27.7)	23 (12.6)	**0.005**	**0.18**
Bipolar I Disorder	12 (4.8)	6 (9.2)	6 (3.3)	0.055	0.12
Bipolar II Disorder	8 (3.2)	3 (4.6)	5 (2.7)	0.46	0.05
Personality Disorder Traits	48 (19.4)	24 (36.9)	24 (13.1)	**<0.001**	**0.26**
Borderline Personality Disorder Traits	42 (16.9)	19 (29.2)	23 (12.6)	**0.002**	**0.20**
Other Personality Disorder Traits	13 (5.2)	10 (15.4)	3 (1.6)	**<0.001**	**0.27**
Substance use disorders	39 (15.7)	13 (20.0)	26 (14.2)	0.27	0.07
Cannabis use disorder	31 (12.5)	9 (13.8)	22 (12.0)	0.70	0.02
Alcohol use disorder	14 (5.6)	6 (9.2)	8 (4.4)	0.14	0.09
Others	6 (2.4)	2 (3.1)	4 (2.2)	0.67	0.03
Trauma- and Stressor-related Disorders	38 (15.3)	8 (12.3)	30 (16.4)	0.43	0.05
Post-traumatic Stress Disorder	20 (8.1)	7 (10.8)	13 (7.1)	0.35	0.06
Adjustment Disorder	19 (7.7)	2 (3.1)	17 (9.3)	0.11	0.10
Anxiety disorders	106 (42.7)	36 (55.4)	70 (38.3)	**0.016**	**0.15**
Panic Disorder	63 (25.4)	23 (35.4)	40 (21.9)	**0.031**	**0.14**
Generalized Anxiety Disorder	37 (14.9)	16 (24.6)	21 (11.5)	**0.011**	**0.16**

	Total (n=248)	**APS (n=65)**	**Non-APS (n=183)**	**P value**	**Effect size**
Social Phobia	24 (9.7)	10 (15.4)	14 (7.7)	0.07	0.11
Others	20 (8.1)	5 (7.7)	15 (8.2)	0.90	0.01
Obsessive-Compulsive disorder	13 (5.2)	6 (9.2)	7 (3.8)	0.093	0.11
Specific Phobia	9 (3.6)	6 (9.2)	3 (1.6)	**0.005**	**0.18**
Other Diagnostic Categories					
Eating Disorders	20 (8.1)	10 (15.4)	10 (5.5)	**0.012**	**0.16**
Enuresis	9 (3.6)	3 (4.6)	6 (3.3)	0.62	0.03
Treatment Characteristics at Time of the Interview n (%)					
Antipsychotics	118 (53.6)	37 (66.1)	81 (49.4)	**0.031**	**0.15**
Antidepressants	112 (50.9)	24 (42.9)	88 (53.7)	0.16	0.09
Mood stabilizers	55 (25.0)	14 (25.0)	41 (25.0)	1.0	0.00
Lithium	41 (18.6)	9 (16.1)	32 (19.5)	0.57	0.04
Anxiolytics	23 (10.5)	7 (12.5)	16 (9.8)	0.56	0.04
Others	21 (9.5)	7 (12.5)	14 (8.5)	0.38	0.06
Antiepileptic drugs	18 (8.2)	6 (10.7)	12 (7.3)	0.42	0.05
ADHD medication	4 (1.8)	0 (0.0)	4 (2.4)	0.24	0.08
Two or more drugs	91 (41.4)	22 (39.3)	69 (42.1)	0.71	0.02
Three or more drugs	25 (11.4)	7 (12.5)	18 (11.0)	0.76	0.02

Annex 11. Severity of Structured Interview of Prodromal Syndromes (SIPS) Assessed Symptoms and Symptom Domains in DSM-5–APS vs. non-APS individuals

	Total (n=248)	**APS (n=65)**	**Non-APS (n=183)**	**P value**	**Effect size**
Structured Interview of Prodromal Syndromes mean± SD					
Positive Symptoms					
Total Positive Symptom Score	3.2± 4.1	7.4±4.6	1.9± 3.3	**<0.001**	**1.5**
Highest Positive Symptom Score	1.8± 1.8	3.5±1.3	1.2± 1.6	**<0.001**	**1.5**
P1 Unusual Thought Content	0.73± 1.4	1.6±1.6	0.41± 1.1	**<0.001**	**0.95**
P2 Suspiciousness	0.84± 1.3	1.8±1.6	0.48± 0.93	**<0.001**	**1.2**
P3 Grandiosity	0.54± 1.2	0.89±1.5	0.41± 1.1	**0.024**	**0.39**
P4 Perceptual Abnormalities/ Hallucinations	0.99± 1.7	2.3±1.9	0.47± 1.2	**<0.001**	**1.3**
P5 Disorganized Communication	0.29± 0.86	0.63±1.1	0.16± 0.68	**<0.001**	**0.58**
Negative Symptoms					
Total Negative Symptom Score	8.0± 6.22	10.4±6.7	7.1± 5.8	**<0.001**	**0.55**
Highest Negative Symptom Score	3.4± 1.83	3.8±1.6	3.2± 1.9	**0.012**	**0.33**
N1 Social Anhedonia	1.5± 1.79	2.2±1.9	1.2± 1.7	**<0.001**	**0.57**
N2 Avolition	2.1± 2.0	2.9±1.7	1.9± 2.0	**0.002**	**0.51**
N3 Expression of Emotions	0.88± 1.5	1.2±1.6	0.75± 1.4	0.061	0.31
N4 Experience of Emotions and Self	0.87± 1.7	1.6±2.3	0.65± 1.4	**<0.001**	**0.54**
N5 Ideational Richness	0.20± 0.65	0.18±0.18	0.21± 0.75	0.88	0.05
N6 Occupational Functioning	2.4± 2.1	2.5±2.4	2.3± 2.0	0.31	0.11
Disorganized Symptoms					
Total Disorganized Symptom Score	3.1± 3.2	4.3±3.7	2.7± 2.9	**<0.001**	**0.51**
Highest Disorganized Symptom Score	2.2± 1.9	2.9±1.7	2.03± 1.9	**0.003**	**0.47**
D1 Odd Behavior or Appearance	0.16± 0.94	0.14±1.4	0.17± 0.71	0.297	0.03
D2 Bizarre Thinking	0.18±0.7	0.48±1.1	0.08± 0.4	**<0.001**	**0.60**
D3 Trouble with Focus and Attention	1.9± 1.8	2.6±1.7	1.66± 1.81	**0.001**	**0.53**
D4 Impairment in Personal Hygiene	0.76± 1.7	0.86±2.1	0.73± 1.54	0.45	0.08

	Total (n=248)	**APS (n=65)**	**Non-APS (n=183)**	**P value**	**Effect size**
General Symptoms					
Total General Symptom Score	8.4± 4.5	11.0± 3.5	7.5± 4.4	**<0.001**	**0.84**
Highest General Symptom Score	4.3± 1.7	5.0±1.1	4.1± 1.8	**<0.001**	**0.55**
G1 Sleep Disturbance	2.3± 1.9	2.8±2.0	2.1± 1.8	**0.002**	**0.38**
G2 Dysphoric Mood	4.0± 2.1	4.5±2.3	3.8± 2.0	**0.004**	**0.34**
G3 Motor Disturbance	0.14± 0.80	0.17±1.4	0.13± 0.52	0.73	0.05
G4 Impaired Stress Tolerance	1.9± 2.1	2.9±2.3	1.6± 1.9	**<0.001**	**0.63**

Annex 12. Illness Severity, Functional Level, Illness Insight and Suicidality in DSM-5–APS vs. non-APS individuals

	Total (n=248)	**APS (n=65)**	**Non-APS (n=183)**	**P value**	**Effect size**
Characteristics					
Illness Severity: Clinical Global Impressions-Severity Scale (CGI-S) mean± SD					
Overall Severity of Illness	4.2± 1.03	4.8± 0.94	3.9± 0.9	**<0.001**	**1.0**
Functional Level: Global Assessment of Functioning-Scale (GAF) mean± SD					
Current GAF	26.8± 16.7	23.0± 11.9	28.1± 17.9	**0.012**	**0.31**
Highest GAF of Past Year	57.7± 14.7	52.2± 16.6	59.7± 13.5	**0.002**	**0.52**
Lowest GAF of Past Year	23.1± 15.0	18.9± 10.2	24.5± 16.0	**0.002**	**0.38**
Global Functioning: Role Scale mean± SD					
Current Role Functioning	5.9±1.8	5.7±1.7	6.1±1.9	0.35	0.20
Global Functioning: Social Scale mean± SD					
Current Social Functioning	6.5±1.7	5.8±1.5	6.9±1.7	**0.003**	**0.66**
Scale to Assess Unawareness of Mental Disorder mean± SD					
Awareness of Mental Disorder	2.2±1.7	2.2±1.6	2.2±1.7	0.98	0.01
Awareness of the Effect of Medication	2.1±1.5	2.2±1.5	2.0±1.5	0.45	0.14
Awareness of the Social Consequences	1.9±1.5	1.9±1.4	1.9±1.5	0.99	0.00
Suicidality, n (%)					
Suicidal Ideation	131 (61.8)	38 (73.1)	93 (58.1)	0.29	0.07
Suicide Attempts	21 (10.0)	8 (15.3)	13 (8.2)	0.19	0.08

Annex 13. Comorbidity and Treatment characteristics in Bipolar Spectrum Disorders

	Total (n=76)	BD-1 (n=24)	BD-NOS (n=29)	MD-NOS (n=23)	P value
Comorbidity					
Personality disorder traits	19 (25.0%)	6 (25.0%)	10 (34.5%)	3 (13.0%)	0.208
Borderline Personality traits	15 (19.7%)	4 (16.6%)	9 (31.0%)	2 (8.7%)	0.119
Other Personality traits	6 (7.9%)	2 (8.3%)	3 (10.3%)	1 (4.4%)	0.725
Anxiety disorders	31 (40.8%)	10 (41.7%)	12 (41.4%)	9 (39.1%)	0.981
Generalized Anxiety Disorder	9 (11.8%)	4 (16.7%)	4 (13.8%)	1 (4.4%)	0.391
Obsessive-Compulsive Disorder	2 (2.6%)	0 (0.0%)	0 (0.0%)	2 (8.7%)	0.094
PTSD	5 (6.6%)	2 (8.3%)	2 (6.9%)	1 (4.4%)	0.856
Panic Disorder	17 (22.4%)	6 (25.0%)	8 (27.6%)	3 (13.0%)	0.427
Social Phobia	15 (19.7%)	4 (16.7%)	5 (17.2%)	6 (26.1%)	0.656
Disruptive behaviour disorders	42 (55.3%)	10 (41.7%)	18 (62.1%)	14 (60.9%)	0.268
ADHD	27 (35.5%)	7 (29.2%)	10 (34.5%)	10 (43.5%)	0.585
Conduct Disorder	10 (13.2%)	2 (8.3%)	5 (17.2%)	3 (13.0%)	0.634
Oppositional Defiant Disorder	18 (23.7%)	5 (20.8%)	6 (20.7%)	7 (30.4%)	0.66
Disruptive Behaviour Disorder NOS	6 (7.9%)	1 (4.2%)	2 (6.9%)	3 (13.0%)	0.512
Substance use disorders	13 (17.1%)	2 (8.3%)	6 (20.7%)	5 (21.7%)	0.384
Alcohol use disorder	7 (9.2%)	1 (4.2%)	3 (10.3%)	3 (13.0%)	0.555
Cannabis use disorder	11 (14.5%)	1 (4.2%)	5 (17.2%)	5 (21.7%)	0.200
Eating disorders	10 (13.2%)	5 (20.8%)	3 (10.3%)	2 (8.7%)	0.399
Enuresis (Not Due to a General Medical Condition)	7 (9.2%)	2 (8.3%)	3 (10.3%)	2 (8.7%)	0.964

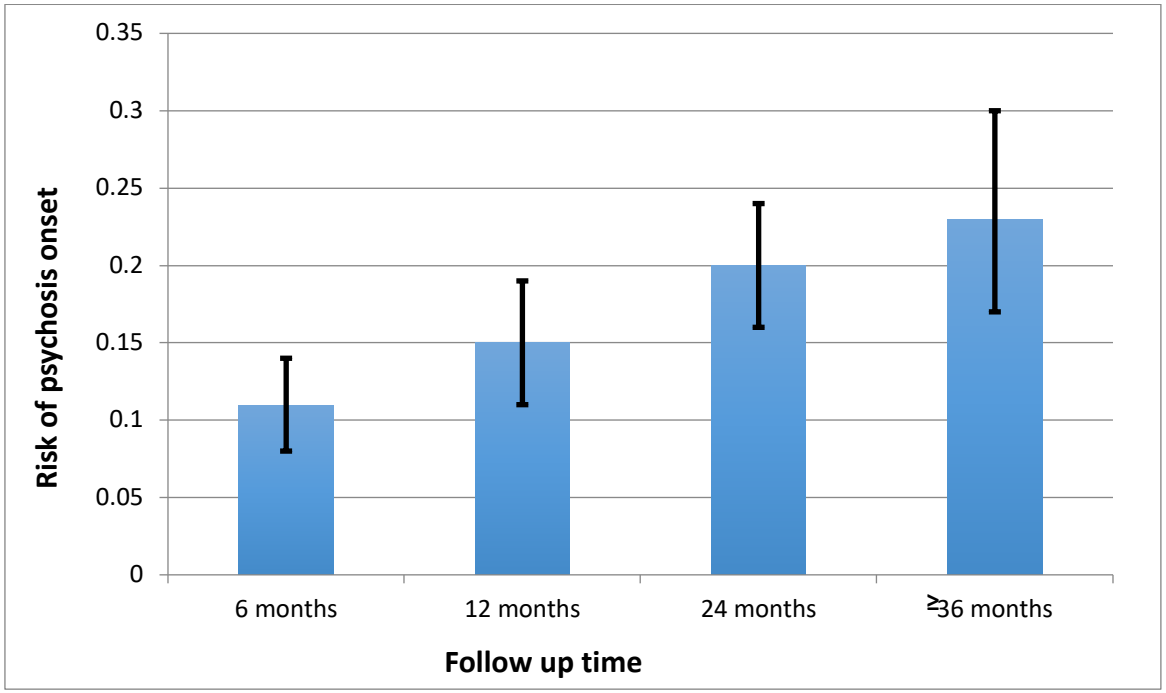
	Total (n=76)	**BD-1 (n=24)**	**BD-NOS (n=29)**	**MD-NOS (n=23)**	**P value**
Treatment					
Antipsychotics	55 (72.4%)	20 (83.3%)	19 (65.5%)	16 (69.6%)	0.331
Typical antipsychotics	3 (3.9%)	2 (8.3%)	0 (0.0%)	1 (4.4%)	0.298
Atypical antipsychotic	52 (68.4%)	18 (75.0%)	19 (65.5%)	15 (65.2%)	0.704
Antidepressants	27 (35.5%)	5 (20.8%)	11 (37.9%)	11 (47.8%)	0.146
Selective serotonin reuptake inhibitors	23 (30.3%)	5 (20.8%)	9 (31.0%)	9 (39.1%)	0.391
Bupropion	3 (3.9%)	0 (0.0%)	2 (6.9%)	1 (4.4%)	0.436
Others	4 (5.3%)	1 (4.2%)	1 (3.4%)	2 (8.7%)	0.673
Mood stabilizers	23 (30.3%)	7 (29.2%)	7 (24.1%)	9 (39.1%)	0.500
Lithium	17 (22.4%)	6 (25.0%)	3 (10.3%)	8 (34.8%)	0.103
Valproate	7 (9.2%)	2 (8.3%)	3 (10.3%)	2 (8.7%)	0.964
Lamotrigine	4 (5.3%)	1 (4.2%)	2 (6.9%)	1 (4.3%)	0.882
Other mood stabilizers	2 (2.6%)	0 (0.0%)	2 (6.9%)	0 (0.0%)	0.189
Anxiolytics	8 (10.5%)	4 (16.7%)	3 (10.3%)	1 (4.3%)	0.388
ADHD medications	9 (11.8%)	1 (4.2%)	4 (13.8%)	4 (17.4%)	0.343

Annex 14. Prevalence of BPSS-P Items Rated at Moderate or Higher Severity in Bipolar Spectrum Disorders

	Total (n=76)	BD-1 (n=24)	BD-NOS (n=29)	MD-NOS (n=23)	P value	INTRAGROUP		
						BD-1 vs. BD-NOS	BD-1 vs. MD-NOS	BD-NOS vs. MD-NOS
BPSS-P Manic symptoms								
1. Mood elevation	49 (64.5%)	23 (95.8%)	20 (69%)	6 (26.1%)	**<0.001**	0.013	<0.001	0.002
2. Irritability	71 (93.4%)	23 (95.8%)	27 (93.1%)	21 (91.3%)	0.819			
3. Inflated self-esteem/grandiosity	20 (26.3%)	13 (54.2%)	7 (24.1%)	0 (0%)	**<0.001**	0.025	<0.001	0.011
4. Decreased need for sleep	38 (50%)	18 (75%)	14 (48.3%)	6 (26.1%)	**0.004**	0.048	0.001	n.s.
5. Over talkativeness	53 (69.7%)	19 (79.2%)	26 (89.7%)	8 (34.8%)	**<0.001**	n.s.	0.002	<0.001
6. Racing thoughts/flight of ideas	49 (65.3%)	22 (91.7%)	19 (65.5%)	8 (36.4%)	**<0.001**	0.024	<0.001	0.039
7. Distractibility	54 (71.1%)	19 (79.2%)	23 (79.3%)	12 (52.2%)	0.057			
8. Increased energy/goal-directed activity	36 (47.4%)	21 (87.5%)	11 (37.9%)	4 (17.4%)	**<0.001**	<0.001	<0.001	n.s.
9. Increased psychomotor activity	47 (61.8%)	19 (79.2%)	17 (58.6%)	11 (47.8%)	0.078			
10. Reckless or dangerous behavior	27 (35.5%)	8 (33.3%)	13 (44.8%)	6 (26.1%)	0.361			
BPSS-P Depression symptoms								
1. Depressed mood	62 (81.6%)	22 (91.7%)	24 (82.8%)	16 (69.6%)	0.145			
2. Anhedonia	45 (60%)	18 (75%)	20 (69%)	7 (31.8%)	**0.005**	n.s.	0.003	0.008
3. Decreased appetite	19 (25.7%)	9 (39.1%)	8 (27.6%)	2 (9.1%)	0.067			
4. Increased appetite	13 (17.3%)	7 (30.4%)	4 (13.8%)	2 (8.7%)	0.122			
5. Insomnia	35 (46.1%)	13 (54.2%)	16 (55.2%)	6 (26.1%)	0.071			
6. Hypersomnia	17 (22.4%)	9 (37.5%)	6 (20.7%)	2 (8.7%)	0.058			
7. Decreased psychomotor activity	22 (29.3%)	11 (47.8%)	10 (34.5%)	1 (4.3%)	**0.004**	n.s.	0.001	0.008
8. Decreased energy	44)57.9%)	15 (62.5%)	22 (75.9%)	7 (30.4%)	**0.004**	n.s.	0.028	0.001
9. Worthlessness/guilt	47 (61.8%)	18 (75%)	22 (75.9%)	7 (30.4%)	**0.001**	n.s	0.002	0.001
10. Decreased concentration	46 (62.2%)	16 (66.7%)	21 (75%)	9 (40.9%)	**0.041**	n.s	n.s.	0.015
11. Indecision	23 (30.7%)	8 (33.3%)	9 (31%)	6 (27.3%)	0.904			
12. Suicidality	52 (69.3%)	17 (70.8%)	22 (75.9%)	13 (59.1%)	0.429			

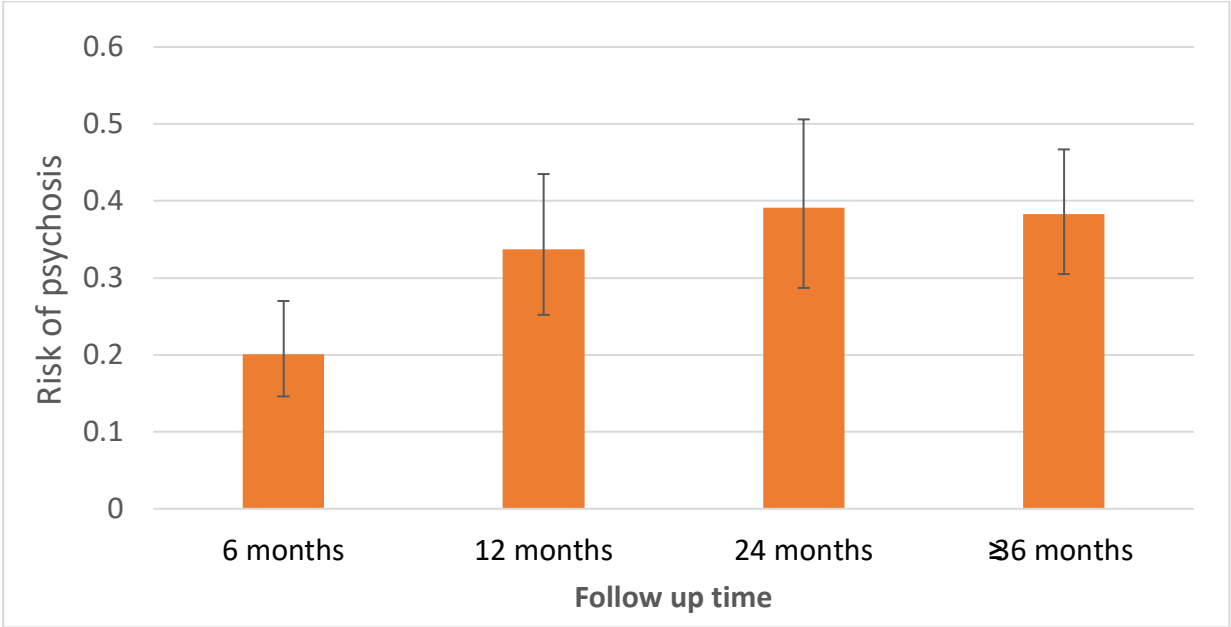
		Total (n=76)	**BD-1 (n=24)**	**BD-NOS (n=29)**	**MD-NOS (n=23)**	**P value**	**INTRAGROUP**		
							BD-1 vs. BD-NOS	BD-1 vs. MD-NOS	BD-NOS vs. MD-NOS
BPSS-P General symptoms									
1.	Mood lability	54 (71.1%)	20 (83.3%)	24 (82.8%)	10 (43.5%)	**0.002**	n.s.	0.004	0.003
2.	Oppositionality	34 (45.9%)	10 (41.7%)	12 (44.4%)	12 (52.2%)	0.756			
3.	Anger/aggressiveness	51 (69.9%)	15 (62.5%)	20 (74.1%)	16 (72.7%)	0.628			
4.	Anxiety	40 (54.8%)	16 (66.7%)	13 (50%)	11 (47.8%)	0.357			
5.	Self-injurious behavior	39 (52.7%)	12 (50%)	18 (66.7%)	9 (39.1%)	0.144			
6.	Obsessions and compulsions	5 (6.9%)	2 (8.7%)	1 (3.8%)	2 (8.7%)	0.739			

Annex 15. Meta-analytical cumulative risk of psychosis onset in DSM-5–APS Error bars indicate 95%CI.



Follow-up	n of studies	Total DSM-5-APS/APSS sample	Risk of psychosis	95%CI	Q	df	I²	P
6-months	12	824	0.11	0.08-0.14	20.77	11	47.04	0.04
12-months	19	1292	0.15[(a)]	0.11-0.19	61.02	18	72.14	<0.01
24-months	18	2212	0.2[(b)]	0.16-0.24	87.22	17	79.36	<0.01
≥36-months	7	721	0.23	0.17-0.30	22.20	6	72.97	<0.01

Annex 16. Meta-analytical cumulative risk of psychosis onset in BLIPS individuals. Error bars indicate 95%CI.



	Follow-up time			
	6 months	**12 months**	**24 months**	**≥36 months**
Overall n. of samples	14	19	14	9
N. of patients analyzed	215	292	239	187
Risk of psychotic recurrence, mean (95%CI)				
BLIPS	0.201 (0.146-0.270)	0.337 (0.252-0.435)	0.391 (0.287-0.506)	0.383 (0.305-0.467)

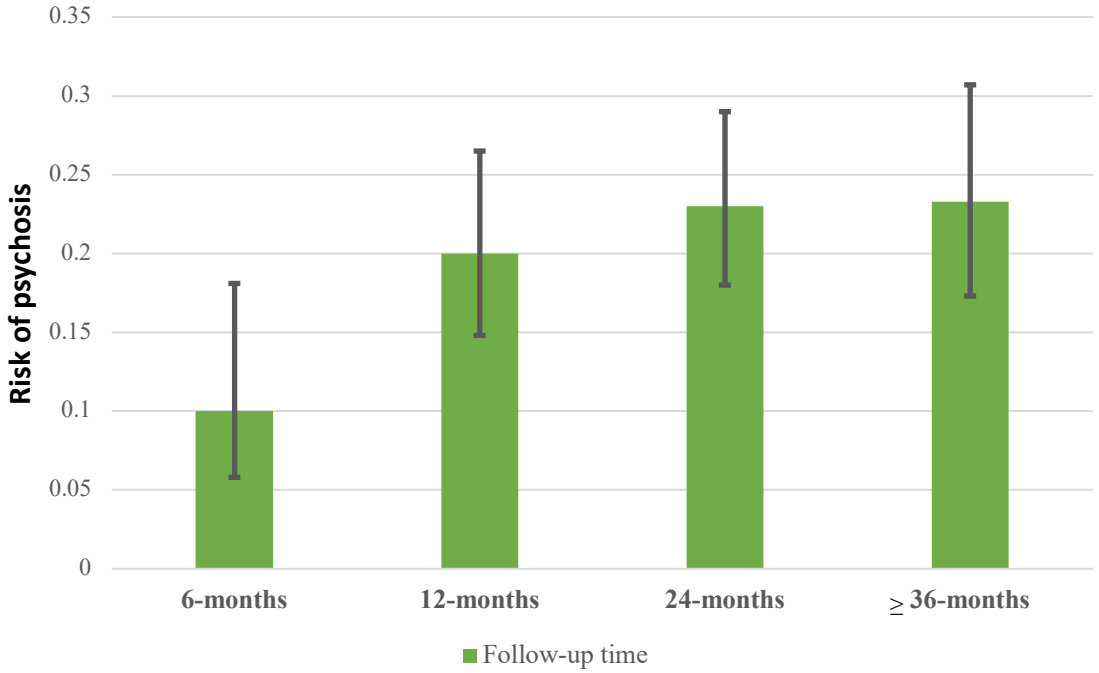
Annex 17. Prognostic factors of psychotic recurrence in brief psychotic episodes

Prognostic factor	**Association with psychotic recurrence**
Male gender	↑(Queirazza et al., 2014, Wang et al., 2018) ; ↔(Aadamsoo et al., 2011, Abe et al., 2006, Fusar-Poli et al., 2017a, Poon and Leung, 2017, Suda et al., 2005)
Younger age	↑(Wang et al., 2018, Aadamsoo et al., 2011, Abe et al., 2006, Poon and Leung, 2017, Queirazza et al., 2014) ; ↔(Rusaka and Rancans, 2014b, Suda et al., 2005, Fusar-Poli et al., 2017a)
Years of education	↔(Aadamsoo et al., 2011)
Marital status	↔(Aadamsoo et al., 2011, Fusar-Poli et al., 2017a)
Employment	↔(Aadamsoo et al., 2011, Fusar-Poli et al., 2017a)
Ethnicity	↔(Fusar-Poli et al., 2017a)
Hazardousness	↔(Aadamsoo et al., 2011)
Family history of mental disorders	↑(Wang et al., 2018) ; ↔(Rusaka and Rancans, 2014b, Suda et al., 2005, Abe et al., 2006, Poon and Leung, 2017)
Poor premorbid social functioning	↑(Suda et al., 2005) ; ↔(Rusaka and Rancans, 2014b, Suda et al., 2005)
Life events	↔(Abe et al., 2006, Suda et al., 2005)
Duration/number of hospitalizations over follow-up	↑(Poon and Leung, 2017, Aadamsoo et al., 2011, Queirazza et al., 2014, Wang et al., 2018) ; ↔(Rusaka and Rancans, 2014b, Suda et al., 2005)
Acute onset	↓(Rusaka and Rancans, 2014a) ; ↔ (Fusar-Poli et al., 2019b, Rusaka and Rancans, 2014b)
Acute stress	↔(Fusar-Poli et al., 2019b)
Duration of psychotic symptoms	↔(Fusar-Poli et al., 2017a, Fusar-Poli et al., 2019b, Wang et al., 2018)
Frequency of episodes over follow-up	↑(Fusar-Poli et al., 2017a) ; ↔ (Suda et al., 2005)
Severity of psychotic symptoms	↔(Fusar-Poli et al., 2017a, Aadamsoo et al., 2011)
Hallucinations	↑(Rusaka and Rancans, 2014a) ; ↔(Rusaka and Rancans, 2014b, Suda et al., 2005)

Thought disorder	↑(Rusaka and Rancans, 2014b) ; ↔(Rusaka and Rancans, 2014b, Suda et al., 2005, Rusaka and Rancans, 2014a)
Delusional ideation	↔(Rusaka and Rancans, 2014a, Rusaka and Rancans, 2014b, Suda et al., 2005)
Polymorphic symptomatology	↓(Rusaka and Rancans, 2014a) ; ↔(Rusaka and Rancans, 2014b, Suda et al., 2005)
Affective disturbances	↔(Rusaka and Rancans, 2014a, Rusaka and Rancans, 2014b)
Depressed mood	↔(Rusaka and Rancans, 2014a, Rusaka and Rancans, 2014b, Suda et al., 2005)
Irritability or mood elation	↔(Suda et al., 2005)
Anxiety	↑ (Rusaka and Rancans, 2014a) ; ↔(Rusaka and Rancans, 2014b, Suda et al., 2005)
Sleep disturbances	↑ (Suda et al., 2005) ; ↔(Rusaka and Rancans, 2014b, Suda et al., 2005, Rusaka and Rancans, 2014a)
Illicit substances	↔(Fusar-Poli et al., 2019b)
BLIPS seriously disorganizing or dangerous	↑(Fusar-Poli et al., 2017a, Fusar-Poli et al., 2019b)
Level of functioning	↔(Aadamsoo et al., 2011, Fusar-Poli et al., 2017a)
Quality of life	↔(Aadamsoo et al., 2011)
Antipsychotic dosage	↑(Wang et al., 2018)

Annex 18. Meta-analytical cumulative risk of psychosis onset in children and adolescents meeting CHR-P criteria

Error bars indicate 95%CI.



Follow-up	n of studies*	Sample size	Cumulative risk of psychosis (95%CI)	Q	df	I ²	P
6-months	4	348	0.104 (0.058-0.181)	9.28	3	67.69	0.026
12-months	7	525	0.198 (0.146-0.263)	12.44	6	51.76	0.053
24-months	7	681	0.230 (0.180-0.290)	12.24	6	50.99	0.057
≥36-months	5	239	0.233 (0.173-0.307)	6.24	4	27.17	0.240

Annex 19. Recommendations for real-world implementation of CHR-P services

Service configuration	
1	Implement a standalone community service (“what”)
2	Train a multidisciplinary team (psychiatrists, clinical psychologists or counsellors, case managers and nurses) (“what”)
Outreach strategy and referrals	
3	Adopt active and passive outreach, primarily targeting healthcare agencies (“how”)
4	Ensure adequate risk enrichment during the recruitment (“how”)
CHR-P service user characteristics	
5	Define CHR-P through established psychometric instruments (not in general population) (“how”)
6	Implement a transitional and transdiagnostic service across adolescents and young adults (“when”)
Interventions	
7	Offer needs-based interventions and psychological interventions (“how”)
8	Titrate the intervention according to the characteristics and risk profile* as well as the values and preferences of the individuals (“how”)
Outcomes	
9	Collect information and target recovery, physical health outcomes, service users’ satisfaction, functioning and quality of life (“how”)
10	Extend clinical monitoring for outcomes for at least three years (“how”)

Annex 20. PRISMA statement and checklist

Section/topic	#	Checklist item
TITLE		
Title	1	Identify the report as a systematic review, meta-analysis, or both.
ABSTRACT		
Structured summary	2	Provide a structured summary including. as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of what is already known.
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).
METHODS		
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.
Eligibility criteria	6	Specify study characteristics (e.g., PICOS length of follow-up) and report characteristics (e.g., years considered. language. publication status) used as criteria for eligibility, giving rationale.
Information sources	7	Describe all information sources (e.g., databases with dates of coverage. contact with study authors to identify additional studies) in the search and date last searched.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.
Study selection	9	State the process for selecting studies (i.e. screening. eligibility. included in systematic review, and, if applicable, included in the meta-analysis).
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms. independently. in duplicate) and any processes for obtaining and confirming data from investigators.
Data items	11	List and define all variables for which data were sought (e.g., PICOS funding sources) and any assumptions and simplifications made.

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.
Summary	13	State the principal summary measures
Risk of bias across studies	15	Specify any assessment of risk of bias (i.e. Newcastle-Ottawa Scale (NOS)). that may affect the cumulative evidence.
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses. meta-regression), if done, indicating which were pre-specified.
RESULTS		
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review with reasons for exclusions at each stage, ideally with a flow diagram.
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size. PICOS follow-up period) and provide the citations.
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).
Results of individual studies	20	For all outcomes considered (benefits or harms), present for each study a summary data for each intervention group
Synthesis of results	21	Present results of study analyzed
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).
DISCUSSION		
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research. reporting bias).
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.
FUNDING		
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data), role of funders for the systematic review.

Annex 21. MOOSE checklist

Criteria	
Reporting of background include	
√	Problem definition
√	Hypothesis statement
√	Description of study outcomes
√	Type of exposure or intervention used
√	Type of study designs used
√	Study population
Reporting of search strategy include	
√	Qualifications of researchers
√	Search strategy, including time period included in the synthesis and keywords
√	Databases and registries searched
√	Use of hand searching
√	List of citations located and those excluded, including justifications
√	Method of addressing articles published in languages other than English
√	Method of handling abstracts and unpublished studies
√	Description of any contact with authors
Reporting of methods include	
√	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested
√	Rationale for the selection and coding of data
√	Assessment of confounding factors
√	Assessment of study quality
√	Assessment of heterogeneity
√	Description of statistical methods in sufficient detail to be replicated
√	Provision of appropriate tables and graphics
Reporting of results should include	
√	Graph summarizing individual study estimates and overall estimate
√	Table giving descriptive information for each study included
√	Results of sensitivity testing
√	Indication of statistical uncertainty of findings

Reporting of discussion include	
√	Quantitative assessment of bias
√	Justification for exclusion
√	Assessment of quality of included studies
Reporting of conclusions include	
√	Consideration of alternative explanations for observed results
√	Generalization of the conclusions
√	Guidelines for future research
√	Disclosure of funding source