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Dear Professor Frangou,

RE: "Diagnostic validity of ICD-10 Acute transient psychotic disorders and DSM-5 Brief psychotic disorder"

We respectfully submit the above paper for publication in European Psychiatry. It is this the first systematic review (100 + papers) that addresses the validity of short-lived psychotic disorders as currently classified under the heading of ICD-10 Acute transient psychotic disorders and DSM-5 Brief psychotic disorder.
The findings of our study enhance the understanding of these diagnostic categories, and offer an opportunity to reconsider how they have been differentiated from schizophrenia and related disorders, building a strong case for their revision in future psychiatric classifications.
This paper has not yet been submitted to any other journal.
No conflict of interest.

Looking forward to hearing from you.

Yours sincerely,

Augusto C. Castagnini MD, DPhil, PhD (Cantab)

# Diagnostic validity of ICD-10 Acute and transient psychotic disorders and DSM-5 Brief psychotic disorder

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**Abstract**

**Background**: Short-lived psychotic disorders are currently classified under "acute and transient psychotic disorders" (ATPDs) in ICD-10, and "brief psychotic disorder" (BPD) in DSM-5. The aim of this study is to review the existing literature and address the validity of ATPDs and BPD.

**Method**: Systematic review of all papers identified through searches in Web of Science and published between January 1993 and December 2016. Reference lists in the located papers provided further sources.

**Results**: A total of 295 articles were found and 100 were selected for inclusion in the review. There were only few studies about the epidemiology, vulnerability factors, neurobiological correlates and treatment of these disorders, particularly BPD was seldom a specific topic of investigation. The available evidence suggests that short-lived psychotic disorders are rare conditions and more often affect women in early to middle adulthood. They are also neither associated with premorbid dysfunctions nor characteristic family predisposition, while there seems to be greater contribution of environmental factors particularly in low- and middle-income countries, and migrant populations. Follow-up studies report a favourable clinical and functional outcome, but case identification has proved difficult owing to high rates of transition mainly either to schizophrenia or, to a lesser extent, affective disorders over the short and longer terms.

**Conclusions**: Although these findings argue against the validity of the above diagnostic categories, it is important that they are kept apart from longer-lasting psychotic disorders both for clinical practice and research. Close overlap between ATPDs and BPD could enhance the understanding of these conditions.

**Key words**: acute transient psychosis, brief psychotic disorder, classification, diagnosis, nosology.

## 1. Introduction

Although the late 19th century Kraepelinian [1] dichotomy of *dementia praecox*, subsequently renamed schizophrenia, and manic-depressive insanity remains central to current psychiatric nosography, its inability to encompass all types of psychosis has made for great unclarity in classification of intermediate categories with adverse effects on psychiatric practice and research, particularly for short-lived psychotic disorders that do not display prominent affective features [2]. Framed in the wake of the WHO study on acute psychoses [3], the category of "acute and transient psychotic disorders" (ATPDs) was introduced in the ICD-10 Classification of Mental and Behavioural Disorders (ICD-10) within the group of "schizophrenia, schizotypal and delusional disorders" [4]. ATPDs were characterized by: acute onset within 2 weeks; polymorphic, schizophrenic or predominantly delusional syndromes; and association with stressful events (Table 1). Acute polymorphic psychotic disorder (APPD) refers to earlier diagnostic concepts such as *bouffée délirante* and cycloid psychosis [5–7], featuring varied delusions, hallucinations, perceptual changes, perplexity and emotional turmoil shifting daily or even faster, and can include schizophrenic symptoms. Complete remission within 1 or 3 months sets the ATPD subtypes with schizophrenic symptoms apart from schizophrenia, as the ICD-10 diagnosis of schizophrenia requires at least 1 month's duration, and the subtypes with polymorphic or delusional features from persistent delusional disorder, which lasts longer than 3 months.

The Diagnostic and Statistical Manual of Mental Disorders (DSM) has, since its fourth edition [8], listed "brief psychotic disorder" (BPD); diagnostic criteria have remained unchanged in DSM-5 including sudden onset of florid psychotic symptoms such as delusions, hallucinations, disorganised speech, and grossly disorganised or catatonic behaviour lasting less than 1 month [9]. It is also possible to specify if BPD follows marked stressors or arises in the post-partum period. Although ATPDs and BPD bear some similarity, comparative studies revealed that the two categories overlap only in part owing to differences in onset, duration and symptomatology [10–15].

It is more than 20 years since ATPDs and BPD have appeared in official psychiatric classifications, but their distinctive features remain uncertain [15,16]. The aim of this paper is to review the literature and address the validity of ATPDs and BPD, then to discuss implications for future classification, clinical practice and research.

## 2. Methods

We conducted a two-step literature search following the guidelines for systematic reviews and meta-analysis provided by the PRISMA statement [17]. Web of Science searches were made using the terms: acute polymorphic psychosis *OR* acute polymorphic psychotic disorder *OR* non-affective acute remitting psychosis *OR* acute transient psychosis *OR* acute transient psychotic disorder) *OR* "acute brief psychosis" *OR* "acute brief psychoses" *OR* "brief psychotic disorder" *OR* "brief psychotic disorders". The search included works in English, French and German, published in peer-reviewed journals between 1 January 1993 and 31 December 2016. Reference lists in the located papers provided further sources. Selection of relevant papers was restricted to studies including at least 10 cases, and diagnosis coded using ICD-10 and DSM-IV/DSM-5 criteria. In addition, follow-up studies required a minimal duration of 12 months, and clearly defined measures of outcome and/or diagnostic stability. Where publications reported overlapping data the most informative or recent were selected.

To assess the validity of ATPDs and BPD, the available evidence was reviewed according to Kendler [18] in 3 main classes of potential validators: a) antecedent validators (i.e. demographic features, family aggregation, premorbid and precipitating factors); b) concurrent validators (biological markers, psychological tests, genetics, symptom measures); and c) prognostic validators (diagnostic stability, course, outcome and response to treatment).

## 3. Results

A total of 295 papers were found, and 100 were selected for inclusion in the systematic review. The PRISMA flow diagram illustrates the number of papers identified, those selected and excluded, and the reasons for exclusion (Figure 1).

### *3.1. Antecedent validators*

#### *3.1.1. Demographic factors of ATPDs*

The annual incidence of ATPDs ranges from 3.9 in the UK to 9.6 in Denmark per 100000 population, and the 2-year and 3-year rates for those with unchanged diagnosis are 6.7 and 1.4 respectively [19–21] (Table 2). ATPDs seem to affect more frequently women or both genders almost equally [21–24], and the mean age of onset is intermediate between schizophrenia and bipolar disorder [21].

Male incidence picks early in the mid-20s, yet the highest rates for women occur ten years later and are greater than those for men over 40 years [21,24].
There are also differences in age and sex distribution across the ATPD subtypes: APPD is more common in women and arises later than both subtypes with acute schizophrenic features, which predominate in young males [25]. No gender difference was found in acute predominantly delusional disorder, which has a later onset than any ATPD subtype [21].
Reports on ATPD prevalence are also varied ranging from 5.8% to 19.0% [19,20,22,23,26], with greater rates often observed in low and middle-income countries, where these conditions are reported to have an earlier age of onset than in high-income ones [27–31].
Further evidence suggests that ATPDs have an increased mortality from both natural and unnatural causes [32,33]. The mortality risk of ATPDs is nearly twice as high in males, and similar to that for schizophrenia, while there seems to be a small but significant higher overall and natural-cause mortality than bipolar disorder. Suicide is the major cause of premature death and accounts for a quarter of excess mortality [33]. Two reports on suicidal behaviour estimated rates of 36% and 55%, with the highest risk during the acute phase characterised typically by rapidly changing and variable delusions ad hallucinations, agitation and mood instability [34,35].
In addition, late-onset ATPDs (over 60 years) are associated with a high risk not only of mortality but also of dementia; in these cases a differential diagnosis from delirium proves often difficult [36].

*3.1.2. Predisposing factors of ATPDs*

Das et al. [37] found that the risk of ATPDs was 3 times higher in first-degree relatives of patients with ATPDs than in family members of schizophrenic patients, while the risk of schizophrenia was significantly increased in the family of patients with schizophrenia. A later study reported that ATPD patients with a family history of mental disorder experienced fewer life events before illness onset than those without family psychiatric antecedents; in keeping with the stress-vulnerability model, family predisposition would produce its effect by increasing emotional reactivity, which renders subjects less likely to cope with adverse events [38].

Jørgensen et al. [39] found that almost two thirds of their cases with ATPDs had an additional diagnosis of personality disorder; this rate dropped one year later probably because personality changes resulted either from psychotic decompensation or psychotropic treatment as most patients recovered and/or discontinued medication.

Marneros et al. [23] observed higher psychiatric morbidity in family members of patients with ATPDs than in relatives of healthy controls, but no significantly raised risk of psychotic disorder. ATPD patients also exhibited lower neuroticism and higher extroversion and conscientiousness than those affected with schizophrenia and/or schizoaffective disorder; in addition, they were more likely to have a better premorbid social functioning than schizophrenic patients [40]. There seems also to be a close relationship between speed of onset and duration of untreated psychosis (DUP), and short DUP would be consistent with diagnosis of ATPDs [41].

Furthermore, a population-based family study [42] revealed that the risk of ATPDs was increased if patients had not only first-degree relatives affected with ATPDs, but also with bipolar disorder, and particularly with schizophrenia; yet the risk of schizophrenia and bipolar disorder was markedly high if patients with schizophrenia and bipolar disorder have family members with the same condition. As regards the ATPD subtypes, the risk of APPD was high in patients having first-degree relatives with either ATPDs or schizophrenia; schizophrenia in family members had the greatest effect on those subtypes featuring schizophrenia-like symptoms; and bipolar disorder did not increase significantly the risk for any ATPD subtype.

*3.1.3. Precipitating factors of ATPDs*

Social and cultural factors are more likely to be associated with ATPDs in low- and middle-income countries [27,38,43,44] than in high-income ones, where only a relatively small number of cases are triggered by life events [10,19,23,45–47]. ATPDs seem also more common in migrant populations [48,49]. Lau et al. [50] reported that the risk of ATPDs in Hong-Kong is two times higher in foreign domestic workers; homesickness and marital problems were the most frequent stressful events. These findings lend support to reports from European countries showing that first- and second-generation immigrants have a greater risk of ATPDs than native populations [51].

Further evidence indicates that stressful events are more often associated with ATPDs than schizophrenia, persistent delusional disorder, schizoaffective disorder or manic disorder [23,44,52–54]. Examination of 1904-1905 Welsh religious revival revealed a significant increase in hospital admissions with brief

polymorphic psychotic symptoms, pointing out that these conditions are part-caused by environmental factors [55].

*3.1.4. Demographic and vulnerability factors for BPD*

No epidemiological study has yet been conducted; available data suggest that BPD is more common in women and accounts for 2.0-7.0% of individuals with a first episode of psychosis [56–60]. The lifetime prevalence of BPD is estimated at 0.05% [61]. It was also found that BPD is not associated with family history of schizophrenia, and more often is triggered by emotional and socio-cultural factors than schizophrenia and/or schizophreniform disorder [62]. Furthermore, patients with BPD exhibit fewer schizoid and schizotypal traits, and enjoy better social and occupational functioning than those with schizophrenia [63].

*3.2. Concurrent validators*

*3.2.1. Symptom measures of ATPDs*

Despite variations in symptom profile, ATPDs are more likely to be characterised by acute onset of fleeting polymorphic features such as delusions and hallucinations, mood changes, anxiety, agitation, insomnia and fewer negative symptoms than schizophrenia, persistent delusional disorder and schizoaffective disorder [23,53,64,65]. Jäger et al. [53] reported that patients with ATPDs have shorter hospital admission and achieved more rapidly functional recovery than those diagnosed with schizophrenia, delusional disorder and/or schizoaffective disorder. Attempts to differentiate schizophrenia from ATPDs on the basis of Schneider's first-rank symptoms (FRS) failed because they occur in both conditions; only negative symptoms seem to be indicative of schizophrenia [53]. There are also diversities in the frequency of ATPD subtypes featuring polymorphic [23,27,64,66], schizophrenic [22,45,47], and predominantly delusional symptoms [19,46].

The field trials of ICD-10 showed that many ATPD subtypes failed to achieve established standards of reliability [67]. More to the point, little evidence supports the division of acute polymorphic psychotic disorder into subtypes "with" or "without" schizophrenic symptoms based on 1 or 3 months' duration, and acute predominantly delusional disorder is a diagnosis by exclusion from polymorphic psychotic disorder, persistent delusional disorder and schizophrenia. In addition, changes between clinical and research diagnosis of ATPDs, the latter made using standardized instruments, suggest little specificity [68].

*3.2.2. Neurobiological factors of ATPDs*

Apart from differences in amplitude of auditory P300 event-related potentials from schizophrenia and healthy controls [69], neither structural nor functional brain changes have been observed in ATPDs. Pepplinkhuizen et al. [70] described a series of metabolic alterations in amino acid pathways by analogy with psychedelic drug induced-psychosis; and Bach et al. [71] reported higher serum levels of bilirubin than in schizophrenia and/or schizoaffective disorder. Rotting et al. [72] examined EEG recordings of ATPD patients, but no significant change was found. More recently, Kanazawa et al. [73] conducted a genome-wide association study of 47 cases with "atypical psychosis", a close variant of ATPDs described in Japan [74], and reported that the putative genes overlap towards those for schizophrenia.

*3.2.3. Symptom measures and cognitive dysfunction of BPD*

Korver-Nieberg et al. [58] observed shorter duration, less emotional distress, fewer negative and disorganized symptoms, higher quality of life and social functioning in BPD than schizophrenia, schizophreniform disorder, schizoaffective disorder and/or unspecified psychosis. Moreover, Lyne et al. [75] found that negative symptoms are rare in BPD, while resulted significantly more frequent in schizophrenia and related disorders.

Although symptoms seem to be less severe in BPD than with in schizophrenia and/or schizophreniform disorder [62], cognitive impairment is common to psychotic patients, but no deficit in attention, memory or executive function was found [63,76]. Yet, BPD patients improved more rapidly, particularly in processing speed, than those with schizophrenia, schizophreniform disorder and/or unspecified psychotic disorder after six months [77].

*3.3. Prognostic validators*

*3.3.1. Diagnostic stability, course and outcome of ATPDs*

The course and outcome of ATPDs have been mapped by about 25 papers with follow-up periods from 1 to 20 years (Table 3). The overall stability of ATPDs was estimated at around 65% on average after 4.5 years [78]. Women are significantly less likely than men to develop another diagnosis [10,19,46,66,78–80]. The risk of relapse based on findings from a large meta-analysis was 13% after 6 months, 30% after 1 year, 38% after 2 years, and 54% after 3 or more years [81]. The greatest diagnostic variability tended to occur in the 24 months following the initial episode mainly either to schizophrenia and related disorders or affective disorders

[24,46]. In addition, there were 30%-60% of patients with ATPDs who enjoyed stable symptomatic remission and/or discontinued medication [10,22,45,82]. They also had better clinical and functional outcomes than patients with schizophrenia, schizoaffective disorders and/or persistent delusional disorder over the short and longer terms [23,65,83].

Besides female gender, good premorbid adjustment, abrupt onset, short DUP and early remission within 4 weeks seem to predict favourable outcome and/or diagnostic stability in ATPDs [19,27,45,54,84], yet the risk of conversion into schizophrenia or schizoaffective disorder seem to be associated with family history of schizophrenia, male gender, age of onset below 35 years, longer hospital admission, and Schneider's FRS [24,45,64,66,80,85,86].

Among the ATPD subtypes, APPD showed a higher diagnostic consistency than those featuring acute schizophrenic or predominantly delusional symptoms, which were more likely to herald schizophrenia and related disorders [25,27,45,47,66,87].

Further evidence suggests that ATPDs in low- and middle-income countries have low rates of recurrence and high temporal stability ranging from 54% to 100% [27,43,88–90]. For example, Sajith et al. [27] reported that nearly three quarters of their series of cases did not develop another diagnosis, and more than half experienced no relapse over three years.

*3.3.2. Diagnostic stability, course and outcome of BPD*

There were 10 studies on course and outcome of BPD with follow-up periods from 15 months to 10 years (Table 4). Over the short term, some surveys found that about two thirds of cases with BPD do not develop another diagnosis and/or remitted rapidly [57,91–93], while others reported far higher transition rates to schizophrenia and related disorders [56,94,95]. The latter findings compare favourable with longer-term follow-up studies showing that many cases with BPD evolved into more severe and persistent affective and/or psychotic disorders [59,60].

Moreover, Pillmann et al. [96] found that patients admitted with BDP experience high rate of relapse but they have significantly better clinical and social outcome than schizophrenic patients. In keeping with meta-analytical findings the overall stability of BPD reached 45% on average within 4.5 years [78], and the risk of recurrence was estimated at 20% after 6 months, 31% after 1 year, 46% after 2 year, 53% after 3 or more years [81].

*3.3.3. Response to treatment of ATPDs*

Khanna et al. [97] compared low and high dose haloperidol in 40 patients with ATPDs, but no significant difference in achieving symptomatic remission was observed over four weeks. Chaudhury et al. [98] reported that risperidone induced fewer extrapyramidal symptoms and proved more effective than haloperidol in reducing both positive and negative symptoms in the early stage of treatment. Agarwal and Sitholey [99] conducted a six-week trial of olanzapine in 23 paediatric patients with ATPDs showing symptom remission and relatively few side effects such as dry mouth, sedation, increased appetite and weight gain.

*3.3.4. Response to treatment of BPD*

Ehlis et al. [100] noted that atypical antipsychotics bring about a positive effect on prefrontal brain functions in cases with BPD using neurophysiological techniques.

## 4. Discussion

To our knowledge, this is the first systematic review that addresses the validity of ICD-10 ATPDs and DSM-5 BPD. It brings about a better understanding of these diagnostic categories and offers an opportunity to reconsider how they have been differentiated from schizophrenia and related disorders, though limited data is available about the epidemiology, vulnerability factors, neurobiological correlates and treatment, particularly BPD has failed to encourage research.

*4.1. Antecedent validity factors*

The existing studies suggests that ATPDs and BPD are rare mental disorders and more often affect women with onset in the early-middle adulthood [19–21,24]. Higher rates have been reported in Scandinavia, in migrant populations and in some developing countries, where these conditions are more often triggered by emotional and socio-cultural factors, owing to the lingering importance of reactive psychosis and to an unwillingness to diagnose schizophrenia in the first episode of psychosis [27,28,38,48–52,101]. Yet cases with schizophrenia show earlier age of onset and are prevalent in males [102].

Similar conditions such as the "non-affective acute remitting psychoses" described by Susser et al. [103] have an uneven geographical distribution with a greater incidence in low- and middle-income countries, mainly in women. These disorders have been frequently observed in the wake of stressful events, fever or systemic infections, and do not conform either to remitting schizophrenia or atypical affective disorders in clinical profile, course and outcome [104–109], but seldom fulfil the diagnostic criteria for both ATPDs and BPD having a modal duration of 2-4 months [110,111].

There also is in ATPDs an increased risk of premature mortality from both natural and unnatural causes, similarly high to that for schizophrenia [33,36].
Further evidence suggests that short-lived psychotic disorders are neither associated with premorbid dysfunctions nor characteristic predisposition [19,23,37,39,40]. Family psychiatric morbidity has a smaller impact on ATPDs than on schizophrenia and bipolar disorder; while ATPDs are likely to have a kinship to schizophrenia [42], at least partly attributable to the fact that this category includes clinical subtypes which are set apart from schizophrenia only by temporal criteria. The relationship between ATPDs and affective disorders remains uncertain [23,42,54].
As regard the clinical subtypes encompassed by ATPDs, APPD is more common in females and occurs later than the subtypes with schizophrenic symptoms [25].

*4.2. Concurrent validity*

It would appear that ATPDs and BPD have the following commonalities: acuteness of onset, variable clinical profile, fewer negative symptoms and shorter duration for episode than schizophrenia and related disorders [23,52,53,62,75,96,111]. However, no convincing evidence of neurobiological correlates - other than changes in amino acids or bilirubin metabolism, auditory P300 amplitude and putative genetic alterations overlapping with those for schizophrenia - fail to support the concurrent validity of these disorders. It has been suggested that acute psychosis in black immigrants would arise from interaction between social adversities and a vitamin D deficit [112].

*4.3. Prognostic validity*

In absence of aetiological factors and biological markers, the validity of diagnostic categories hinges mainly on their predictive power, as it is expected that they prove useful in making predictions of treatment and outcome. Follow-up studies report quite variable patterns of course and outcome for both ATPDs and BPD, pointing out that the risk of recurrence is high with subsequent transitions either to schizophrenia and related disorders or, to a lesser extent, affective disorders [10,19,24,46,56,59,60,78,81,95]. Apart from female gender, the other factors predicting favourable outcome and/or diagnostic stability in ATPDs such as good premorbid adjustment, short DUP and early remission need to be replicated.
A distinctive feature of ATPD patients is the lack of cognitive deterioration and impaired functioning; they fare better than those with schizophrenia, schizoaffective disorder and/or delusional disorder, though a relatively small number enjoyed stable remission and discontinued medication [10,22,45,65,82].

Moreover, APPD has a better course and higher diagnostic stability than the subtypes featuring schizophrenic or predominantly delusional features [25,27,45,66].

There may also be variations in course and outcome of ATPDs between high-income countries and low- and middle-income ones, where these disorders tend to have lower rates of relapse and diagnosis changes, and are more often associated with sociocultural factors [27,43,88–90]. This raises the question of whether environmental factors mediated by emotion-driven pathways not only trigger the onset [38], but also make the outcome of acute psychoses more favourable, yet insidious-onset psychosis would be associated with cognitive impairment, negative symptoms and poor outcome [113,114].

### *4.4. Implications for clinical practice and research*

ATPDs and BPD may cause difficulty in assessment and treatment. First, it is not easy to identify cases in practice because of the lack of distinctive clinical features and too restrictive temporal criteria. Differential diagnosis includes early schizophrenia or affective psychosis, substance-induced psychosis, psychosis due to brain dysfunction or general medical conditions, and simulation psychosis. Secondly, follow-up studies report a tendency to recur and high rates of transition to longer-lasting psychotic and affective disorders. These are probably the reasons why ATPDs and BPD have been often left out from epidemiological surveys of first-episode psychosis, and hence the frequency of those who experience acute onset, florid psychotic symptoms and early remission remains uncertain.

Thirdly, individuals with acute psychosis usually require hospital admission owing to disorganized behaviour, impaired insight, aggressive and/or suicidal acts; in these cases, antipsychotic medication is prescribed not only for acute symptomatology but also for prevention of recurrences [16]. In absence of any evidence and guidance [15,16,115], high-dose or prolonged usage of antipsychotics need to be considered cautiously, as they can induce a number of adverse effects; atypical antipsychotics are also more likely to be associated with increased risk of cardiovascular disease, diabetes and premature mortality [116]. It will be rewarding for future treatment trials to identify the most appropriate therapy for patients with acute psychosis.

Further research is expected to address the relationship of ATPDs, BPD and operational definitions currently used to describe individuals "at high risk" of psychosis such as "brief limited intermittent psychotic symptoms" (BLIPS/BIPS) [117]. Preliminary findings indicate that BLIPS tend to conform more to the ATPD subtypes with schizophrenic features probably because the Schneiderian FRS are common to both conditions and young males were preponderant in the sample

studied [118]. In addition, BLIPS are reported to have the same risk of recurrence as ATPDs and BPD, yet the risk for first-episode schizophrenia is significantly higher over the short and longer terms [81].

### *4.5. Implications for psychiatric classification*

In view of the scepticism aroused by the heterogeneity of ATPD category, the proposed revision for the forthcoming ICD-11 would restrict it to APPD with a duration shorter than 3 months, while the remaining subtypes with schizophrenic and predominantly delusional symptoms would be redistributed into other classes of the newly renamed F2 section "schizophrenia spectrum and other primary psychotic disorders" [119]. These changes would bring the ATPD category closer to non-affective acute remitting psychoses [110], but it seems questionable whether APPD may be itself a reliable diagnosis owing to intrinsic instability (that is, symptoms change in type and intensity daily or even more frequently). Little evidence also support the continuity between APPD and the clinical concepts to which it refers such as *bouffée délirante* and cycloid psychosis [120–123].
A more pragmatic solution, as akin to the DSM category of BPD, would be to select the clinical features that lend themselves to easier assessment and hence offer at least greater diagnostic reliability such as acute onset, florid psychotic symptoms and brief duration [15,110]. Close overlap between ATPDs and BPD might have benefits not only for clinical practice, but also for research, where diagnostic accuracy is essential.

### *4.6. Limitations*

Little data about antecedent, concurrent and predictive factors precluded accurate assessment of BPD validity. Situation is different in ATPDs: while earlier studies were small and probably not powered enough to produce meaningful findings, recently published papers included larger samples, but differences in case ascertainment, age cut-offs, study design, cultural setting, length of follow-ups, and distribution of ATPD subtypes make comparison difficult. Another possible issue affecting concurrent and prognostic validity hinges on the paucity of neurobiological findings, prospective cohort studies, and treatment trials.

## 5. Conclusions

These findings suggest that ATPDs and BPD have clinical and epidemiological which are likely to distinguish them from schizophrenia and related disorders, but the lack of neurobiological correlates, high risk of recurrence and subsequent diagnosis change argue against their validity. Nonetheless, it is desirable that

these categories are revised and kept separate from longer-lasting psychotic disoders both for clinical practice and research.

**Disclosure of interest**

The authors declare that they have no competing interest.

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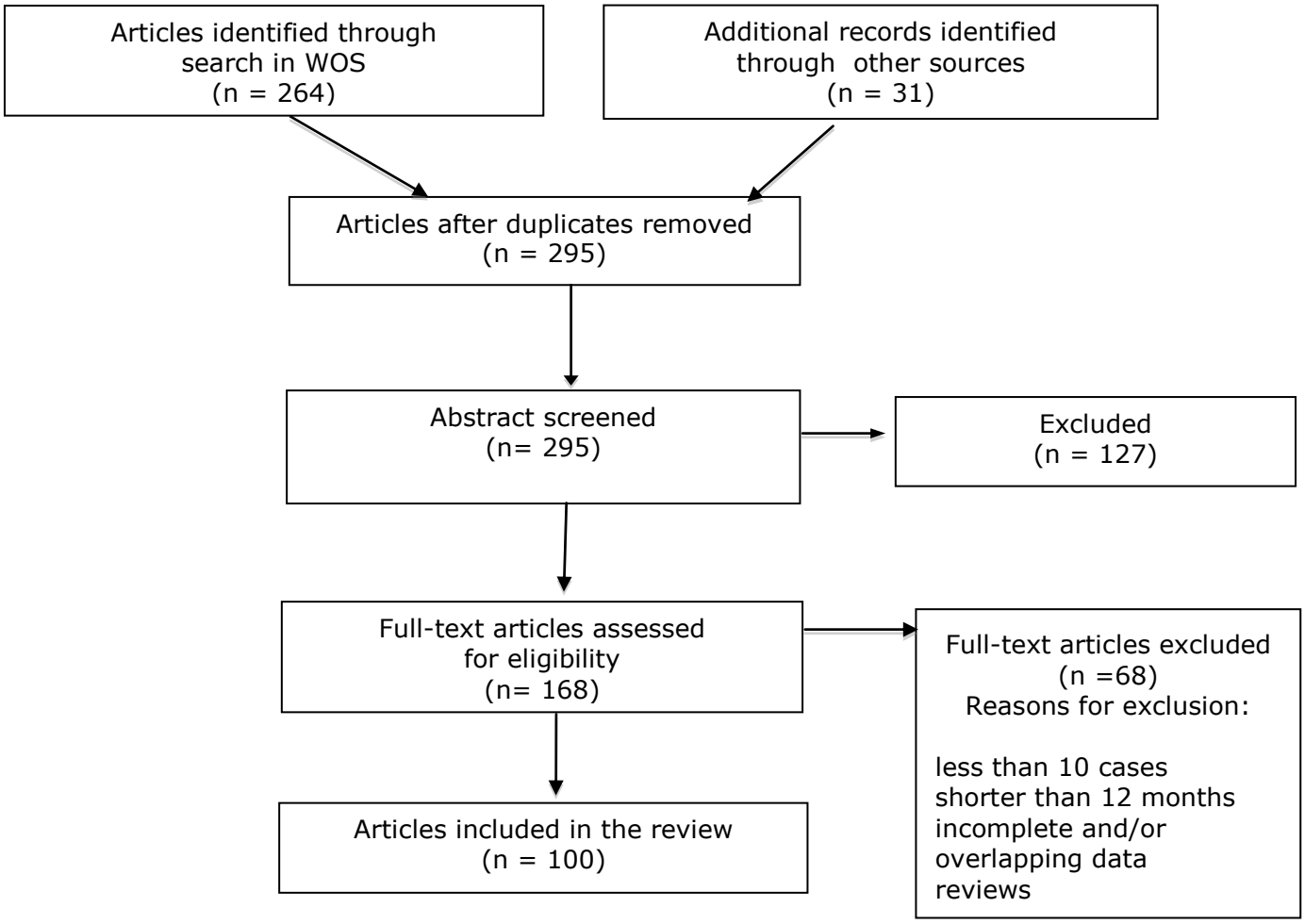
**Figure 1** PRISMA flow diagram showing the number of papers identified, those selected and excluded, and the reason for exclusion



**Table**

Table 1 ICD-10 F23 Acute and transient psychotic disorders (ATPDs) and DSM-5 298.9 Brief psychotic disorder (BPD)

| | ATPDs | BPD |
|---|---|---|
| Symptoms | Polymorphic, schizophrenic and predominantly delusional[≠] | Delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behaviour |
| Onset | Acute onset within 2 weeks* | Not specified |
| Duration | 1 or 3 months | 1 day to less than 1 month with full return to premorbid functioning |
| Specify if with | Acute stress within 2 weeks | Marked stressor or onset within 4 weeks post-partum |
| Exclusion | Substance-induced psychosis, organic disorders, manic and depressive disorder | Affective disorder, substance-induced psychosis, psychosis due to medical conditions, psychotic disorder NOS |

[≠]ATPD category comprises six subtypes: 'acute polymorphic psychotic disorder' (F23.0), which can include schizophrenic symptoms (F23.1); 'acute schizophrenia-like psychotic disorder' (F23.2); 'acute predominantly delusional psychotic disorder' (F23.3); and 'other' and 'unspecified' acute and transient psychotic disorders (F23.8-9).

*Acute onset is defined as a change from a state without psychotic features to a clearly psychotic state within 2 weeks or less. It is also possible to specify "abrupt onset within 48 hours".

**Table 2** Antecedent and concurrent validators for ICD-10 acute and transient psychotic disorders (ATPDs)

| Study | Demographic features |
|---|---|
| Singh et al. [19] | 32/162 cases of FEP had ATPDs (19%); incidence 3.9/100000. After 3 years, this rate dropped to 1.4 with a reversal of sex-rate ratio for women. |
| Castagnini et al. [20] | ATPD incidence 9.6 /100000 over 15 years based on data from DPCR; mean age significantly later in women than men (46.2 vs 37.8 years). |
| Castagnini & Foldager [21] | All in- and out-patients aged 15-64 years enrolled in the DPCR with ATPDs (n = 3350), SZ (n = 4576), and bipolar disorder (n = 3200) in 1995-2008; ATPD incidence 6.7/100000, mean age intermediate between SZ and bipolar disorder, no sex difference. |
| Queirazza et al. [24] | Consecutive admissions (n = 2923) from the Scottish Morbidity Record in 1997-2010. ATPD incidence 4.1/100000, significantly greater in men than women (4.6 vs 3.6); mean age at onset higher in women than men (41.8 vs 33.8 years). |
| Esan & Fawole [30] | First admissions with ATPDs (n = 124) in Nigeria; overall mean age 29.5 years; no sex difference. |
| Mehta et al. [31] | Patients admitted with ATPDs (n = 185) in India; no significant sex difference; mean age 27.0 years; most cases were married, unemployed and/or living in rural areas. |
| Castagnini & Bertelsen [32] | 87/503 (17.3%) patients with ATPDs had died (70% aged over 65 years) over 6-years, accounting for excess morality from both natural (SMR 2.9) and unnatural causes (SMR 9.2). |
| Castagnini et al. [33] | ATPD mortality between 15 and 64 year olds significantly raised from natural (SMR 3.9) and unnatural causes (SMR 7.3); particularly suicide (SMR 14.7). Mortality risk of ATPDs (SMR 4.7) was twice as high in men and similarly high to SZ. |
| Kørner et al. [36] | ATPDs over 60 years associated with a high risk of mortality and dementia. |
| | **Family aggregation and premorbid functioning** |
| Marneros et al. [23] | Family members of ATPD patients (n= 42) had higher psychiatric morbidity than FDRs of healthy controls, but no significantly raised risk of psychotic disorder. |
| Das et al. [37] | Family study comparing ATPDs (n = 40) and SZ (n = 40); ATPD risk was 3 times higher in FDRs of ATPD patients; yet the risk of SZ was lower in the family of ATPD patients than those with SZ. |
| Das et al. [38] | 13/44 (33%) cases with ATPDs were triggered by acute stress, and 11 had a family history of mental disorder; they experienced fewer life events than those without family psychiatric antecedents. |
| Jørgensen et al. [39] | Nearly two-thirds of ATPD patients (n = 51) had a diagnosis of personality disorder; this rate dropped one year later. |
| Pillmann et al. [40] | Comparative study of ATPDs (n= 42), SZ, schizoaffective disorder and healthy controls using the 5-NEO Factor Inventory. No significant difference between ATPD patients and healthy controls; yet those with schizoaffective disorder and SZ had higher neuroticism and lower extroversion and conscientiousness. |
| Castagnini et al. [42] | Genetic epidemiological study of all cases enrolled in the DPCR with ATPDs (n = 2537), SZ (n = 10639), and BD (n = 5292) in 1996-2008; family psychiatric morbidity effects a smaller increase of risk for ATPDs (RR 1.6) than for both SZ and bipolar disorder. |
| | **Precipitating factors/social adversities** |
| Krahl & | ATPDs more frequently diagnosed in southeast Asian migrant workers in Malaysia than |

| | |
|---|---|
| Hashim [48] | native populations. |
| Shaltout et al. [49] | ATPDs were preponderant among young foreign workers in hospital admissions from Qatar. |
| Lau et al. [50] | Foreign domestic workers in Hong-Kong have a risk of ATPDs twice as high as local populations. |
| Alexandre & Ribeiro [51] | ATPDs more common in first- and second-generation black immigrants from African Portuguese speaking countries; most were males and had an earlier illness onset than indigenous population. |
| Linden et al. [55] | Historical report showing significantly increased admission rates for short-lived psychotic disorders linked to 1904-1905 Welsh religious revival. |
| | **Symptom measures** |
| Marneros et al. [23] | Consecutive admissions with ATPDs (n= 42) and control groups with SZ, and schizoaffective disorder. ATPDs featured more often changing and varied delusions, anxiety and mood instability. |
| Pillmann et al. [40] | Comparative study of ATPDs (n = 41) and delusional disorder (n = 43). ATPDs display varied and fleeting symptoms and fared significantly better over a mean follow-up of 10-12 years. |
| Esam & Fawole [52] | Cross-sectional study of hospital admissions with ATPDs (n = 124) and SZ (n = 243) in Nigeria; anxiety and excitement more prevalent in ATPDs. |
| Jäger et al. [53] | Cross-sectional study of patients with SZ (n = 951), ATPDs (n = 116), delusional disorder (n = 51), and schizoaffective disorder (n = 354). ATPDs had fewer negative symptoms, shorter duration and better functioning than SZ. |
| Kampman et al. [68] | Little specificity of ATPD diagnosis probably due to unwillingness to diagnose SZ in the first-episode of psychosis. |
| | **Neurobiological factors** |
| Sahoo et al. [69] | Differences in auditory P300 amplitude from schizophrenia and healthy controls. |
| Pepplinkhuizen et al. [70] | Polymorphic psychotic symptoms associated with metabolic changes in amino acid pathways. |
| Bach et al. [71] | Higher serum levels of bilirubin in ATPD patients than those with SZ and/or schizoaffective disorder. |
| Rotting et al. [72] | No significant difference in EEG recordings between ATPD patients and those with SZ and/or schizoaffective disorder. |
| Kanazawa et al. [73] | Genome-wide association study of 47 cases with atypical psychosis showing that putative genetic alterations overlapped with those for SZ. |

ATPDs: acute and transient psychotic disorders; DPCR: Danish Psychiatric Central Register; SMR: standardized mortality risk; FEP: first-episode psychosis; SZ: schizophrenia.

**Table 3** Prognostic validators for ICD-10 acute and transient psychotic disorders (ATPDs)

| Study | N/F-up | Length | Diagnostic stability, course and outcome |
|---|---|---|---|
| Jørgensen et al. [10] | 51/46 | 1 y | 52% ATPDs (1/3 recurrent course), 17% changed to SZ and/or delusional disorder, 8% affective disorders. |
| Singh et al. [19] | 32 | 3 y | FEP study: 35% ATPDs (2/3 recurrent), 35% SZ or delusional disorder, 19% affective disorders, 9% other. Female gender and good premorbid adjustment predicted diagnostic stability. ATPD mean GAS score >70. |
| Jäger et al. [22] | 94/73 | 3-7 y | ATPDs: 42% single episode, 58% recurrent course, 12% persistent impairment. Negative and/or depressive symptoms associated with unfavourable prognosis. |
| Queirazza et al. [24] | 2923 | 4-7 y | Case-record study; 54% ATPDs; 13% SZ, 12% affective disorders. Age below 30 years, male gender, and longer first admission associated with increased risk and earlier transition to SZ |
| Castagnini & Foldager [25] | 5426 | 9.3 y | Case register study; APPD more common in women, higher stability and lower rates of recurrence than the remaining subtypes with schizophrenic or delusional features. |
| Sajith et al. [27] | 45 | 3 y | Prospective study of APPD; 73% same diagnosis, 22% BD, 4% unspecified psychosis; admission shorter than 1 month, and abrupt onset predicted temporal stability. |
| Okasha et al. [43] | 50 | 1 y | WHO study on acute psychoses (Egyptian cohort); 74% had ATPDs and 54% did not change diagnosis (2/3 full remission, 14% recurrent course); 20% SZ and 26% affective disorders. |
| Aadamsoo et al. [45] | 153/107 | 2 y | Prospective study; 52 (49%) ATPDs (2/3 full remission, GAF score >70; 30% discontinued medication), 50% SZ/schizoaffective disorder. APPD more common in women, later age of onset and fewer changes to SZ. |
| Castagnini et al. [46] | 5426 | 7.3 y | Case register study: ATPD overall stability 45% (62% by 1 year, 56% by 2 years, 48% by 5 years); SZ and related disorder 31%, affective disorders, 13%, other 8%. Women were less likely to develop another diagnosis. |
| Rusaka & Rancans [47] | 294/144 | 5.6 y | Retrospective study: 15% ATPD recurrent course, abrupt onset, polymorphic symptoms and anxiety associated with diagnostic stability. |
| Castagnini et al. [54] | 47 | 1 y | WHO study on acute psychoses (Aarhus cohort); 47/91 ATPDs: 28 (60%) did not change diagnosis, 28% affective disorders, 13% SZ/schizoaffective disorder. Nearly all patients with unchanged diagnosis had full remission. |
| Heslin et al. [60] | 29 | 8 y | FEP study; ATPDs: 4 (17%) retained the same diagnosis, 7 (29%) SZ, 6 (25%) affective disorders, 6 (25%) other. |
| Suda et al. [64] | 25 | 9.7 y | Case-note study; 15 (60%) ATPDs, 40% SZ; ATPD episodic course and longer remission than cases converting to SZ. |
| Salvatore et al. [66] | 55 | 2 y | FEP study; ATPDs: 62% did non change diagnosis; 30% polymorphic psychotic disorders vs 72% schizophrenia-like disorder evolved into longer-lasting affective or psychotic disorders. |
| Remberk et al. [79] | 46 | 8 y | Prospective EOP study; ATPD diagnosis and female gender associated with better clinical and functional outcome than SZ. |

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|---|---|---|---|
| Björkenstam et al. [80] | 868 | 5 y | Swedish case register study; 41% ATPDs, 22% SZ/schizoaffective disorder, 8% BD, 29% other. The risk of conversion into SZ or BD was twice as high for those with family members with SZ or BD. |
| Pillmann & Marneros [82] | 42/39 | 7 y | Prospective study; 54% ATPDs (3/4 recurrent episodes), 30% affective disorders, 18% SZ and schizoaffective disorder. ATPDs: 30% stable remission discontinued medication (GAS score > 80). |
| Möller et al. [83] | 30 | 15 y | First admission psychosis study; ATPDs: 30% single episode, 50% remitting course and 20% chronic course. ATPDs fared better than SZ and delusional disorder. |
| Chang et al. [84] | 17 | 5 y | FEP study: 35% ATPDs, 35% SZ, 12% schizoaffective disorder and 18% BD. |
| Rusaka & Rancans [85] | 102/41 | 2.2 y | Prospective study: 20% ATPD recurrent course; thought disorder predicted transition to SZ. |
| Poon & Leung [86] | 87 | 20 y | Case-note study of first admissions in Hong Kong; one third unchanged diagnosis; diagnostic changes associated with young age, family psychiatric morbidity and high rates of recurrence. |
| Abe et al. [87] | 16 | 12 y | Retrospective study; 10 (63%) ATPDs (2/3 recurrent course), 30% SZ and personality disorder. |
| Amini et al. [88] | 10 | 1 y | ATPD diagnosis remained unchanged, only one case relapsed. |
| Thangadurai et al. [89] | 87 | 13 m | Case-note study: 64% ATPDs, 11% recurrent course; 26% SZ, 9% affective disorders. |
| Narayanaswamy et al. [90] | 57/43 | 2 y | Retrospective study: 63% ATPDs (50% recurrent course); 21% BD, 16% SZ or unspecified psychosis. |
| | | | **Response to treatment** |
| Khanna et al. [97] | 40 | 4 wk | Clinical trial comparing low (5mg) and high (20 mg) dose haloperidol; no significant difference in achieving symptomatic remission. |
| Chauhdury et al. [98] | 30 | 4 wk | Randomized trial comparing haloperidol and risperidone; the latter proved more effective in reducing both positive and negative symptoms in the early phase of treatment. |
| Agarwal & Sitholey [99] | 23 | 6 wk | Open trial of olanzapine in patients aged 6-16 years showing symptomatic improvement and relatively few side effects. |

APPD: acute polymorphic psychotic disorder without schizophrenic symptoms; BD: bipolar disorder; EOP: early onset psychosis; FEP: first episode psychosis; GAF/S: Global Assessment of Functioning/scale; SZ: schizophrenia.

**Table 4** Antecedent, concurrent and predictive validators for DSM-5 Brief psychotic disorder

| Study | Vulnerability factors |
|---|---|
| Ngoma et al. [62] | BPD is not associated with family history of SZ and more often triggered by emotional and socio-cultural factors than SZ and/or SFD. |
| Lee et al. [63] | BPD exhibits fewer schizoid and schizotypal traits, and better social and occupational functioning than SZ. |
| **Study** | **Symptom measures and cognitive dysfunctions** |
| Korver-Nieberg et al. [58] | Cross-sectional study showing shorter duration, less emotional distress, fewer negative and disorganized symptoms, and higher quality of life in BPD than SZ and related disorders. |
| Ngoma et al. [62] | BPD differs from both SZ and SFD in terms of cognitive and social functioning, positive symptoms and excitement. |
| Lee et al. [63] | Symptoms are less severe in BPD than SZ, but no difference in attention, memory and executive function. |
| Lyne et al. [75] | Negative symptoms were significantly fewer in BPD than in SZ spectrum disorders. |
| Ngoma et al. [76] | Although patients with BPD, SZ and SFD were more severely impaired than healthy controls, no selective deficit was found. |
| Ayesa-Arriola et al. [77] | BPD patients improved more rapidly than those with SZ, SFD and psychosis NOS after six months. |
| | **Diagnostic stability, course and outcome** |
| Schwartz et al. [56]* | 3/11 cases (27%) first admitted with BPD did not change diagnosis after 2 years. |
| Salvatore et al. [57]* | 22/36 cases (61%) with BPD did not develop another diagnosis after 2 years. |
| Kingston et al. [59]* | Many cases with BPD had rapid remission after the initial episode, but 80% developed longer lasting psychotic and affective disorders over 6 years. |
| Heslin et al. [60]* | 3/13 cases (23%) with BPD retained the same diagnosis after 8 or more years. |
| Schimmelmann et al. [91]* | 8/11 cases (73%) with BPD did not change diagnosis at 18 months follow-up. |
| Rahm & Culberg [92]* | Two-thirds of cases with BPD (n = 21) recovered; the remaining patients developed mainly SZ and/or affective psychosis over 3 years. |
| Haahr et al. [93]* | Diagnostic stability of BPD (n =20) reduced from 75% after the first year to 60% after 2 years; most transitions were to SZ and/or affective disorders. |
| Rufino et al. [94]* | 7/31 cases (23%) with BPD from an emergency service did not change diagnosis after 15 months; no difference in clinical and functional outcome from SFD and affective disorders. |
| Subramaniam et al. [95]* | 4/13 cases (31%) with BPD did not change diagnosis: short hospital stay and high premorbid functioning predicted diagnostic stability. |
| Pillmann et al. [96] | 23 admissions with BPD had high rates of relapse but significantly better clinical and social outcomes than patients with SZ over 2.5 years. |
| | **Response to treatment** |
| Ehlis et al. [100] | Atypical neuroleptics seem to have a positive effect on prefrontal brain functions. |

*First-admission/episode psychosis study;
BPD: brief psychotic disorder**;** SFD: psychosis NOS: not otherwise specified; schizophreniform disorder; SZ: schizophrenia.