Original Investigation | META-ANALYSIS

Prognosis of Brief Psychotic Episodes
A Meta-analysis

Paolo Fusar-Poli, MD, PhD; Marco Cappucciati, MD; Ilaria Bonoldi, MD; L. M. Christy Hui, PhD; Grazia Rutigliano, MD; Daniel R. Stahl, PhD; Stefan Borgwardt, MD, PhD; Pierluigi Politi, MD, PhD; Aaron L. Mishara, PsyD; Stephen M. Lawrie, MD; William T. Carpenter Jr, MD, PhD; Philip K. McGuire, MD, PhD

IMPORTANCE The prognostic significance of competing constructs and operationalizations for brief psychotic episodes (acute and transient psychotic disorder [ATPD], brief psychotic disorder [BPD], brief intermittent psychotic symptoms [BIPS], and brief limited intermittent psychotic symptoms [BLIPS]) is unknown.

OBJECTIVE To provide a meta-analytical prognosis of the risk of psychotic recurrence in patients with remitted first-episode ATPD, BPD, BIPS, and BLIPS and in a benchmark group of patients with remitted first-episode schizophrenia (FES). We hypothesized a differential risk: FES > ATPD > BPD > BIPS > BLIPS.

DATA SOURCES The Web of Knowledge and Scopus databases were searched up to May 18, 2015; the articles identified were reviewed as well as citations of previous publications and results of a manual search of the reference lists of retrieved articles.

STUDY SELECTION We included original articles that reported the risk of psychotic recurrence at follow-up for patients in remission from first-episode ATPD, BPD, BLIPS, BIPS, and FES.

DATA EXTRACTION AND SYNTHESIS Independent extraction by multiple observers. Random-effects meta-analysis was performed, and moderators were tested with meta-regression analyses, Bonferroni corrected. Heterogeneity was assessed with the I^2 index. Sensitivity analyses tested the robustness of the results. Publication bias was assessed with funnel plots and the Egger test.

MAIN OUTCOMES AND MEASURES Proportion of patients with baseline ATPD, BPD, BLIPS, and BIPS who had any psychotic recurrence at 6, 12, 24, and 36 or more months of follow-up.

RESULTS Eighty-two independent studies comprising up to 11 133 patients were included. There was no prognostic difference in risk of psychotic recurrence between ATPD, BPD, BLIPS, and BIPS at any follow-up ($P > .03$). In the long-term analysis, risk of psychotic recurrence (reported as mean [95% CI]) was significantly higher in the FES group (0.78 [0.58-0.93] at 24 months and 0.84 [0.70-0.94] at ≥36 months; $P < .02$ and $P < .001$, respectively) compared with the other 4 groups (0.39 [0.32-0.47] at 24 months and 0.51 [0.41-0.61] at ≥36 months). There were no publication biases. Sex and exposure to antipsychotic medication modulated the meta-analytical estimates ($.002 < P < .03$).

CONCLUSIONS AND RELEVANCE There are no prognostic differences in risk of psychotic recurrence between ATPD, BPD, BLIPS, and BIPS constructs of brief psychotic episodes. Conversely, there is consistent meta-analytical evidence for better long-term prognosis of brief psychotic episodes compared with remitted first-episode schizophrenia. These findings should influence the diagnostic practice and clinical services in the management of early psychosis.

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Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Paolo Fusar-Poli, MD, PhD, Department of Psychosis Studies, Institute of Psychiatry PO63, De Crespigny Park, SE58AF London, England (paolo.fusar-poli@kcl.ac.uk).

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The nomenclature of these acute disorders is as uncertain as their nosological status....Systematic clinical information that would provide definitive guidance on the classification of acute psychotic disorders is not yet available, and the limited data and clinical tradition that must therefore be used instead do not give rise to concepts that can be clearly defined and separated from each other.
World Health Organization[1]

Key Points

Question: What is the prognostic significance of competing operationalizations for brief psychotic episodes?

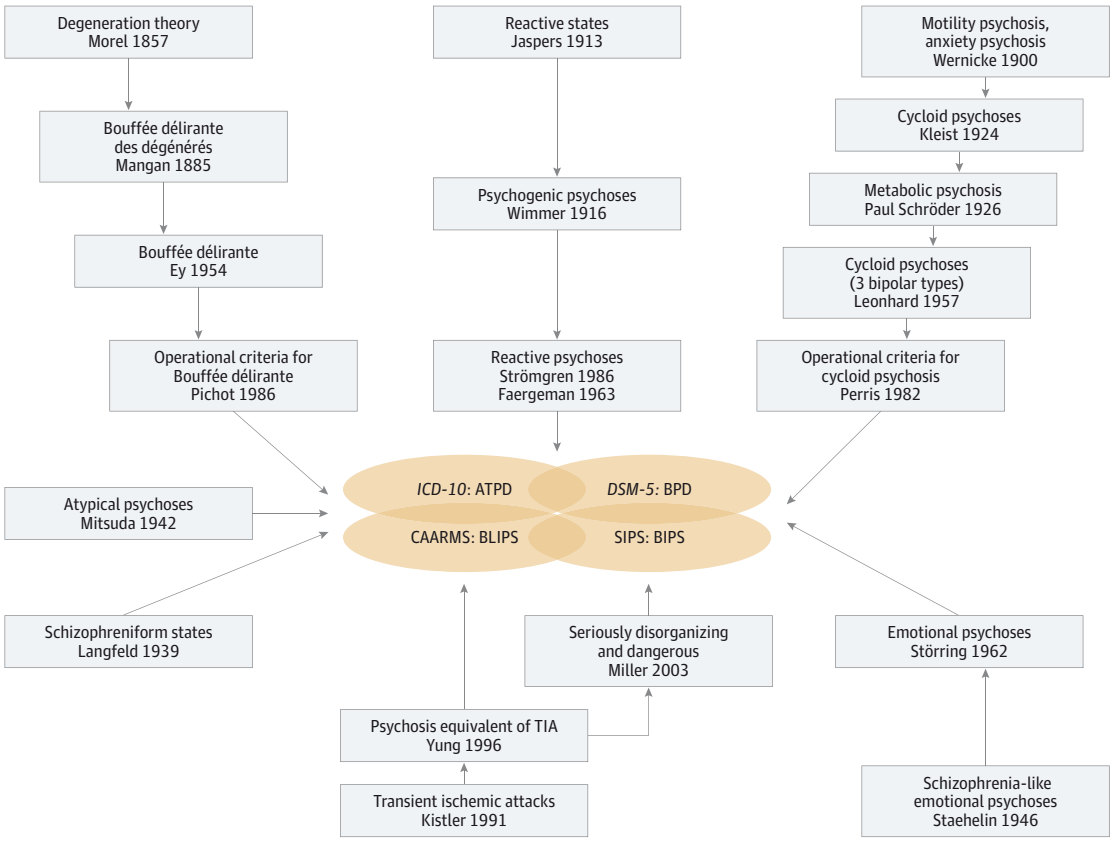
Findings: No prognostic difference was found between different operationalizations of brief psychotic episodes at any follow-up time point. In the long term, risk of psychotic recurrence was significantly higher in remitted first-episode schizophrenia compared with the 4 groups of brief psychotic episodes.

Meaning: Current data may influence the diagnostic practice and clinical services in the management of early psychosis.

As psychotic disorders of "dramatic symptomatology"[2] but remitting course, brief psychotic episodes represent one of the most intriguing paradoxes in psychiatry. In 1863, Kahlbaum first distinguished the typical progressive nature of psychotic forms (*vesania typica*) from a separate group of disorders (*dysphrenia*) that appeared in an acute and severe form but then remitted with a full recovery "without leaving a lasting alteration in the elements that serve its expression."[3(p67)] Kahlbaum's classification did not become popular. Instead, the nosography of Kraepelin dominated psychiatry and shaped today's diagnostic system.[2] Brief psychotic episodes have been difficult to accommodate as a "third psychosis" in the Kraepelinian dichotomy of dementia praecox and manic-depressive insanity.[4] Brief psychotic episodes have been repeatedly reconceptualized and operationalized without finding a widely accepted nosographic cataloguing as *bouffée délirante*,[5] cycloid psychoses,[6] reactive psychoses,[7] emotional psychoses,[8] atypical psychoses,[9] or schizophreniform state[10] (**Figure 1**[5,6,8,10-27]).

The nosographic nomadism of brief psychotic episodes continues today. The World Health Organization has brought the above clinical concepts into the *International Statistical Classification of Diseases, 10th Revision* (*ICD-10*) diagnostic category of acute and transient psychotic disorders (ATPDs), with

Figure 1. Historical Genealogy of Current Competing Diagnostic Constructs for Brief Psychotic Episodes



Information available in multiple publications.[5,6,8,10-27] Adapted from Marneros and Pillmann.[14] ATPD indicates acute and transient psychotic disorder; BIPS, brief intermittent psychotic symptoms; BLIPS, brief limited intermittent psychotic symptom; BPD, brief psychotic disorder; CAARMS, Comprehensive Assessment of At-risk Mental State; *ICD-10*, *International Statistical Classification of Diseases, 10th Revision*; SIPS, Structured Interview for Prodromal Syndromes; TIA, transient ischemic attack.

Table 1. Current Competing Diagnostic Operationalizations for Brief Psychotic Episodes

Characteristic	Brief Psychotic Episodes			
	Clinical High-Risk Classification		Standard Classification	
	BIPS[29]	BLIPS[30]	ATPD[1]	BPD[28]
Symptoms	At least 1 of the SOPS P1-P5 scales is scored 6	At least 1 of the CAARMS P1, P2, or P4 severity scales is scored 6 or P3 is scored ≥5	Delusions, hallucinations, incomprehensible or incoherent speech, or any combination of these	At least 1 of the following symptoms: at least 1 must be (1), (2), or (3): (1) delusions, (2) hallucinations, (3) disorganized speech (eg, frequent derailment or incoherence), (4) grossly disorganized or catatonic behavior
Onset	Symptoms should have reached a psychotic level of intensity in the previous 3 mo	Symptoms should have been present in the previous 12 mo and for not >5 y	Symptoms should have an acute onset, ie, the time interval between the first appearance of any psychotic symptoms and the presentation of the fully developed disorder should not exceed 2 wk	Symptoms should have a sudden onset, ie, a change from a nonpsychotic state to a clearly psychotic state within 2 wk, usually without a prodrome
Duration and frequency	Up to 3 mo, at a frequency of at least several minutes per day at least once per month but <1 h/d for 4 d/wk in the past month	Up to 7 d, at a frequency of at least 3-4 times/wk when lasting at least 1 h or at least a daily presence when lasting <1 h	F23.0: acute polymorphic psychotic disorder without symptoms of schizophrenia: up to 3 mo, for at least several hours F23.1: acute polymorphic psychotic disorder with symptoms of schizophrenia: up to 1 mo, for the majority of time F23.2: acute schizophrenia-like psychotic disorder: up to 1 mo, for the majority of time F23.3: other acute, predominantly delusional psychotic disorder: up to 3 mo, for the majority of time	At least 1 d, up to 1 mo
Level of functioning	No social/occupational dysfunction requirement	30% Drop in SOFAS score from premorbid level, sustained for 1 mo within past 12 mo or SOFAS score <50 for previous 12 mo or longer	No social/occupational dysfunction requirement	No social/occupational dysfunction requirement
Exclusion criteria	Symptoms are seriously disorganizing and dangerous	NA	NA	NA
	Symptoms are strongly intertwined temporally with substance use episodes (substance-induced psychosis may be considered)	Symptoms occur only during peak intoxication from a substance known to be associated with psychotic experiences (eg, hallucinogens, amphetamines, or cocaine)	Evidence of recent psychoactive substance use sufficient to fulfil the criteria of intoxication (F1x.0), harmful use, (F1x.1), dependence (F1x.2), or withdrawal states (F1x.3 and F1x.4); presence of organic brain disease (F0) or serious metabolic disturbances affecting the central nervous system (does not include childbirth): perplexity, misidentification, or impairment of attention and concentration fulfill the criteria for delirium, not induced by alcohol and other psychoactive substances (F05-A)	Symptoms are due to the direct physiologic effects of a substance (eg, drug of abuse, medication) or to a general medical condition
	Symptoms are better accounted for by another *DSM* diagnosis	NA	Symptoms meet diagnostic criteria for manic episode (F30), depressive episode (F32), or recurrent depressive disorder (F33)	Symptoms are better explained by major depressive or bipolar disorder with psychotic features
	Past psychosis ruled in according to information obtained through the initial screening and evaluated using the POPS	Person has had a previous psychotic episode (treated or untreated)	NA	Symptoms are better explained by another psychotic disorder (eg, schizophrenia or catatonia)
	NA	Symptoms do not resolve spontaneously (ie, they resolve with antipsychotic medication)	NA	NA

Abbreviations: ATPD, acute and transient psychotic disorder; BIPS, brief intermittent psychotic symptoms; BLIPS, brief limited intermittent psychotic symptoms; BPD, brief psychotic disorder; CAARMS, Comprehensive Assessment of At-risk Mental State; NA, not applicable; POPS, Presence of Psychotic Symptoms; SOFAS, Social and Occupational Functioning Assessment Scale; SOPS, Scale of Prodromal Symptoms, version 5.

6 subtypes, stating that an ATPD is a short, remitting episode of psychosis that may last up to 3 months.[1] Similarly, in the *DSM-5*, the American Psychiatric Association has introduced the diagnostic category of brief psychotic disorder (BPD), describing brief psychotic episodes with a duration of less than 1 month and with full recovery to the premorbid status.[28] Although ATPD and BPD address similar constructs, major operationalization differences exist in terms of their symptomatic features, symptom duration (3 months in ATPD vs 1 month in BPD), and subtypes (schizophreniform-like disorders are included in ATPD) (**Table 1**). Previous investigations tend to suggest that patients with ATPD and BPD may fare better overall compared with patients with schizophrenia,[31] but the recurrence of subsequent psychotic episodes in ATPD and BPD may be as frequent as in schizophrenia.[32] To our knowledge, we provide here the first meta-analysis of these studies. The current meta-analytical approach is of particular relevance given that operationalization differences may affect their prognostic concordance,[33] and the diagnostic stability of brief psychosis is questionable.[34]

One further complication is that, during the past 2 decades, brief psychotic episodes have been reclassified

into prepsychotic at-risk states,[35] as operationalized with the brief and limited intermittent psychotic symptoms (BLIPS) concept[36]: "young people with a history of fleeting psychotic experiences that spontaneously resolved within 1 week"[11(p8)] without the use of antipsychotics. Such a decision was based on the speculation that BLIPS are the psychosis equivalent of transient ischemic attacks observed in neurology: sudden neurologic abnormalities resembling a full stroke but diminishing within 24 hours, with complete clinical recovery[12] and a limited risk of stroke.[37] A 7-day cutoff period was introduced to define a "clinically meaningful point"[38(p134)] at which time antipsychotic treatment was justified. A few years later, the duration of brief intermittent psychotic symptoms (BIPS) was extended from 7 days to 3 months by other authors (Table 1).[13] In a recent meta-analysis,[39] we demonstrated the prognostic distinction between BLIPS and/or BIPS and the other 2 high-risk subgroups of attenuated psychosis syndrome and genetic risk and deterioration syndrome. Yet, the actual prognostic significance of BLIPS and BIPS and their at-risk state validity as opposed to frank psychosis (as for ATPD and BPD) are unclear.[40] Because of this nonclarity, the presence of the 4 competing diagnostic constructs for brief psychotic episodes (ATPD, BPD, BLIPS, and BIPS) is a major source of "Babylonian confusion,"[41] offering little to guide prognosis or treatment and representing an untenable challenge for patients, caregivers, health care professionals, and researchers. Paradoxically, depending on the local availability of high-risk services, young adults presenting with brief psychotic episode features may receive either a diagnosis of established psychosis (eg, ATPD and/or BPD)[42] and antipsychotic treatment or an at-risk diagnosis (eg, BLIPS and/or BIPS)[43] and recommended psychological interventions.[44] Prognostic uncertainty is also a major source of heterogeneity undermining research and hindering the discovery of reliable biomarkers to be used in the clinic.[45] Although the founders of the clinical high-risk paradigms had recommended that "the prodrome construct should also be compared and contrasted with *DSM-IV* conceptualizations of fully psychotic disorders,"[13(p706)] to our knowledge, this process has never been tested at the meta-analytical level.

To our knowledge, this is the first large-scale meta-analysis primarily testing the differential prognostic significance (predictive validator)[46] of remitted, first-episode ATPD, BPD, BLIPS, and BIPS. We also chose to compare these disorders with remitted first-episode schizophrenia (FES) to provide a clinical benchmark. On the basis of spontaneous remission without antipsychotic treatment (in BLIPS and/or BIPS) and symptom duration (≤7 days for BLIPS, <4 days/week during 3 months for BIPS, ≤1 continuous month for BPD, and ≤3 continuous months for ATPD), our primary hypothesis was that the risk of a subsequent psychotic recurrence progressively increased across these 4 competing constructs (ATPD > BPD > BIPS > BLIPS). The secondary hypothesis was that this risk was higher in the benchmark group of remitted FES.

Methods

Search Strategy

Three investigators (M.C., L.M.C.H., and G.R.) conducted 2-step literature searches. First, the Web of Knowledge database was searched, incorporating both the Web of Science and MEDLINE. The search was extended until May 18, 2015, including only English-language abstracts. Several combinations of the following key words were used: *acute and transient psychotic disorder*, *brief psychotic disorder*, *brief intermittent psychotic symptoms*, *brief limited intermittent psychotic symptoms*, ICD, DSM, *psychosis risk*, *first-episode psychosis*, *first-episode schizophrenia*, *diagnostic stability*, *remissio*n, and *relapse*. We then used Scopus to investigate citations of possible previous reviews or meta-analyses on the development of another episode of psychosis from an initial brief psychotic episode and performed a manual search of the reference lists of retrieved articles. Articles identified through these 2 steps were then screened for the selection criteria on the basis of review of the abstracts. The articles identified with this selection process were assessed for eligibility on the basis of full-text review following the Meta-analysis of Observational Studies in Epidemiology checklist (eTable 1 in the Supplement).[47]

Selection Criteria

Studies were eligible for inclusion if the following criteria were fulfilled: (1) were original studies published in English; (2) included a baseline group of patients with a diagnosis of remitted first-episode brief psychotic episodes as defined according to standard international classification (ATPD and BPD),[1,28] the clinical high-risk paradigm (BLIPS and BIPS),[29,30,48] or a comparison benchmark group of remitted FES[1,28] (with studies included as discussed below); and (3) reported the risk of psychotic recurrence at at least 1 follow-up time (6, 12, 24, or ≥36 months). Per definition, ATPD, BPD, BLIPS, and BIPS are brief and remitting. Patients with BLIPS and/or BIPS have not received antipsychotics or have received minimal treatment. Those with ATPD and/or BPD have a favorable response to antipsychotics[49] and are often (76%[50]) antipsychotic free at follow-up; therefore, maintenance medication is used less often than with schizophrenia.[31] Some clinical guidelines indicate that "the available evidence is not sufficient to support the use of atypical antipsychotics to treat brief psychotic disorder."[51] Accordingly, to minimize the potential confounding effect of illness chronicity and prolonged antipsychotic treatments, FES studies were included if they had investigated patients with remitted first episodes (as defined in eTable 2A in the Supplement). When data were not directly presented, they were indirectly extracted from associated data or corresponding authors were contacted to retrieve additional data. Exclusion criteria were (1) abstracts, pilot data sets, and articles published in languages other than English; (2) studies that did not use the internationally validated diagnoses for ATPD, BPD, BLIPS, BIPS, and FES; (3) studies with overlapping data sets; (4) clinical high-risk samples belonging to the genetic risk and deterioration syndrome or

attenuated psychosis symptoms subgroups only; (5) FES studies with samples who had not experienced full remission from their first episode; and (6) studies with samples of multi-episode or chronic psychosis. In the case of multiple publications derived from the same study population, we selected articles reporting the largest and most recent data set. The literature search was summarized according to the PRISMA guidelines.[52]

Recorded Variables

Data extraction was independently performed by 2 investigators (M.C. and G.R.). To estimate the primary outcome variable, we extracted the baseline sample size and the number of patients with any psychotic recurrence at follow-up. To estimate the secondary outcome, we collected the number of patients who developed schizophrenia or affective psychoses at follow-up. We collected additional moderators as indicated in the Statistical Analysis section and performed quality assessment as detailed in eMethods in the Supplement.

Statistical Analysis

The outcome measure was the risk of psychotic recurrence in patients who experienced remission from their first episode of ATPD, BPD, BLIPS, or BIPS (primary outcome) and FES (secondary outcome). This risk was calculated as the proportion of baseline patients who had any psychotic recurrence at 6, 12, 24, or 36 or more months follow-up. Meta-analysis was conducted with the metaprop package[53] of Stata, version 13.1. This package is specifically developed for pooling proportions in a meta-analysis of multiple studies. The 95% CIs are based on score (Wilson).[54] Because proportions were often expected to be small, we used the Freeman-Tukey double arcsine transformation[55] to stabilize the variances and then perform a random-effects meta-analysis implementing the Der Simonian-Laird method.[56] The influence of moderators was tested using subgroup (type of antipsychotic treatment, study design, and remission criteria in FES groups) and meta-regression (publication year, mean age, proportion of females, exposure to antipsychotics from baseline to follow-up, diagnostic criteria used to assess the psychotic episodes at follow-up, and quality assessment) analyses. The slope of the meta-regression line (β coefficient: direct [+] or inverse [−]) indicates the strength of an association between moderator and outcome. The meta-regressions were Bonferroni corrected for multiple testing. Between-study heterogeneity was assessed using Q statistics with the proportion of the total variability in the effect size estimates being evaluated with the I^2 index,[57] which does not depend on the number of studies included. Because meta-analysis of observational studies is supposed to be characterized by significant heterogeneity, random-effect models were used. In addition, sensitivity analyses were conducted to investigate the influence of each study on the overall risk estimate by omitting one study at a time using Stata's user-written function (metaninf).[58] A study was considered to be influential if the pooled mean estimate without it was not within the 95% CIs of the overall mean. Publication bias was assessed with the metafunnel function of Stata, which produced funnel plots for assessing small-study reporting bias in meta-analyses,[59] and with the Egger test[60] using the metabias[61] function of Stata. Supplementary analyses are detailed in eMethods in the Supplement.

Results

Database

The literature search (**Figure 2**) identified 82 independent articles, with some contributing more than 1 sample. We identified a total of 93 independent samples: 27 ATPD, 22 BPD, 13 BLIPS, 10 BIPS, and 21 FES. The numbers of patients at baseline and at each follow-up time point are reported in **Table 2**. Age, sex, diagnostic instrument used to assign the baseline and follow-up diagnoses, duration of follow-up, and exposure to antipsychotics for each included sample are detailed in eTable 2a and eTable 2b, and the list of excluded articles is detailed in eTable 3 in the Supplement.

Meta-analytical Prognosis of Brief Psychotic Episodes

The 93 independent samples reported primary outcome data at different follow-up time points (Table 2). Across all time points, no significant differences were found in the risk of psychotic recurrence between ATPD, BPD, BLIPS, and BIPS (**Figure 3** and Table 2), with all $P > .03$ (Table 2).

Comparison With Remitted Schizophrenia

We found a significantly higher risk of psychotic recurrence in the FES group compared with the other 4 groups at 24 ($P < .02$) and 36 or more ($P < .001$) months (Figure 3 and Table 2). Subgroup analyses (eFigure 1A-C in the Supplement) identified a modulating effect of antipsychotic treatment in the short term (ie, 6 and 12 months) but found no effect for remission criteria and study design.

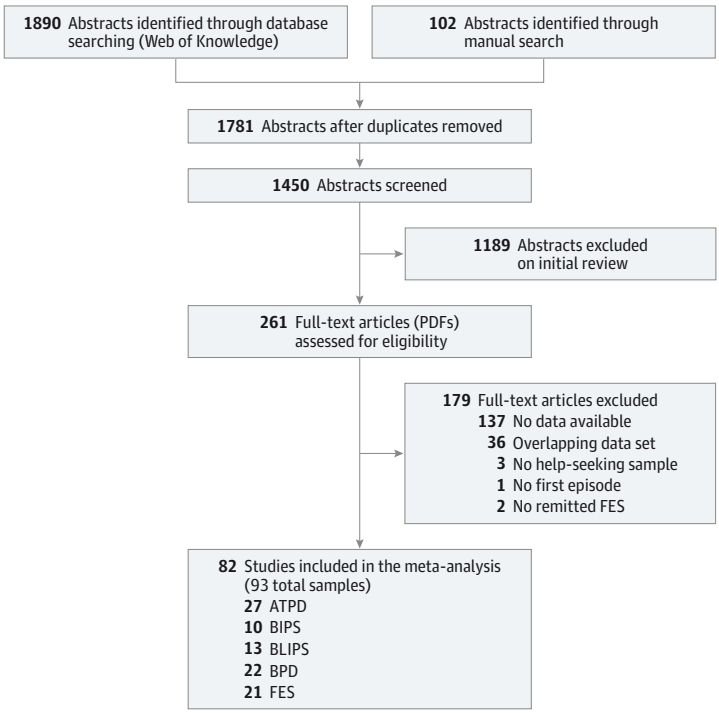
Meta-regression, Publication Bias, and Sensitivity Analysis

Meta-regressions investigating year of publication, mean age, proportion of females, exposure to antipsychotics from baseline to follow-up, diagnostic criteria used to assess the brief psychotic episode at follow-up, and quality assessment are reported in eTable 4 in the Supplement. At an uncorrected threshold for multiple comparisons, there was a significant effect for sex (12 [$P = .03$] and 24 [$P = .02$] months) and antipsychotic exposure (6 [$P = .02$], 12 [$P = .002$], and 24 [$P = .004$] months). Sensitivity analyses (eResults in the Supplement) confirmed the robustness of the findings. There was no evidence of publication bias as indicated by visual inspection of the funnel plots (eFigure 2A-C in the Supplement) and by the Egger test for small-study effects ($P > .05$ at all time points).

Supplementary Analyses

No meta-analytical differences in the risk of developing schizophrenia at 24 months were observed between the ATPD, BPD, BLIPS, and BIPS groups (eFigure 3A and B in the Supplement). No meta-analytical differences in the risk of developing affective psychoses were detected between the ATPD, BPD, BLIPS, BIPS, and FES groups (eFigure 4 in the Supplement).

Figure 2. PRISMA Flow Diagram



ATPD indicates acute and transient psychotic disorder; BIPS, brief intermittent psychotic symptoms; BLIPS, brief limited intermittent psychotic symptom; BPD, brief psychotic disorder; and FES, remitted first-episode schizophrenia.

Table 2. Prognostic Meta-analysis of Brief Psychotic Episodes and Remitted FES

Characteristic	Follow-up, mo			
	6	12	24	≥36
No. of samples	25	46	35	42
No. of patients analyzed[a]	1311	1883	1669	11 133
Risk of psychotic recurrence, mean (95% CI)[b]				
BLIPS	0.08 (0.00-0.23)	0.28 (0.08-0.52)	0.32 (0.11-0.57)	0.30 (0.12-0.52)
BIPS	0.22 (0.09-0.36)	0.35 (0.23-0.48)	0.43 (0.26-0.61)	0.46 (0.32-0.61)
ATPD	0.13 (0.09-0.18)	0.30 (0.19-0.42)	0.38 (0.27-0.48)	0.54 (0.41-0.66)
BPD	0.20 (0.08-0.36)	0.31 (0.12-0.52)	0.46 (0.31-0.60)	0.53 (0.34-0.72)
FES	0.30 (0.15-0.48)	0.42 (0.30-0.54)	0.78 (0.58-0.93)	0.84 (0.70-0.94)
BLIPS vs BIPS vs ATPD vs BPD test for between-group heterogeneity (*Q*)	4.71	0.90	1.20	3.65
P value	.19	.83	.75	.30
BLIPS vs BIPSvs ATPD vs BPD vs FES test for between-group heterogeneity (*Q*)	7.63	2.36	11.97	16.97
P value	.11	.67	.02	<.001

Abbreviations: ATPD, acute and transient psychotic disorder; BIPS, brief intermittent psychotic symptoms; BLIPS, brief limited intermittent psychotic symptoms; BPD, brief psychotic disorder; FES, remitted first-episode schizophrenia.

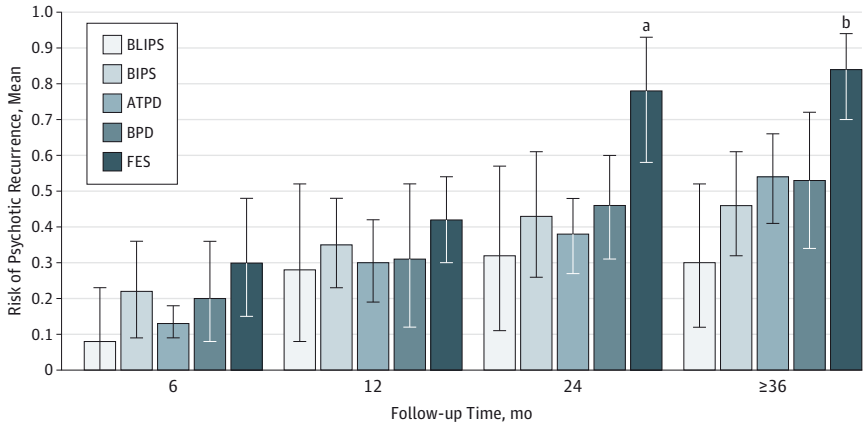
[a] The number of patients in each ATPD, BPD, BLIPS, BIPS group depends on the follow-up time. At baseline, the numbers were BLIPS, 168; BIPS, 125; BPD, 308; ATPD, 10 645; and FES, 1250. The index episode is defined at the remission of the first episode of BLIPS, BIPS, ATPD, BPD, and FES. Details on the definition of the index episode are appended in eDiscussion 4 in the Supplement.

[b] The overall risk of psychotic recurrence across BLIPS, BIPS, ATPD, and BPD combined: 6 months, 0.12 (95% CI, 0.07-0.17); 12 months, 0.30 (95% CI, 0.22-0.39); 24 months, 0.39 (95% CI, 0.32-0.47); and 36 or more months, 0.51 (95% CI, 0.41-0.61).

Discussion

Although short, the intensity and polymorphism of brief psychotic episodes present a clinical challenge. To address this challenge, we report what we believe to be the first meta-analytical review of prognosis from a large data set comprising 82 studies with up to 11 133 patients with remitted first-episode ATPD, BPD, BLIPS, and BIPS compared with those in FES remission. Contrary to our primary hypothesis, there was no prognostic difference between patients with ATPD, BPD, BLIPS, or BIPS at all time points. In line with our secondary hy-

Figure 3. Meta-analytical Prognosis of Brief Psychotic Episodes During Follow-up Time



ATPD indicates acute and transient psychotic disorder; BIPS, brief intermittent psychotic symptoms; BLIPS, brief limited intermittent psychotic symptoms; BPD, brief psychotic disorder; and FES, remitted first-episode schizophrenia.

[a] $P < .05$ compared with BLIPS, BIPS, ATPD, and BPD.

[b] $P < .001$ compared with BLIPS, BIPS, ATPD, and BPD.

pothesis, the risk of psychotic recurrence in the long term (24 and ≥36 months) was significantly higher in the FES group compared with the other 4 groups.

This novel study has provided combined, robust meta-analytical evidence from 11 133 patients with first-episode, brief psychotic episodes in contrast to single studies, in which the sample size of brief psychotic episodes is relatively small. Our primary findings of no meta-analytical prognostic differences in the risk of psychotic recurrence between ATPD and BPD are in line with original data indicating good concordance between the 2 constructs, further supporting the claim that there is no "clinical, practical, theoretical reason to separate them.[14(p15)] An earlier study[33] in 42 patients with ATPD found that 62% also fulfilled the BPD criteria. A follow-up study[62] in 343 patients with their first psychiatric hospitalization showed that the diagnoses were ATPD in 29% and BPD in 25%, for an overall κ score of 0.71. Other studies conducted in 500 patients[63] and 403 patients[64] with a first brief psychotic episode confirmed similar 2-year[63] and 10-year[64] prospective consistency across ATPD and BPD. Despite this consistency, some notable differences between *DSM-5* and *ICD-10* remain (Table 1). For example, schizophreniform features are coded within the ATPD (subtype acute schizophrenia-like psychotic disorder), although they are coded as an independent schizophreniform disorder in the *DSM-5*. Some of these controversies will be addressed by the diagnostic revision planned in the next *ICD* manual (*ICD-11*),[34] in which only the subtype polymorphic psychotic disorder without symptoms of schizophrenia (F23.0) will be retained as ATPD (eDiscussion 1 in the Supplement).

The absence of a meta-analytical prognostic difference between BLIPS and BIPS calls into question the strict 7-day duration of BLIPS. The psychosis threshold is higher in the BIPS than in the BLIPS construct (psychotic symptoms may last for >7 days to 3 months); at the same time, the psychosis threshold is lower in the BIPS than in the BLIPS since the BIPS symptoms should not have urgency features[65] ("urgency is any positive psychotic symptom that is seriously disorganizing or dangerous no matter what the duration"[29(p15)]). These 2 differences may counterbalance each other and hence explain their comparable risks of psychotic recurrence over time, further suggesting a need for some psychometric standardization across the 2 competing definitions.[66]

In addition, our meta-analysis suggests that BLIPS and BIPS are prognostically overlapping with ATPD and BPD (Table 2), which challenges both the validity of BLIPS and BIPS as high-risk states for psychosis onset and the arbitrary use[67] of psychosis severity thresholds in this field to discriminate between high-risk states and frank psychotic disorders.[65] The overlap is confirmed by our supplementary analysis showing a similar risk of brief psychotic episodes developing into schizophrenia in BLIPS and BIPS (21%) and in ATPD and BPD (15%) by 24 months (eFigure 3B in the Supplement). The speed of progression to psychotic recurrence is also similar, with a mean time to diagnosis of less than 2 years for both BLIPS and BIPS[68] and ATPD.[69] Although the founders of the BIPS concept acknowledged that "patients whose fully psychotic experience is of sufficient short duration to meet *DSM* criteria for brief psychotic disorder could potentially meet prodromal criteria,"[13(p707)] our meta-analysis is the first convincing evidence supporting this notion. Our prognostic overlap is further corroborated by converging evidence indicating that BLIPS and BIPS present distinctive diagnostic,[40] psychopathological,[35] prognostic,[39] and therapeutic needs[70] when compared with the other high-risk groups.[39] The level of risk of BLIPS and BIPS is comparable to that of ATPD and BPD (current finding) and significantly higher than that of attenuated psychosis symptoms and genetic risk and deterioration syndrome.[39] Therefore, the mixture of BLIPS and BIPS and attenuated psychotic symptoms seems unjustified as a homogeneous group expressing a unitary level of risk for psychosis onset. In addition, because indicated prevention strategies[71,72] target people at high risk who do not meet the diagnostic criteria for a disorder[73] (ie, with attenuated psychosis symptoms), it is problematic that BLIPS and BIPS fall outside this framework qualifying as prevention of psychotic recurrence[73] (eDiscussion 2 in the Supplement).

One possible option would be to drop BLIPS and BIPS from the clinical high-risk rubric. This deletion would mirror the approach of excluding BLIPS and BIPS in the recent *DSM-5* cat-

egory of attenuated psychosis syndrome.[74] However, adopting only the attenuated psychosis symptoms subgroup would prevent research in individuals with BLIPS and BIPS, who have a particularly high risk of psychosis. Furthermore, exclusion of the BLIPS and BIPS may cause a further significant drop in transition risks.[75] Innovative strategies combining homogeneous high-risk samples with attenuated psychotic symptoms only and neurodevelopmental deficits may yield a clinically significant risk enrichment (3-year risk of psychosis of 28%).[76] A more complex option would be to accept the notion that BLIPS and BIPS represent a distinct and separate group at higher risk of psychotic recurrence than the attenuated psychotic group[39] that prognostically overlaps with ATPD and BPD, in the hope of harmonizing the 4 competing constructs. This overlap would better fit the notion of different levels of risk purported by the clinical staging model.[77] However, it would also require redefining the psychotic threshold to be used in this clinical staging model. For instance, a duration of psychotic symptoms from 1 day to 1 month could be used to demarcate brief psychotic episodes from attenuated psychotic symptoms and from persisting psychotic disorders. Compromising on the 1-month duration for brief psychotic disorders would also align BLIPS and BIPS with ATPD in *ICD-11* and BPD in *DSM-5*. Such a cross-diagnostic approach would fit with the *DSM-5*—which uses the level, number, and duration of psychotic signs and symptoms to demarcate psychotic disorders from each other[78]—together with the new Clinician-Rated Dimensions of Psychosis Symptom Severity[79] scale. ATPD and BPD frequently represent up to 6% of all first-episode psychoses,[64] with an incidence of approximately 4 per 100 000 per year.[69] Therefore, a conceptual model encompassing 2 distinct clinical stages of attenuated psychotic symptoms and brief psychotic episodes may significantly increase the clinical ability to predict later development of persisting (ie, lasting more than 1 month) psychotic disorders. Indeed, early accounts have suggested that diagnostic instability and reported that change in ATPD and BPD is evident in approximately half of the patients.[69] Given the lack of data to guide evidence-based treatment recommendations and clinical management of BPDs, the combined model may also facilitate future research and the development of tailored guidelines to prevent persisting psychotic disorders.

To provide a clinical benchmark, we used a comparison group of patients with remitted FES as a secondary outcome. We showed that brief psychotic episodes have a better long-term outcome than remitted FES after 24 months. The lower risk of psychotic recurrence was remarkable at 36 or more months, when most patients with FES who had previous remission had developed another psychotic episode compared with only half of those with an initial brief psychotic episode (defined as ATPD, BPD, BLIPS, and BIPS). Supplementary analyses showing no significant differences at 6 and 12 months may suggest a possible protective effect of antipsychotic medications on psychotic recurrence (eFigure 1A in the Supplement), although there were no effects for the type of antipsychotic discontinuation (eFigure 1B in the Supplement) or the criteria used to define remission (eFigure 1C in the Supplement). Nevertheless, these findings should be interpreted cautiously because this study was not primarily designed to test the effect of antipsychotic treatment on prevention of psychotic recurrence.[80-82] Overall, the reduced risk of psychotic recurrence among brief psychotic episodes is in line with earlier claims (in 1997[83]) and later findings indicating an overall more favorable outcome in the domains of social disability, psychological impairment, and general functioning[84] compared with patients in the schizophrenia spectrum. Because our findings are robust and not affected by publication bias, they may serve as reliable predictive validators[46] for the delineation of brief psychotic episodes from remitted first-episode schizophrenia (eDiscussion 3 in the Supplement). Data from this study could also be useful for future designation of early intervention programs and for the development of specific treatment guidelines or clinical services addressing the specific needs of these patients. For example, our risk estimates at different time points are clinically useful, allowing health care professionals to inform patients and caregivers about the likely risks at a particular time after their index episode (eDiscussion 4 in the Supplement).

There are some limitations to this study. Evidence of absence is not absence of evidence.[85] However, our meta-analysis included a large data set with up to 11 133 patients when some statistically significant findings were obtained. Furthermore, we did not investigate outcomes other than psychotic recurrence. There is some evidence that a substantial proportion of patients with ATPD may show nonpsychotic affective episodes during follow-up.[84] In addition, we did not include affective psychoses as an additional comparison group. For example, the association between brief psychotic episodes and bipolar affective disorders has been questioned.[86] However, pilot literature searches did not uncover enough data for a quantitative meta-analysis of the 2 points above. Finally, the actual proportion of baseline diagnostic overlap between BLIPS and BIPS versus ATPD and BPD remains unknown.

Conclusions

We found meta-analytical evidence for a better long-term prognosis of brief psychotic episodes compared with remitted first-episode schizophrenia but no prognostic differences between ATPD, BPD, BLIPS, and BIPS. Achieving diagnostic consensus across competing diagnostic constructs will greatly assist future attempts to identify the most effective ways to prevent psychotic recurrence after initial brief psychotic episodes.

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Author Affiliations: Department of Psychosis Studies, King's College London, Institute of Psychiatry, London, England (Fusar-Poli, Cappucciati, Bonoldi, Rutigliano, McGuire); OASIS Service, South London and the Maudsley National Health Service Foundation Trust, London, England

(Fusar-Poli); Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy (Fusar-Poli, Cappucciati, Bonoldi, Politi); Department of Psychiatry, University of Hong Kong, Hong Kong SAR, China (Hui); Department of Biostatistics, King's College London, Institute of Psychiatry, London, England (Stahl); Department of Psychiatry, University of Basel Psychiatric Clinics, Basel, Switzerland (Borgwardt); Department of Clinical Psychology, Chicago School of Professional Psychology, Southern California Campus, Los Angeles, California (Mishara); Division of Psychiatry, University of Edinburgh, Edinburgh, Scotland (Lawrie); Maryland Psychiatric Research Center, University of Maryland School of Medicine, Baltimore (Carpenter); Veterans Affairs Capitol Health Care Network, Mental Illness Research, Education, and Clinical Center, Veterans Integrated Service Network, Baltimore, Maryland (Carpenter).

Author Contributions: Dr Fusar-Poli had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Fusar-Poli, Cappucciati, Politi, Mishara, Carpenter, McGuire.
Acquisition, analysis, or interpretation of data: Fusar-Poli, Cappucciati, Bonoldi, Hui, Rutigliano, Stahl, Borgwardt, Lawrie, Carpenter, McGuire.
Drafting of the manuscript: Fusar-Poli, Cappucciati.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Fusar-Poli, Cappucciati, Stahl.
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Study supervision: Fusar-Poli, Borgwardt, Politi, Lawrie, McGuire.

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