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ACUTE AND TRANSIENT PSYCHOTIC  
DISORDER (ATPD) DYNAMIC  
DEVELOPMENT AND PARTICULARITIES  
IN DIAGNOSTICS AND TREATMENT  
IN LATVIA

Summary of Doctoral Thesis  
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## ABBREVIATIONS

ATPD	– Acute transient psychotic disorder;
SLE	– Stressful life events; SLE
DSM III	– Diagnostic and Statistical Manual of mental disorders, 3 <sup>rd</sup> edition
DSM IV	– Diagnostic and Statistical Manual of mental disorders, 4 <sup>th</sup> edition
DSM V	– Diagnostic and Statistical Manual of mental disorders, 5 <sup>th</sup> edition
OSD	– Overall stability of diagnosis
BPD	– Brief psychotic disorder
M	– Mean
Mini	– Mult short MMPI version
MMPI	– Minnesota Multiphasic Personality Inventory
<i>P</i>	– <i>p</i> value
PANSS	– Positive and Negative Syndrome Scale
PET	– Positron emission tomography
PTSD	– Post traumatic stress disorder
WHO	– World Health Organization
PubMed	– USA National database
RCPA	– Riga Centre of Psychiatry and Addiction disorders.
SD	– Standard deviation
SPSS	– Statistical Package for the Social Sciences
ICD-10	– 10 <sup>th</sup> International Classification of Disease
ICD-11	– 11 <sup>th</sup> International Classification of Disease
VBM	– Voxel based morphometry is a neuroimaging analysis technique

# INTRODUCTION

## 1.1. Background

Acute and transient psychotic disorder (ATPD; F23) was added to the WHO International Classification of Diseases (ICD-10) as a separate syndromological unit in 1992. (1)

ATPD is a disorder characterized by acute onset, psychotic symptomatology, and rapid resolution. There are relatively few large epidemiological studies that employ standardized assessment methods to investigate this disorder. This leaves important clinical questions unaddressed. We lack sufficient information on the long-term diagnostic stability of acute psychosis, epidemiological and clinical characteristics, the association of the disorder with stress, and on its relationship with schizophrenia. (2, 3)

However, the popularity of ATPD studies has increased sharply over the last few years. From 2009 through 2011, only few articles appeared in the USA National Library of Medicine National Institutes of Health (PubMed) database. (4–10).

In 2012 much more new studies on the topic were published (11–18). This increased research attention may be due to the active debate over ATPD's place in the next revision of the International Classification of Diseases, ICD-11.

International study results show that the prevalence of the disorder is very variable. (2)

In the UK, prevalence is reported at 3.9 cases per 100,000 of the population, while in Denmark prevalence is reported to be 9.6 (3, 19). In 2009, the prevalence of ATPD in Latvia was reported as high as 10 per 100,000 populations via official statistics. (20) The overall stability rates of ATPD diagnosis in follow-up studies range from 34.0% to 73.0% (follow-up period

from 1 to 5 years) and convert mainly either to F2 schizophrenia and related disorders or to F3 affective disorders (2, 4, 14, 21).

Systematic epidemiological studies with standardized methods of the ATPD are rare.

One of the largest retrospective studies in Europe was a 6-year analysis of re-admission patterns of 503 patients from a cohort of the Danish psychiatric central register (3).

The largest prospective study, the HASBAP study, assessed the epidemiology of ATPD, possible long-term prognostic factors and attempted to identify differences between patients with ATPD and those with schizophrenia (2).

Stressful life events have been associated with an increased risk of mental disorders.

In 1986 Strömberg (22) described the concept of reactive (psychogenic) psychosis. To some degree, it was included in DSM III as a “brief reactive psychosis” and in the DSM IV as a “brief psychotic disorder” (23, 24). Over the last two decades there are relatively few new studies published on this topic. A study from London shows, that stressful events, especially in preceding 3 months, may trigger the first episode of psychosis (25). Another study showed that stressful life events occur more frequently in the six month prior to the onset of the ATPD episode, compared to the same period before to the onset of manic episode (26).

The literature data from controlled clinical trials on research topic is not available.

Most clinicians still treating ATPD like any other psychoses, mainly using antipsychotics and sedatives.

BP Chaudhuri and colleagues tried to find out whether there are differences in ATPD treatment with risperidone or haloperidol. They have concluded that risperidone should be the first choice in the ATPD treatment. (27)

Several recently published reports questioning practice of using in treatment of psychoses high doses of antipsychotic preparations. (28) A. Khanna objective of the study was to compare the high and low doses of haloperidol efficacy in treatment of ATPD patients. (28)

There have been some studies on ATPD comorbidity with personality features, but scientists did not find a close relationship. (29, 30)

One of the key researches in this field is Pillmann F., R. Blöink, S. Balzuweit, A. Haring, A. Marneros study. (29)

The results show that 1) ATPD patients do not differ in any way from the other population, and 2) ATPD patient's personality does not differ significantly from the general population. (29)

In another study on this subject P. Jergensen with colleagues analyzed other ATPD sample of patients (n = 51). (30) The findings of this study suggest that patients characterized by good level of premorbid social functioning before manifestation of ATPD disorder. (30)

Consequently, there is little known about the epidemiology of ATPD, its clinical aspects and prognosis, as well as etiological and pathological mechanisms associated with this disorder.

In Latvia there have been no previous studies regarding the clinical features, course, and outcome and associated sociodemographic characteristics of ATPD or on stressful life events prior to the first episode.

## **1.2. The aim of the research**

The aim of this study was to describe stressful life events and personality profiles before the first ATPD episode; to analyze the overall stability and longitudinal changes of the diagnosis; to describe the clinical features and to identify treatment particularities in Latvia.

### **1.3. The tasks for reaching the aim of the research**

It is necessary to carry out the following tasks for reaching the aim:

1. To analyze Riga's Centre of Psychiatry and Addiction (RCPA) disorders patient database from 01.01.2004.–31.12.2006. to identify all ATPD patients (F23, ICD-10) for retrospective part of the study and to observe this patients till 31.12.2010.

2. To identify Riga's Centre of Psychiatry and Addiction disorders (RCPA) all ATPD patients hospitalized from 09.01.2010.–30.03.2011 for prospective part of the study and to observe this patients till 31.10.2012.

3. To set the longitudinal changes of the diagnosis, overall stability of diagnosis and the associated sociodemographic characteristics in ATPD patients hospitalized Riga's Centre of Psychiatry and Addiction disorders (RCPA).

4. To describe the clinical features of the index episode of ATPD patients.

5. To identify stressful life events before the first episode of ATPD.

6. To analyze personality profiles of ATPD patients.

7. To set results of treatment of ATPD patients hospitalized Riga's Centre of Psychiatry and Addiction disorders (RCPA).

8. To analyze outpatient care departments ("Veldre", "Sarkandaugava" un "Ļermontova") patients database from 01.01.2004.–31.12.2006. and to identify all ATPD (F23, ICD-10) patients after first hospitalization in RCPA consulting outpatient care departments ("Veldre", "Sarkandaugava" un "Ļermontova") and to observe this patients till 31.12.2010.



#### **1.4. The hypothesis of the research**

1. ATPD symptoms during first episode of disorder differs from schizophrenia symptoms.
2. Potential ATPD association with stressful life events before the first episode.
3. Potential ATPD correlation with personality profiles before the first episode.

#### **1.5. The topicality and novelty of the research**

This is the first research in Latvia, retrospectively and prospectively conducted a detailed clinical study of ATPD. Novelty was also a detailed study of clinical features during first episode of psychosis.

There have been only a few studies also examined stressful life events, but Latvian study conducted rather large cohort of patients ( $n = 300$ ; retrospective part). To evaluate the results of treatment of ATPD patients, first time in Latvia, were used “Positive and Negative Syndrome” (PANSS) as well as “Mini-Mult” questioner, for patient personality profile identification. (31, 34) Study results could help to predict the development of disease and to provide the possible basis for potential changes to ICD-11.

## **2. MATERIAL AND METHODS**

The study was held at RCPAD, the largest hospital in the country (with approximately 440 beds) which provides care for approximately 40% of the Latvian population. And in all Riga's outpatient care departments ("Veldre", "Sarkandaugava" un "Ļermontova").

### **2.1. Retrospective part of the research**

In the retrospective chart review study we identified all consecutive patients who were hospitalized for the first time with a diagnosis of Acute and Transient Psychotic Disorder (ATPD) according to ICD-10 (1) at the Riga's Centre of Psychiatry and Addiction Disorders (RCPA), Latvia during 3-year period (01.01.2004.–31.12.2006). To analyze longitudinal changes of diagnosis we observe these patients till 31.12.2010.

### **2.2. Prospective part of the research**

In the prospective follow-up study we identified all patients who were admitted for the first time with a diagnosis of Acute and Transient Psychotic Disorder (ATPD) according to ICD-10 (1) at the Riga Centre of Psychiatry and Addiction Disorders (RCPAD), Latvia during a 15 month period (from 09.01.2010.–30.03.2011.). To analyze longitudinal changes of diagnosis we observe these patients till 31.10.2012.

### **2.3. Outpatient care department part of the research**

We used patient's database from 01.01.2004.–31.12.2006. To analyze outpatient care departments ("Veldre", "Sarkandaugava" un "Ļermontova") patients from 01.01.2004.–31.12.2006. and to identify all ATPD (F23, ICD-10)

patients after first hospitalization in RCPA consulting outpatient care departments (“Veldre”, “Sarkandaugava” un “Ļermontova”) and to analyze longitudinal changes of diagnosis we observe this patients till 31.12.2010.

## **2.4. Comparison of the groups**

For the purpose of comparison patients were divided into three groups. The first “pure” ATPD patient group included all patients who were not re-hospitalized and patients, who were later re-hospitalization with a diagnosis of ATPD. The second group consisted of patients with re-hospitalization with schizophrenia (F20, ICD-10, WHO, 1993) (1). The third group comprised all ATPD patients whose diagnosis during the follow-up period was changed to other diagnosis.

The primary aim was to compare the first and second groups of patients for clinical features during first episode of disease, to identify precipitating stressful life events and possible prognostic factors for diagnosis conversion. Demographics and clinical features during the index episode were assessed as in Marneros et al. (2)

To analyze the longitudinal changes in the ATPD diagnosis group, the patients were followed up until 31.10.2012. Relapse was defined as the occurrence of a major affective syndrome or of psychotic symptoms leading to hospitalization. No patients died during observation period.

Stressful life events (SLE) were assessed using methods in the HASAP study, which is in accordance with the criteria generally used in life-event research. Events occurring during the six months prior to the index episode were considered. (2) We identify 8 major negative stressful life events: death of significant other, separation / divorce, serious illness/operation, serious problems at work, change of job / school, major journey, relocation of residence and serious problems at family.

## **2.5. Mini-Mult for personality features determination**

To determine the personality features for each patient, the Mini-Mult scale by Kincannon, the short version of The Minnesota Multiphasic Personality Inventory (MMPI) scale was used, one day before discharge from initial admission. (31–33)

The Mini-Mult scale consists of 71 items from 11 of the 13 standard MMPI scale. (31) The Mini-Mult contains 3 rating scales: a Scale of Lie (L), a Scale of Integrity (F), and a Scale of Correction (K) and 8 basic scales: Hypochondry (Hs), Depression (D), Hysteria (Hy), Psychopathy (Pd), Paranoid (Pa), Psychasthenia (Pt), Schizoid (Se), and Hypomania scales (Ma). (31)

## **2.6. The Positive and Negative Syndrome Scale (PANSS)**

All ATPD patients were assessed with the Positive and Negative Syndrome Scale (PANSS) at admission and discharge (30) PANSS is a semi-structured clinical interview containing 30 items rated along a 7-point continuum (1=absent, 7=extreme). The assessment provides separate scores in several clinical domains, including positive symptoms (7 items), negative symptoms (7 items), and general psychopathology (16 items). (34)

## **2.7. ICD-10 diagnostic research criteria for ATPD**

ICD-10 Diagnostic Research Criteria for ATPD: (1)

G1. An acute onset of delusions, hallucinations, incomprehensible or incoherent speech, or any combination of these. The time interval between the first appearance of any psychotic symptoms and the presentation of the fully developed disorder should not exceed two weeks.

G2. If transient states of perplexity, misidentification, or impairment of attention and concentration are present, they do not fulfill the criteria for organically caused clouding of consciousness as specified in F05 A.

G3. The disorder does not meet the symptomatic criteria for manic episode (F30), depressive episode (F32), or recurrent depressive disorder (F33).

G4. No 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). The continued moderate and largely unchanged use of alcohol or drugs in amounts or frequencies to which the subject is accustomed does not necessarily rule out the use of F23; this must be decided by clinical judgement and the requirements of the research project in question.

G5. Most commonly used exclusion criteria: absence of organic brain disease (F0) or serious metabolic disturbances affecting the central nervous system (this does not include childbirth).

A fifth character should be used to specify whether the acute onset of the disorder is associated with acute stress (occurring within two weeks prior to evidence of first psychotic symptoms).

F23.x0 without associated acute stress and F23.x1 with associated acute stress.

For research purposes it is recommended to further specify the onset of the disorder from a non-psychotic to a clearly psychotic state as either: abrupt (onset within 48 hours), or acute (onset in more than 48 hours but less than two weeks).

### **F23.0 Acute polymorphic psychotic disorder without symptoms of schizophrenia**

- A. The general criteria for acute and transient psychotic disorders (F23) must be met.
- B. The symptomatology is rapidly changing in both type and intensity from day to day or within the same day.

- C. The presence of any type of either hallucinations or delusions, for at least several hours, at any time since the onset of the disorder.
  - (1) Symptoms from at least two of the following categories, occurring at the same time: Emotional turmoil, characterized by intense feelings of happiness or ecstasy, or overwhelming anxiety or marked irritability;
  - (2) Perplexity, or misidentification of people or places;
  - (3) Increased or decreased motility, to a marked degree.
- E. Any of the symptoms listed in Schizophrenia F20, G1.1 and G1.2 that are present, are only present for a minority of the time since the onset, i.e. criterion B of F23.1 is not fulfilled.
- F. The total duration of the disorder does not exceed three months.

**F23.1 Acute polymorphic psychotic disorder with symptoms of schizophrenia**

- A. Criteria A, B, C, and D of acute polymorphic psychotic disorder (F23.0) must be met.
- B. Some of the symptoms specified for schizophrenia (F20.0–F20.3) must have been present for the majority of the time since the onset of the disorder, but not necessarily meeting these criteria completely, i.e. at least any one of the symptoms in F20, G1.1a to G1.2g.
- C. The symptoms of schizophrenia in B above do not persist for more than one month.

**F23.2 Acute schizophrenia-like psychotic disorder**

- A. The general criteria for acute and transient psychotic disorders (F23) must be met.
- B. The criteria for schizophrenia (F20.0–F20.3) are met, with exception of the duration criterion.

- C. The disorder does not meet the criteria B, C and D for acute polymorphic psychotic disorder (F23.0).

The total duration of the disorder does not exceed one month.

### **F23.3 Other acute predominantly delusional psychotic disorder**

- A. The general criteria for acute and transient psychotic disorders (F23) must be met.
- B. Relatively stable delusions and / or hallucinations are present, but they do not fulfil the symptomatic criteria for schizophrenia (F20.0–F20.3).
- C. The disorder does not meet the criteria for acute polymorphic psychotic disorder (F23.0).
- D. The total duration of the disorder does not exceed three months.

Any other acute psychotic disorders that are unclassifiable under any other category in F23 (such as acute psychotic states in which definite delusions or hallucinations occur but persist for only small proportions of the time) should be coded here. States of undifferentiated excitement should also be coded here if more detailed information about the patient's mental state is not available, provided that there is no evidence of an organic cause. (1)

## **2.8. Statistical analyses**

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS), version 19.0. In addition have been considered indicators of central tendency (mean, median) and dispersion parameters – standard deviation (SD), standard error (SE) as well as the 25<sup>th</sup> and 75<sup>th</sup> percentile. Results were considered statistically significant if p-value was less than or equal to 0.05.

To assess the difference between the two groups for parametric data was used Mann-Whitney U-test for two-sample comparison. Proportional to the

normal distribution of data consistency was determined using the Kolmogorov-Smirnov test. Qualitative difference in the patient population was used for evaluation of the Pearson chi-square ( $\chi^2$ ), or Fisher's exact test.

An association between variables was used for nonparametric Spearman rank correlation test.

In order to determine the potential impact of external factors on the subsequent development of the patients' diagnoses (for the “pure” ATPD patient group, and for the patients who were later readmitted with a diagnosis of schizophrenia) all demographic variables, clinical features, SLE, personality profile data was included in logistic regression analysis. For selected data with statistically significant p-value (less than or equal to 0.05.) were used binary logistic regression (Wald test).

The study protocol was approved by the local Ethics Committee.



### 3. RESULTS

#### 3.1. Retrospective part of the research

A total of 314 patients were first-time hospitalized with an ATPD diagnosis in RCPAD during the 3-year period. By consensus of authors, 20 patients were excluded, because they did not fulfil ICD- 10 criteria for ATPD. Out of remaining 294 patients 54% ( $n = 159$ ) were women. The average age at the first psychotic episode was 35.7 ( $SD = 12.3$ ; 95%  $CI \pm 3.6$ ) years for women, and 30.0 ( $SD = 10.8$ ; 95%  $CI \pm 3.7$ ) for men, ( $p < 0.0001$ ).

68.3% (201) of patients were directed to RCPAD by emergency medical services, and 20.4% (60) by the RCPAD outpatient care department. We found that only 10.2% (30) of patients had heredity of psychiatric disorders in their family history. 44.2% (130) of patients were married, 27.2% (80) of patients had a general secondary education, 35.0% (103) had a vocational secondary education, and 30.6% (90) had completed higher education.

During their first psychotic episode, patients were treated in the hospital an average of 31.6 hospital bed-days ( $SD = 9.2$ , 95%  $CI \pm 4.9$ ).

Over a follow-up period of, on average, 6.1 years, 51% (150) of patients were not re-hospitalized and ATPD relapses we found in 15.0% (22) of re-hospitalized patients. Diagnosis was changed to schizophrenia in 73.0% (105) of re-hospitalized patients, not statistically significantly different between genders.

Diagnosis conversion into schizophrenia took place for 40.0% of patients within the first six months, for 64.8% within the first year and for 81.0% within the first two years. For the majority of patients (85%) the diagnoses was changed at the second hospitalization. Change to other diagnosis occurred in 12.0% (17) of patients, the majority of these 94.0% (16) were women  $p = 0.0006$ . The overall stability rate of ATPD diagnosis in our sample reached 58.5%. The longitudinal changes of diagnosis are presented in figure 1

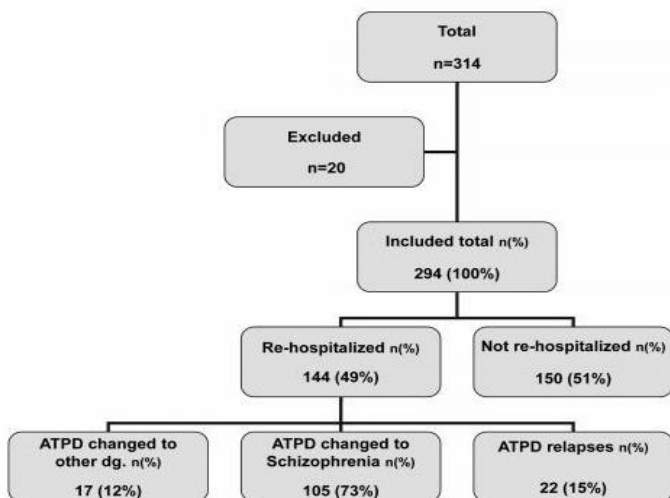


Figure 1. Longitudinal changes of acute and transient psychotic disorder (ATPD) diagnosis of the study group

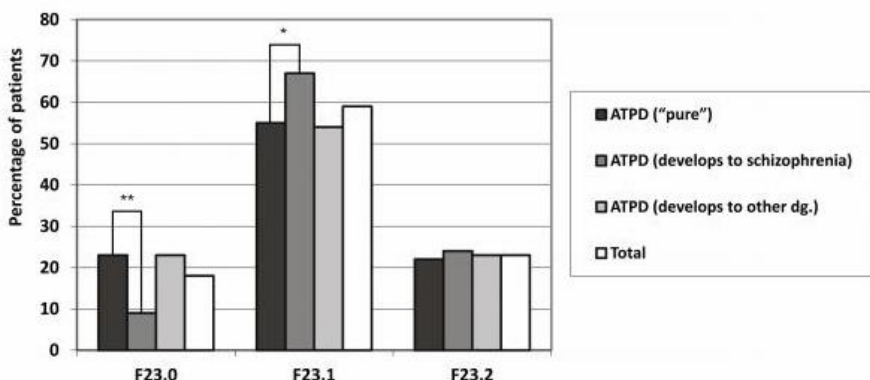
## Follow-up & out-patient care

During the follow-up period, the outpatient care department was visited by only 9.3% (16), of the of the “pure”ATPD patients ( $n = 172$ ). In the group of patients that was not re-hospitalized, ( $n = 150$ ) only 6.6% (10) of patients visited the outpatient care department. Of patients that was re-hospitalized with the diagnosis of ATPD ( $n = 22$ ), 27.2% (6) of patients visited the outpatient care department  $p = 0.007$ .

## Initial diagnosis & clinical features

Comparing ATPD subgroups during the first episode of psychosis, 18.0% (54) of patients had acute polymorphic psychotic disorder without symptoms of schizophrenia (F23.0), 59% (173) had acute polymorphic psychotic disorder with symptoms of schizophrenia (F23.1), and 23.0% (67)

had acute schizophrenia like psychotic disorder (F23.2). At the RCPAD 15 patients had been diagnosed F23.3 (9), F23.8 (4) and F23.9 (2). After independent diagnostic assessment in accord with ICD-10 criteria by the authors, they were re-diagnosed to F23.0 (7), F23.1 (5) and F23.2 (3). ATPD F23.0 diagnosis was statistically significantly more frequent for “pure” ATPD patients 23% (40) than for ATPD that later developed into schizophrenia 9.0% (10),  $p < 0.001$ , figure 2.



**Figure 2. ATPD subgroups during the first episode of psychosis**  
 (\* $p < 0.05$ ; \*\* $p < 0.001$ ; Fisher exact test)

Clinical features e.g. hallucinations were found in 32% (93) of patients; in 44.0% (46) of patients with ATPD that later developed into schizophrenia and in 26.0% (44) of the “pure” ATPD patients ( $\chi^2 = 9.8$ ;  $p < 0.01$ ) (Figure 3.). Affective disturbance was found in 34.0% (101) of patients; in 37% (64) of the “pure” ATPD patients and in 27% (28) of patients with ATPD that later developed into schizophrenia ( $\chi^2 = 3.2$ ;  $p = 0.08$ ). Anxiety was recorded in 58.0% (171) of the cases; in 65.0% (111) of the “pure” ATPD patients and in 51% (54) of the patients with ATPD, that later developed into schizophrenia ( $\chi^2 = 4.6$ ;  $p = 0.03$ , Figure 3.).

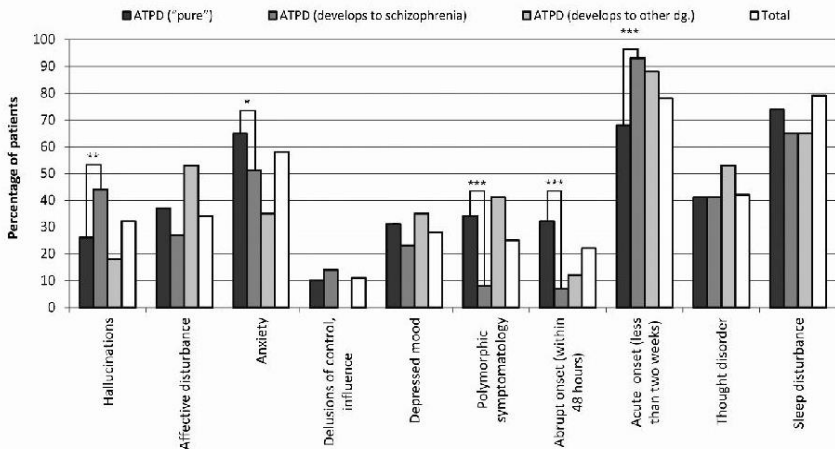


Figure 3. Symptomatology of the first episode of acute and transient psychotic disorder (ATPD)

\*  $p < 0.05$ , \*\*  $p < 0.002$ , \*\*\*  $p < 0.0001$  Chi-square, with Yates' correction, two-tailed

During the index episode, abrupt onset (i.e. within 48 hours) was found in 22% (64) patients. An abrupt ATPD onset was more frequent in patients with “pure” ATPD 32% (55), than for patients with ATPD which later developed into schizophrenia 7% (7) ( $\chi^2 = 24.0$ ;  $p < 0.0001$ , Figure 3.).

A total of 25% (73) of patients had typical polymorphic symptomatology; 34.0% (58) of the “pure” ATPD patients and in 8.0% (8) of patients with ATPD that later developed into schizophrenia ( $\chi^2 = 24.4$ ;  $p < 0.0001$ , Figure 3.)

### Stressful life events prior to diagnosis

Associated acute stress as defined by ICD-10 was seen in only 3.4% (10). Stressful life events within six months prior to diagnosis of the first episode were found in 43.8% (129) of patients, in 43.4% (56) of the women and 56.5% (73) of the men ( $\chi^2 = 4.4$ ;  $p = 0.03$ ). The most common specific events observed were recent unemployment, change of job or school and serious problems at work (including: financial difficulty/bankruptcy, dismissal,

conflict with employer, a large mortgage or loan, foreclosure of mortgage or loan) at frequencies of 30.2%, 29.4% and 17.0% respectively (Table 1).

Gender differences were found for specific stressful life events; separation/divorce, a serious illness / operation, serious family problems and serious work problems affected statistically significantly more women than men, whereas “moving house” (moving the whole family to a new place of residence – new city, country) affected significantly more men than women (Table 1).

Table 1.

**Stressful life events within 6 months before the first episode**

<b>Stressful life events</b>	<b>Men n=73 (56.5%)</b>	<b>Women n=56 (43.4%)</b>	<b>Total n n=129 (43.8%)</b>	<b>p value between genders*0.03</b>
Death of significant other	8.2% (6)	19.6% (11)	13.1% (17)	0.06
Separation/divorce	8.2% (6)	26.7% (15)	16.2% (21)	0.007
Change of job or school	26.0% (19)	33.9% (19)	29.4% (38)	0.33
“Moving house” <sup>1</sup>	23.2% (17)	5.3% (3)	15.5% (20)	0.006
Serious illness/operation	9.5% (7)	23.2% (13)	15.5% (20)	0.04
Serious problems in family <sup>2</sup>	13.7 (10)	28.5% (16)	20.1% (26)	0.04
Serious problems at work <sup>3</sup>	10.9% (8)	25.0% (14)	17.0% (22)	0.05
Major journey <sup>4</sup>	12.3% (9)	21.4% (12)	16.2% (21)	0.22
Unemployment Total n	25.1% (34) n=135	34.6% (55) n=159	30.2% (89) n=294	0.09

\* Fisher’s exact test, two-tailed

<sup>1</sup> “Moving house” – moving the whole family to a new place of residence (new city, country)

<sup>2</sup> Serious problems in family (including: major change in health or behaviour of family member, betrayal of spouse, conflict with spouse)

<sup>3</sup> Serious problems at work (including: financial difficulty/bankruptcy, dismissal, conflict with employer, a large mortgage or loan, foreclosure of mortgage or loan)

<sup>4</sup> Major journey (long trip abroad; from 1–6 month)

## 3.2. Prospective part of the research

During a 15 month period, 102 patients were admitted with a first-time diagnosis of ATPD. 60.7% (62) of these patients were females. The average age at first psychotic episode for females was 40.2 (SD = 13.4; 95% CI  $\pm$  6.9), and for males was 29.0 (SD = 10.2; 95% CI  $\pm$  6.5), ( $p < 0.0001$ ).

Only 15.6% (16) of patients had heredity of psychiatric disorders in their family history. 24.5% (25) of patients had a general secondary education, 34.3% (35) had a vocational secondary education, and 25.4% (26) had completed higher education. 30.3% (31) of the patients were married. Patients with a “pure” ATPD diagnosis were significantly more likely to be married than the other patients, and composed 80% (25) of the married patient group ( $p=0.0001$ ). During their first psychotic episode, patients were treated in the hospital an average of 21.6 hospital bed-days (SD = 9.9, 95% CI  $\pm$  3.9).

The group of patients whose ATPD diagnosis was later changed to schizophrenia were treated longer upon their first psychotic episode than patients from the “pure” ATPD group (20.0 vs. 26.4 bed-days,  $p = 0.004$ ).

Table 2.

**The longitudinal changes of diagnosis**

	<b>Total %, n</b>	<b>Men %, n</b>	<b>Women %, n</b>	<b>p value between genders*</b>
<b>Number</b>	<b>100 % (102)</b>	<b>39.3 %* (40)</b>	<b>60.7%* (62)</b>	<b>0.003</b>
Not rehospitalized	59.8% (61)	40.0% (24)	60.0% (37)	0.06
Re-hospitalized	40.2% (41)	39.0% (16)	61.0% (25)	0.07
ATPD change to Schizophrenia	70.7% (29)	44.8% (13)	55.2% (16)	0.5
ATPD relapse	19.6% (8)	37.5% (93)	62.5% (5)	0.6
ATPD change to other dg.	9.7% (4)	0.0% (0)	100.0% (4)	0.02

(ATPD) acute and transient psychotic disorder; (dg.) diagnosis

Over a follow-up period averaging 26.5 months, 59.8% (61) of patients were not readmitted. The longitudinal changes of diagnosis are presented in Table 2. The overall stability rate of ATPD diagnosis in our sample reached 67.4% ( $p = 0.0001$ ).

### Clinical features and initial diagnosis

The distribution of initial diagnosis is described in Table 5. A diagnosis of ATPD “without schizophrenic symptoms” (F23.0) was significantly more common amongst “pure” ATPD patients (63.7 %;  $p = 0.01$ ).

Table 5.

**The distribution of initial diagnosis**

<b>ICD-10 ATPD subtypes</b>	<b>ATPD („pure”) %, n=69</b>	<b>ATPD (change to Schizophrenia %, n=29</b>	<b>ATPD (change to other dg.) %, n=4</b>	<b>*p value</b>
<b>F23.0</b>	<b>63.7%*(14)</b>	<b>22.7%* (5)</b>	<b>13.6% (3)</b>	<b>*0.01</b>
F23.1	69.0% (44)	31.2% (20)	0.0% (0)	0.0001
F23.2	69.0% (11)	25.0% (4)	6.2% (1)	0.03

(ATPD) acute and transient psychotic disorder; (dg.) diagnosis

Clinical features e.g. hallucinations were found in 33.3% (34) of patients, affective disturbance was found in 36.2% (37). During the index episode, abrupt onset (i.e. within 48 hours) was found in 32.3% (33) patients. A total of 32.3% (33) of patients had typical polymorphic symptomatology. The clinical features are described in Table 6.

Table 6.

**Clinical features of index ATPD episode**

<b>Clinical features</b>	<b>ATPD ("pure") 67,6%, n= 69</b>	<b>ATPD (change to Schizophrenia) 28.5%, n= 29</b>	<b>ATPD (change to other dg.) 3.9%, n= 4</b>	<b>Total n 100%, n=102</b>	<b>p value</b>
Hallucinations	31.8% (22)	34.5% (10)	50.0% (2)	33.3% (34)	0.8169
Affective disturbance	34.7% (24)	34.5% (10)	75.0% (3)	36.2% (37)	1.0000
Anxiety	65.2% (45)	62.0% (18)	75.0% (3)	64.7% (66)	0.8193
Delusions	100.0% (69)	100.0% (29)	100.0% (4)	100.0% (102)	1.0000
Depressed mood	40.5% (28)	34.5% (10)	0.0% (0)	37.2% (38)	0.6531
Polymorphic symptomatology	40.5% (28)	37.9% (11)	50.0% (2)	32.3% (33)	1.0000
Abrupt onset (i.e. within 48 hours)	30.4% (21)	33.3% (11)	25.0% (1)	32.3% (33)	1.0000
Acute onset (i.e. within 2 weeks)	69.5% (48)	62.0% (18)	75.0% (3)	67.6% (69)	1.0000
Thought disorder	33.3% (23)	34.5% (10)	25.0% (1)	33.3% (34)	1.0000
Sleep disturbance	85.5% (59)	93.1% (27)	100.0% (4)	88.2% (90)	0.5006

(ATPD) acute and transient psychotic disorder; (dg.) diagnosis

**Stressful life events prior to diagnosis**

Associated acute stress as defined by ICD-10 was seen in only 1.0% (1) of patients. Stressful life events occurring in the six months prior to the index episode were found for 51.0% (50) of patients. There were not found any statistically significant differences for specific stressful life events between the groups.



## Treatment during the first psychotic episode

60.7% (62) of patients received first-generation antipsychotics (FGA) (avg. dose 12.5 mg/day haloperidol equivalent) as the main medication for the treatment of their first episode of psychosis, while 39.3% (40) received second-generation antipsychotics (SGA) (avg. dose 7.6 mg/day haloperidol equivalent) as treatment.

ATPD patients whose diagnosis was later changed to schizophrenia were more likely to be treated with FGA (79.3%,  $p = 0.03$ ) than patients from the “pure” ATPD patient group, while “pure” ATPD patients were more likely than others to be treated with SGA (45.0%,  $p = 0.04$ ). Benzodiazepines were used for 85.2% (87) of patients with an average dosage of 18.8 mg/day of diazepam equivalent. In 18.6% (19) of cases, anticonvulsants were used and in 3.9% (4), antidepressants. To reduce the adverse effects of antipsychotics during treatment, Trihexyphenidyl was used in 91.1% (93) of cases.

## Personality profiles

Almost a fifth of the patients, 18 (17.6%) had a personality profile within the norm and among these patients those with a “pure” ATPD diagnosis 14 (77.8%) were more likely ( $p = 0.0006$ ) to have a personality profile within the norm than 3 patients who later changed to schizophrenia. Results are presented in Table 7.

Table 7.

### Personality profiles

Mini-mult scales	ATPD (“pure”) 62.1%, n= 46	ATPD (change to Schizophrenia) 33.7%, n= 25	Total n 100%, n=74	p value
Hypochondry	10.8% (5)	20.0% (5)	13.5% (10)	0.3072
Depression	21.7% (10)	12.0% (3)	17.5% (13)	0.3584

Table 7 (continued)

Hysteria	17.4% (8)	28.0% (7)	20.2% (15)	0.3654
Psychopathy	10.8% (5)	24.0% (6)	16.2% (12)	0.1778
Paranoid	26.0% (12)	8.0% (2)	18.9% (14)	0.1163
Psychasthenia	13.0% (6)	8.0% (2)	13.5% (10)	0.7037
Schizoid	21.7% (10)	16.0% (4)	18.9% (14)	0.7568
Hypomania	6.5% (3)	12.0% (3)	8.1% (6)	0.6582

(ATPD) acute and transient psychotic disorder

### PANSS scale

All ATPD patients were assessed with the PANSS scale. 68.6% (70) patients were observed 3 times during their first hospitalization: 1–2 days after hospitalization (baseline), in the middle of treatment, and 1–2 days before discharge from the hospital (discharge), 18.6% (19) were observed 2 times (baseline and discharge) and 12.7% (13) only once (baseline), due to very short hospitalization times. Analyzing the first days of hospitalization (baseline  $n = 102$ ), we found the following PANSS scores: PANSS total  $118.2 \pm 3.5$ , and PANSS positive  $38.6 \pm 2.4$ . Among the patients which were observed 2 times (baseline and discharge,  $n = 89$ ) PANSS total (baseline) was  $117.9 \pm 8.2$ , and PANSS total before discharge  $60.8 \pm 4.2$ . The PANSS total change from baseline was  $57.1 \pm 2.3$ . None of the differences between the groups or changes between the groups reached statistically significant differences.

### Regression analysis

In order to determine the potential impact of external factors on the subsequent development of the patients' diagnoses all demographic variables, clinical features, SLE, personality profile data was included in logistic regression analysis. For selected data with statistically significant p-value (less than or equal to 0.05.) were used binary logistic regression (Wald test).

Thought disorder was found in 24.6% of the “pure” ATPD patients and in 58.6% of patients with ATPD that later developed into schizophrenia. Difference was statistically significant by both Pearson Chi-Square and Fisher's Exact test ( $p = 0.002$ ). Between the two variables exists a weak statistically significant relevance (Spearman correlation value 0.326), but thought disorder can be strong statistically significant “predictor” of ATPD diagnosis conversion to schizophrenia (in binary logistic regression Wald's criterion was rather high 9.435).

## 4. DISCUSSION

In recent years, Acute and Transient Psychotic Disorders have received increased attention in the psychiatric research setting. This attention may be prompted by an opportunity to improve classification during the revision of the 11<sup>th</sup> International Classification of Disease (ICD-11). To contribute to this effort, the aims of our study were to describe the clinical features of the index episode of ATPD in patients in Latvia; to analyze changes in the diagnosis longitudinally; and to explore potential correlations between the socio-demographic characteristics of patients and their disease characteristics. We tried also to identify the longitudinal diagnostic stability of ATPD diagnosis in Latvia, and correlate stressful life events before the first episode to characteristics of the progression of the disease. We hope that our study results can help to predict the development of disease and inform potential changes to ICD-11.

The sample at RCPAD can be regarded as a representative sample of the clinical inpatient population with ATPD in Latvia, as the hospital is the largest hospital in the country (with approximately 440 beds) and provides care for approximately 40% of the Latvian population. As of 2010, our previous study found on average 73 new ATPD cases a year, which gives an incidence figure above 8.1 cases per 100.000 inhabitants. (35)

This incidence is high in comparison to the “Nottingham” study, which had only 3.9 cases per 100.000 population (19), but closer to a Danish cohort study which identified an incidence of 9.6 per 100.000 population. (3)

In agreement with previous studies we found higher prevalence of ATPD in females. (2, 3, 21, 36, 37) Women composed 60.7% of the population diagnosed with ATPD in this study. This is similar to the proportion observed by Aadamsoo et al. in Estonia (60.0%). (4) The average age at first psychotic episode in our study was higher for women than for men; this is also in

agreement with previous studies. (2)

There are only a few studies investigating the familial psychiatric morbidity of individuals with ATPD. Marneros et al. reported a higher rate of mental disorders among family members of patients with ATPD than among the relatives of healthy controls, but no significantly raised occurrence of psychotic disorders among these family members was found. (2) In our study, only 15.6% (16) the patients were found to have a family history of psychiatric disorder.

We also surveyed the level of formal education among this patient body. Similarly to data reported Marneros et al., about one quarter of the patients in this study had completed higher education. (2)

30.3% (35) of the patients were married. Interestingly, patients with a “pure” ATPD diagnosis were significantly ( $p = 0.0001$ ) more likely to be married than the other patients, and composed 80% (25) of the married patient group. This data is similar to the data reported by Aadamsoo et al., in which about 42.3% of ATPD patients were married, as compared to only 11.4% of patients with a schizophrenia diagnosis. (4) This may indicate that before the first episode of psychosis, the level of social functioning is higher among the group of patients with a “pure” ATPD diagnosis than among those with a diagnosis which changes to schizophrenia.

During the first psychotic episode, patients were treated in the hospital an average of 21.6 hospital bed-days. This is similar to other ATPD studies. Interestingly, the group of patients whose ATPD diagnosis was later changed to schizophrenia were treated longer upon their first psychotic episode than patients from the “pure” ATPD group ( $p = 0.004$ ).

Only a little more than 40% of patients were readmitted during the follow-up period. This can indicate a better prognosis for ATPD than for schizophrenia. If the ATPD diagnosis was changed, in 70.7% of cases it was changed to a diagnosis of schizophrenia. This is similar to Aadamsoo et al.’s

data, where 64.0% of changed ATPD diagnoses were changed to schizophrenia. (4)

Although the follow-up period averaged only 26.5 months, our previous retrospective study with a follow up period of 6 years showed that diagnosis conversion took place within the first 2 years after initial hospitalization for 81.0% of patients. (35) Thus, we believe that our current study data captures a significant portion of the trends in diagnosis conversion for ATPD patients.

ATPD has lower rates of relapse in developing countries as compared to industrialized countries, and has a relatively high diagnostic stability in Europe. (21) The overall stability rate in our study was high (67.4%; 2.2 years follow-up period), and this is close to data reported by Marneros (54.0%; 4.7 years follow-up period), Jørgensen (52.0%; 3 years follow-up period) and Castagnini et al. (48.4%; 5 years follow-up period). (2, 14, 36)

Aadamsoo et al. reported a lower stability rate, at 34.0% (2 years follow-up period). (4) This may be due to the methodological differences between our studies. We used methods similar to those in Castagnini et al., which includes patients who were not readmitted after the first episode, but Aadamsoo et al. did not include that kind of patients in her calculations. (4, 9)

The percentage of F23.0 patients in our study population, at 21.5% (22), was smaller than that described by Aadamsoo (at 25.0%) in Estonia, but F23.1 diagnosis was much more frequent at 62.7% of patients in the Latvian study (compared to the Estonian study's rate of 29.0%). (4) This finding may demonstrate differences in diagnostic interpretations by the psychiatrists in the two neighboring countries. Studying the changes in diagnosis longitudinally for patients with F23.0 diagnoses vs. those with F23.1 diagnoses, we determined that patients with an F23.0 diagnosis were significantly more likely to be a patient whose diagnosis remained "pure" ATPD. Similar results were found in both Japan and Estonia. (4, 37) This could play a significant role in the development of amendments to the new classification (ICD-11).

Some differences between the clinical features of the first episode of psychosis associated with a “pure” ATPD diagnosis versus those associated with ATPD which was later converted to schizophrenia was observed. The Latvian study shows, that thought disorder was found in 58.6% of patients with ATPD that later develops into schizophrenia ( $p = 0.002$ ) with a statistically significant relevance (Spearman correlation value 0.326). This can be strong statistically significant “predictor” of ATPD diagnosis conversation to schizophrenia (in binary logistic regression Wald's criterion was high 9.435). It can be concluded, that in first episode ATPD patients with thought disorder chance to get diagnosis conversation to schizophrenia was in a 4.3 times higher (Odds Ratio).

Studies of reactive psychosis (which is included in ICD -10 under ATPD diagnosis and DSM IV under Brief psychotic disorder) were very popular in Scandinavia during the 1970 and 1980s. (1, 22–24, 38–42) All of these studies identified a correlation between the onset of ATPD and stressful life events preceding the first episode of psychosis. (2, 18, 21, 26) We also found that a large proportion of patients in our study had experienced stressful life events during the six months prior to their first psychotic episode. Thus, our research supports the argument that stressful life events are an important factor that can facilitate development of this disease.

Our data shows that the use of first-generation antipsychotics (Haloperidol in an average dosage of 12.5 mg/day) was still more common than the use of second-generation antipsychotics for the treatment of the first episode of psychosis in Latvia (60.7% vs. 39.3%). This data strongly differs from Estonian data, where only 1% of patients received first-generation antipsychotics. This may be due to differences in traditions of treatment between the two countries. (4)

In the literature there is a considerable number of reports on the correlation of premorbid personality with schizophrenia, however, there is a

lack of research about correlation of ATPD with premorbid personality profile. (42) Empirical data presented by Jorgensen et al. who in a sample of 51 ATPD patients assessed with the International Personality Disorder Examination (IPDE) and found relatively high prevalence of personality disorders and ATPD. (30)

Marneros and Pillmann in their study used the Neuroticism-Extroversion-Openness Five Factor Inventory (NEO-FFI) self-rating scale. They found no differences between healthy controls and ATPD patients (n=42). (29) We used the “Mini-Mult” scale by Kincannon unlike the Neuroticism-Extroversion-Openness Five Factor Inventory (NEO-FFI) used in other studies, more objectively indicates the personality profile. (2, 31) In our study 17.6% had a personality profile within the norm and were from the “pure” ATPD diagnosis group. This may indicate that before the first episode of psychosis, the level of social functioning is higher among the group of patients with a “pure” ATPD diagnosis than among those with a diagnosis which changes to schizophrenia.

A large portion of ATPD patients showed deviations from the norm in personality profiles, similar to that found by Jorgensen and co-workers, where 63% ATPD patients also had a prevalence of personality disorders. (30)

Latvian results are close to the data from other studies, but when we tried to compare “Mini-Mult” scores between the “pure” ATPD group, and that which later converted to schizophrenia, we could not find any statistically significant differences. (30)

All ATPD patients were assessed with the PANSS scale. This is the first published ATPD study to our knowledge s to use the PANSS scale in assessment. (34) Interestingly, of the 13 patients with only a single PANSS observation (due to their very short hospitalization period – about 1 week), 6 were later diagnosed with schizophrenia. This might suggests that untreated psychosis is more likely to progress to a chronic condition. We compared



PANSS scores obtained from patients on the first two days of their hospitalization (baseline) to those from their last two days prior to discharge. We identified no statistically significant differences between the “pure” ATPD and ATPD which was later converted to schizophrenia groups, because PANSS scores for each patient was very similar. High score in change from the baseline shows the positive result of ATPD patient treatment during hospitalization.

The limitations of this study are similar to those of other studies. No structured life-events scale was used and life-event data may have been influenced by recall bias, as was demonstrated in the “Nottingham” study. (19)

The most important limitation is that differences in interview methods, sampling or clinical assessment as compared to previous studies can bias the results, particularly in terms of diagnostic stability and outcomes for ATPD subtypes. (4)

The limitations of the personal profile results are intrinsic to the “Mini-Mult” method. Some authors argue that the “Mini-Mult” shows success in screening, but that for descriptive features the full MMPI is preferable and personality assessment of patients occurs after first psychotic episode. (43)

In the Latvian study the sample size was rather small and the follow-up period was shorter than in other studies. Due to this, the study may be underpowered for finding statistically significant differences between the groups of patients.

## 5. CONCLUSIONS

Half of the patients were hospitalized only once during follow-up period ATPD overall stability of diagnosis was high.

In the subgroup of re-hospitalized patients, the most common diagnostic change was to schizophrenia, which took place within the first two years of the illness.

During index episode of the first psychotic episode clinical features of “pure” ATPD group and ATPD which changes to schizophrenia differs and this data could help to predict further development of disease.

Outpatient care department was visited by only a small proportion of ATPD patients.

Stressful life events before the first episode occurred in large proportion of ATPD patients and we don't find correlation between ATPD and personality disorders.

ATPD treatment in Latvia differs from treatment guideline recommendations.

### **The hypothesis of the research**

- ATPD symptoms during first episode of disorder differs from schizophrenia symptoms – was confirmed.
- Potential ATPD association with stressful life events before the first episode – was not confirmed.
- Potential ATPD correlation with personality profiles before the first episode – was not confirmed.

## **Practical recommendations**

1. Potential changes to ICD-11: to consider important role of stressful life events before 6 month prior first psychotic episode and deliberate to change definition in ATPD criteria from “the total duration of the disorder does not exceed three months” to “the total duration of the disorder does not exceed one month” for all subcodes (F23.0, F23.1, F23.2 and F23.3).
2. Recommend to use international treatment guidelines for the treatment of the first episode of psychosis in Latvia.
3. Some demographic and clinical features at the first episode of the disease, as thought disorder, could help to predict further development of disease and this should to consider in everyday practise.

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## 7. PUBLICATIONS

### **Publications (scientific articles) on the study research topic**

**Rusaka M**, Rancāns E. A prospective follow-up study of first-episode acutetransient psychoticdisorder in Latvia. Ann Gen Psychiatry. 2014; 6(13):1–4.

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**Rusaka M**, Rancāns E. First-episode transient psychosis: clinical features and stressful life events before development of disorder in Latvia. Rīga Stradiņš University, Research Articles in Medicine and Pharmacy 2010. (2011) 46.–50.lpp.