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Personalized medicine begins with the phenotype: identifying antipsychotic response phenotypes in a first-episode psychosis cohort

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Aims: Here, we present a clustering strategy to identify phenotypes of antipsychotic (AP) response by using longitudinal data from patients presenting first-episode psychosis (FEP).
Method: One hundred and ninety FEP with complete data were selected from the PEPs project. The efficacy was assessed using total PANSS, and adverse effects using total UKU, during one-year follow-up. We used the Klm3D method to cluster longitudinal data.
Results: We identified four clusters: cluster A, drug not toxic and beneficial; cluster B, drug beneficial but toxic; cluster C, drug neither toxic nor beneficial; and cluster D, drug toxic and not beneficial. These groups significantly differ in baseline demographics, clinical, and neuropsychological characteristics (PAS, total PANSS, DUP, insight, pIQ, age of onset, cocaine use and family history of mental illness).
Conclusions: The results presented here allow the identification of phenotypes of AP response that differ in well-known simple and classic clinical variables opening the door to clinical prediction and application of personalized medicine.

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Key words: antipsychotic; psychosis; first-episode; predictive factors; personalized medicine; clustering

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See Appendix 1 for the authors present in PEPs Group.

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Significant outcomes

- Longitudinal data of antipsychotic (AP) efficacy and toxicity allows identification of AP response phenotypes using clustering techniques in first-episode psychotic patients (FEP).
- Identified AP response phenotypes differ in baseline clinical variables (PAS, total PANSS, DUP, insight, pIQ, age of onset, cocaine use and family history of mental illness).
- Identified AP response phenotypes open the door to modifications of current clinical guidelines and application of personalized medicine.

Limitations

- Although our sample comprised patients with FEP, they are not antipsychotic-naïve patients
- The sample size, although represents one of the largest cohorts of FEP patients with longitudinal data in the literature, limits its statistical power and did not allow the study of subgroups

Introduction

Schizophrenia exhibits great heterogeneity when it comes to the efficacy of antipsychotics (APs) in treating it and the susceptibility of patients to developing side-effects. Prescribing the most effective compound to each individual sufferer would solve this problem; however, the question of which AP to prefer for treatment is controversial (1, 2). No overall best AP exists, given that each compound has a unique and specific profile of efficacy and side-effects, based on its unique pharmacodynamic and pharmacokinetic profile.

Therefore, the selection of the best compound for each patient is a difficult procedure that has to take into account a large number of factors, including the profile of the patient's symptoms and their severity, the efficacy of previous treatments, medical comorbidities, and the patient's preferences and family history. Genetic factors are another source of variability but the inclusion of pharmacogenetic markers into clinical practice is suboptimal (3, 4). Clinical guidelines are usually of little help as they mainly suggest the use of classes of APs, while differences across a single class of compounds are not usually reported (5). Unfortunately, AP prescription is still largely based on clinical experience and a trial-and-error strategy (3).

Within this setting, the concepts of personalized medicine and precision medicine have recently gained the attention of many researchers (6). The idea behind is to offer clinicians a guide to enable them to personalize treatment based on the best available evidence of effectiveness and tolerability for each patient (7, 8). However, several aspects

have limited the identification of AP response markers, such as the variability in the definitions of AP response phenotypes across studies (9) and the heterogeneity of the course of the disease. First-episode psychosis (FEP) patients have less variability in their exposure to antipsychotics and thus are better suited to the study of predictors of therapeutic outcomes than chronic patients (10, 11). Appropriate medication in FEP is especially relevant considering that this cohort of patients tends to be more sensitive to the effects of AP and more vulnerable to side-effects (12). Evaluations of the efficacy of AP medication have not demonstrated superiority of any individual agent for FEP patients (13); however, recent evidence suggests that there may be some efficacy benefit for individual second-generation antipsychotics (SGAs) (2). In addition, the risk of long-term neurological effects such as tardive dyskinesia given by first-generation APs (FGAs) has led to a consensus among some guideline development groups that SGAs are preferable in FEP (14). These evidences have been interpreted in guidelines by suggesting that risperidone, olanzapine, and amisulpride should be used as one of the two APs recommended before a trial of clozapine is considered (14). However, some guidelines relegate olanzapine to a second-line treatment, mainly because of the relatively high risk of metabolic side-effects and weight gain (15).

Aims of the study

The main objective of the present study is thus to identify phenotypes of antipsychotics response considering both efficacy and toxicity. We aim to achieve this by applying clustering techniques to longitudinal data from patients presenting first-episode psychosis. Our hypothesis is that response trajectories during the first year of treatment can be used to identify different phenotypes of antipsychotics response that could be identified by baseline clinical variables.

Material and methods

This study is part of the project 'Phenotype–genotype interaction: application of a predictive model in first psychotic episodes, FIS PI080208' (known as the PEPs study, from the Spanish abbreviation for first psychotic episode). A complete description of the protocol for the PEPs study has been published previously (16–18). This longitudinal two-year prospective follow-up study presents clinical parameters from different assessments/visits: baseline, two-month, six-month, one-year, and two-year follow-up. For the purpose of the present study, (1) we extracted data from two-month, six-month and one-year visits for the clustering analysis; (2) baseline data were used to identify clinical predictors for the obtained clusters; and (3) data from the two-year follow-up visit were used to evaluate long-term response of the obtained clusters.

Participants

During the recruitment period (2009-2012), 335 subjects who presented FEP and 253 matched healthy controls were included in the PEPs Project. From the initial FEP sample, 302 participants received at least one antipsychotic prescription during the follow-up period. Of these, 234 (77.5%) participated in the pharmacogenetic and therapeutic module that included reports and evaluations of adverse reactions. A total of 190 FEP patients included in this module (81.2%) provide the complete data for clustering analysis: Positive and Negative Syndrome Scale (PANSS) score and the Udvalg for Kliniske Undersøgelser (UKU) side-effect rating scale score for three consecutive visits (two months, six months, and one year). This observational period was selected as at these points the two scales were collected jointly.

Being a naturalistic study, there were no specific guidelines for treatment, so patients received AP treatment based on the clinician's decision. Dosing, co-medications, or treatment changes were based only on clinical necessity. Prior treatment with APs did not exceed 12 months at study entry (19).

The study was approved by the Ethics Committees of all the participating centers, and informed consent was obtained from all the participants or their legal guardians.

Clinical assessment

At baseline, a complete evaluation was performed by collecting demographic data, environmental risk factors (20), premorbid adjustment scale (PAS) score, age at onset of the illness, duration of untreated psychosis (DUP), duration of treated psychosis (DTP), and clinical scale scores (PANSS) (21).

As a measurement of AP efficacy, improvement in clinical symptomatology was assessed using the Spanish validated version of the PANSS (22). The PANSS results were collected at each visit during the PEPs study (23). We computed the total PANSS score at two months, six months, and one year for clustering analysis. Subsequent analyses considered the different subscales from all visits: positive, negative, and general. Insight was assessed via item G12 of the PANSS at baseline (23).

The UKU side-effect rating scale (24) was used to assess the type and severity of the side-effects.

For clustering analysis, we collected total UKU score (included the four major domains: psychic, neurological, autonomic, and other side-effects) at two months, six months, and one year. At baseline, the UKU was not assessed.

Prolactin levels (sample size ranging from 137 to 157) (25), extrapyramidal symptoms (EPS) using the Simpson Angus Scale (SAS) (sample size ranging from 161 to 188) (26), and waist circumference (sample size ranging from 118 to 162) (27) were used as measures of the main side-effects reported in the present study (19). This information was collected at three different time points: after two months, six months, and one year, except for waist circumference, which was recorded at every visit.

The neuropsychological battery used in the PEPs project (see reference for a complete description) (17), conducted at the 2-month visit to ensure clinical stability, measured the estimated premorbid intelligence quotient (pIQ) (by means of the vocabulary subtest of the WAIS-III in adults or WISC-IV in children), attention (Conners' Continuous Performance Test-II: CPT-II), working memory (Digit Subtest and the Letters and Numbers Subtest of the WAIS-III in adults or WISC-IV in children), executive functions (Wisconsin Card Sorting Test), and verbal memory (España-Complutense Verbal Learning Test for adults and children: TAVEC and TAVECi). Principal component analysis (PCA) was performed (using oblimin rotation with Kaiser normalization) with all the neuropsychological variables, and they were grouped into four cognitive domains: verbal memory, sustained attention, executive function, and working memory (17). For the present study, we collected the factorial punctuations of each domain resulting from the PCA ($n = 169$).

The prescribed daily doses of Aps at baseline, and the two-month, six-month, and one-year assessments were converted into an estimated equivalent amount of chlorpromazine following the current international consensus and expressed as chlorpromazine equivalent daily dose (CEDD) (18, 19).

In order to assess patient adherence to treatment, measures of AP plasma levels (data available for 110 participants) were used. When the reported plasma level of the AP or its metabolite was below the expected values (28) at any time point, according to prescribed dosage and cytochrome genotype (29), patients were considered non-adherent.

Statistical analysis

Clinical, self-rated, and demographic variables were measured using descriptive statistics and are described with means (SD) and percentages. Normal distributions of the data were confirmed using the Shapiro–Wilk test; and equality of the variance between groups was assessed by means of Levene's test.

In order to identify homogenous clusters of total PANSS and total UKU trajectories for those patients with at least three measurements (after two months, six months, and one year), we used the Kml3D R package, which uses K-means, an unsupervised non-parametric hill-climbing algorithm, to identify distinct clusters and assign individuals to unique clusters working on joint trajectories (30). To determine the optimum number of clusters, we considered the Calinski and Harabatz (CH), the Ray and Turi (RT), Davies and Bouldin (DB) and BIC criterion (30, 31).

Longitudinal differences between clusters in symptoms and adverse reactions at different time points were assessed using general linear models with repetitive measures, using time as within-subjects factor and cluster classification as between-subjects factors. For these variables with between-subjects significant differences, post hoc Bonferrroni test was applied.

Differences in sociodemographic and clinical characteristics between clusters were assessed using two-tailed χ^2 tests on categorical data and one-way ANOVA for continuous variables. For these variables with significant differences after Bonferroni correction ($P < 0.001$), post hoc Bonferroni tests were assessed. All analyses were performed using SPSS (version 22.0, Chicago, IL, USA) for Windows.

Results

Figure 1a shows the trajectories of total PANSS and total UKU at three time points (after 2, 6, and 12 months) for each participant and the mean trajectory of each cluster identified by the Kml3D algorithm. After considering several criteria, four was the optimum number of clusters for our analysis, according to the clinical relevance of the clusters and the sample size in each cluster. As could be expected, the four clusters differ significantly in their total PANSS ($F_3 = 137.6$, $P < 0.001$) and total UKU scale ($F_3 = 118.2$, $P < 0.001$) trajectories. Post hoc analysis confirmed that the four clusters differed in their total PANSS pattern across time (cluster to cluster comparison $P < 0.001$). Regarding UKU patterns, post hoc analysis identified two separate groups, one formed by clusters A and C (A vs. C $P > 0.05$), and another formed by clusters B and D (B vs. D $P > 0.05$) (A or C vs. B or D $P < 0.001$).

Table 1 shows the baseline characteristics for the total sample and stratified according to the four

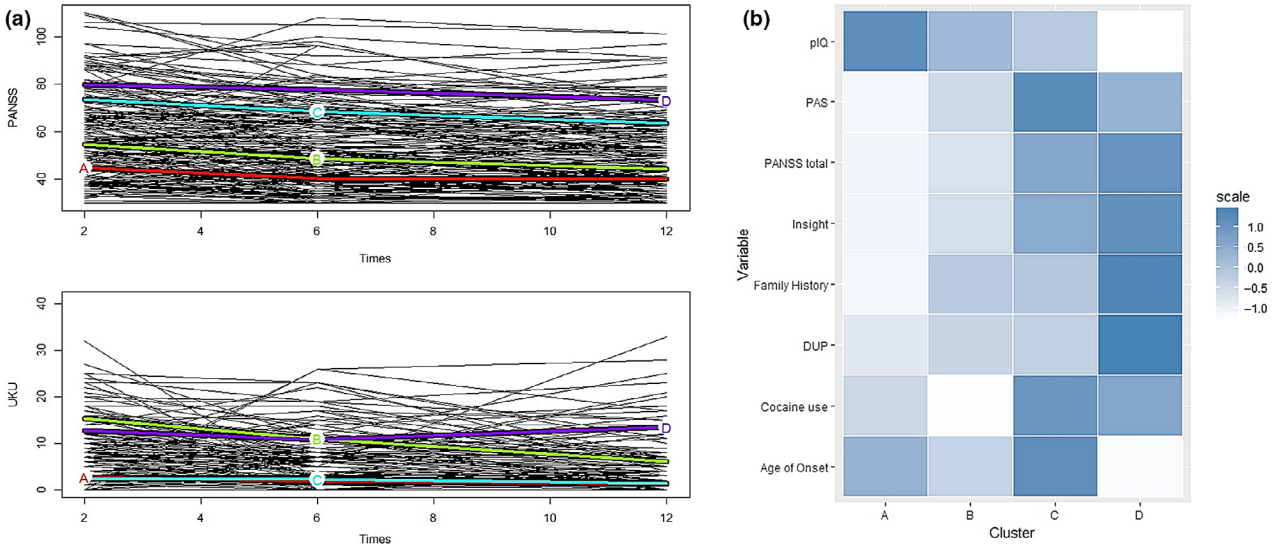

Fig. 1. (a) Trajectories of total PANSS and total UKU for each participant and the mean trajectory of each cluster identified by the Kml3D algorithm. (b) Heatmap of clinical characteristics significantly different among clusters (ANOVA $P < 0.05$).

clusters identified. Significant differences between the clusters were observed for several variables (Figure 1b). However, only differences in PAS, DUP, total PANSS, and insight remained significant after Bonferroni corrections ($P > 0.001$). We also observed significant differences in two neurocognitive domains measured at two months (verbal memory and working memory). Cluster A and B are characterized by lower punctuations than clusters C and D in PAS (A vs. C $P < 0.001$, A vs. D $P = 0.015$, B vs. C $P = 0.002$) and PANSS (A vs. C $P < 0.001$, A vs. D $P < 0.001$, B vs. C $P < 0.001$, B vs. D $P < 0.001$); and higher punctuations than clusters C and D in verbal memory (A vs. C $P = 0.001$, A vs. D $P = 0.007$, B vs. C $P = 0.006$, B vs. D $P = 0.021$). Cluster A and B can be differentiated from each other because cluster A has a shorter DUP (A vs. B $P = 0.032$), lower insight (A vs. B $P = 0.026$) and better performance in working memory (A vs. B $P = 0.02$) than cluster B. Finally, cluster D has a longer DUP (C vs. D $P = 0.001$) and higher insight (C vs. D $P = 0.045$) than cluster C.

Regarding pharmacological treatment, patients from clusters B were treated more often with risperidone than cluster A ($P = 0.001$) and C ($P = 0.003$). No significant difference in baseline daily dosage was observed. When we analyzed the dosage evolution over the study, we observed significant differences between clusters in the follow-up (Figure 2, Table S1). Starting from baseline, cluster A benefited from a quick reduction in AP dosage, significantly different from cluster D at two months ($P = 0.005$) and six months ($P = 0.004$), and significantly different from cluster C after six months ($P = 0.01$) and one year ($P = 0.003$). Regarding concomitant treatments (mood stabilizers, antidepressants, anxiolytics), no significant difference in baseline were observed between clusters (Table 1).

We analyzed the trajectories of the different domains of the PANSS scale (positive, negative, and generalized symptoms) over the two-year follow-up period (Figure 2, Table S1). As could be observed, the trajectories, that is the pattern of change over time, showed subscale difference among clusters: positive ($F_3 = 32.6$, $P < 0.001$), negative ($F_3 = 40.43$, $P < 0.001$), and general ($F_3 = 47.86$, $P < 0.001$). Post hoc analysis identified two separate groups for the positive and general subscale, one formed by clusters A and B (A vs. C $P > 0.05$), and another formed by clusters C and D (C vs. D $P > 0.05$) (A or B vs. C or D $P < 0.001$). Regarding negative symptoms, clusters A and B could be differentiated (A vs. B $P = 0.008$; A vs. C or D $P < 0.001$; B vs. C or D $P < 0.001$), but clusters C and D were indistinguishable from each other (C vs. D $P > 0.05$). We also analyzed mean value differences at each data point. At baseline, clusters A and B had less symptomatology than cluster C and D, but they are indistinguishable from each other. However, after two and six months, cluster B showed a delayed response, compared to cluster A, to negative (2M $P < 0.001$, 6M $P < 0.001$) and generalized symptoms (2M $P = 0.05$, 6M $P < 0.001$). After one and two years, no differences could be observed between both clusters, A and B. Cluster C showed better response than cluster D regarding positive symptoms after two ($P = 0.047$), six ($P = 0.006$),

Table 1. Baseline sociodemographic, clinical, pharmacological, and environmental characteristics of the 190 participants of the present study, stratified according to the inferred clusters

		Clusters				
	All	A	B	C	D	Statistic‡
N (%)	190	79 (41.5)	42 (22.1)	40 (21.1)	27 (14.2)	
Sociodemographic Variables						
Gender *N* (%)						
Male	131 (68.6)	52 (65.8)	27 (64.3)	31 (77.5)	19 (70.3)	$\chi^2 = 3.07$ $P = 0.545$
Female	59 (31.4)	27 (34.2)	15 (35.7)	9 (22.5)	8 (29.7)	
Caucasian *N* (%)	168 (88.4)	69 (89.6)	35 (83.3)	39 (97.5)	24 (88.8)	$\chi^2 = 4.9$ $P = 0.175$
Educational Level *N* (%)						
Primary	46 (24.2)	13 (16.4)	9 (21.4)	12 (30.0)	11 (40.7)	$\chi^2 = 16.0$ $P = 0.013$
Secondary	110 (57.9)	43 (54.4)	28 (66.6)	24 (60.0)	14 (51.8)	
Superior	34 (17.8)	23 (29.1)	5 (11.9)	4 (10.0)	2 (7.4)	
Employment status *N* (%)						
Active worker	46 (24.6)	23 (29.1)	9 (21.4)	10 (26.3)	4 (15.3)	$\chi^2 = 10.7$ $P = 0.097$
Student	83 (44.4)	38 (48.1)	21 (50.0)	10 (26.3)	14 (53.8)	
Unemployed	58 (31.0)	18 (22.8)	12 (28.6)	18 (47.3)	8 (30.8)	
Socioeconomic status *N* (%)						
High	48 (25.7)	21 (27.3)	13 (31.7)	5 (12.5)	8 (29.6)	$\chi^2 = 13.1$ $P = 0.041$
Medium *N*	109 (58.3)	34 (44.1)	18 (43.9)	32 (80.0)	15 (55.5)	
Low	30 (16.0)	12 (15.6)	10 (24.4)	3 (7.5)	4 (14.9)	
Family history of mental illness, Yes *N* (%)	70 (38.6)	21 (28.0)	16 (41.0)	16 (42.1)	17 (62.9)	$\chi^2 = 11.6$ $P = 0.008$
Migrant status, Yes *N* (%)	28 (14.7)	10(12.6)	10 (23.8)	2 (5.0)	5 (18.5)	$\chi^2 = 8.32$ $P = 0.080$
Clinical Variables						
Age (years), mean ± SD	23.60 ± 6.0	24.01 ± 5.9	22.69 ± 6.1	25.42 ± 5.9	21.19 ± 5.3	$F = 2.43$ $P = 0.049$
DUP (days), mean ± SD	110.4 ± 149.7	67.06 ± 90.7	98.95 ± 83.42	106.87 ± 124.3	246.67 ± 272.1	$F = 8.28$ $P < 0.001^{1,2,3,4,5,6}$
DTP (days), mean ± SD	42.72 ± 67.6	45.65 ± 68.7	40.47 ± 75.1	50.50 ± 75.9	28.62 ± 32.5	$F = 0.59$ $P = 0.668$
Insight, mean ± SD	3.50 ± 1.61	3.02 ± 1.7	3.30 ± 1.5	4.02 ± 1.4	4.40 ± 1.2	$F = 7.29$ $P < 0.001^{1,2,3,5,6}$
PAS, mean ± SD	37.54 ± 23.8	28.84 ± 18.1	35.40 ± 20.8	53.15 ± 21.8	44.04 ± 33.1	$F = 8.84$ $P < 0.001^{2,3,4,5}$
PANSS total ± SD	74,11 ± 24,2	64,64 ± 22,4	69,64 ± 21,20	85,75 ± 19,82	91,51 ± 24,01	$F = 14.98$ $P < 0,001^{2,3,4,5}$
UKU total ± SD*	6,98 ± 7,54	2,65 ± 3,01	15,25 ± 6,41	2,47 ± 2,84	12,74 ± 8,17	$F = 76.16$ $P < 0,001^{1,2,3,4,5,6}$
Neuropsychological Variables*						
pIQ, mean ± SD	93.14 ± 15.1	97.20 ± 15.4	92.63 ± 13.4	90.81 ± 12.8	85.37 ± 16.1	$F = 3.75$ $P = 0.006$
Verbal Memory, mean ± SD	257.72 ± 82.5	278.18 ± 78.9	277.59 ± 73.2	214.90 ± 77.8	218.10 ± 81.3	$F = 6.15$ $P < 0.001^{2,3,4,5}$
Executive Function, mean ± SD	157.75 ± 44.1	164.38 ± 44.7	148.40 ± 40.3	157.64 ± 46.9	148.55 ± 38.1	$F = 2.90$ $P = 0.024$
Attention, mean ± SD	87.70 ± 14.7	85.13 ± 11.2	92.28 ± 17.4	89.70 ± 16.8	87.88 ± 16.9	$F = 1.71$ $P = 0.150$
Working Memory, mean ± SD	68.30 ± 14.4	72.76 ± 15.2	64.55 ± 12.0	66.59 ± 13.5	62.71 ± 13.4	$F = 3.83$ $P = 0.005$
Toxic habits						
Tobacco use, Yes *N* (%)	116 (61.3)	51 (64.5)	21 (50.0)	24 (60.0)	18 (69.2)	$\chi^2 = 5.13$ $P = 0.162$
Alcohol use, Yes, *N* (%)	85 (44.9)	41 (58.9)	15 (35.7)	17 (42.5)	12 (46.1)	$\chi^2 = 5.45$ $P = 0.141$
Cannabis use, Yes N (%)	68 (35.9)	26 (36.7)	10 (23.8)	15 (37.5)	13 (50.0)	$\chi^2 = 4.73$ $P = 0.192$
Cocaine use, Yes *N* (%)	16 (8.4)	5 (6.3)	0 (0)	7 (17.5)	4 (14.8)	$\chi^2 = 9.51$ $P = 0.023$
Pharmacological Variables						
Antipsychotic. *N* (%)						$\chi^2 = 119.46$ $P < 0.001$
Amisulpride	3 (1.7)	1 (1.3)	1 (2.5)	1 (2.9)	0 (0.0)	$\chi^2 = 0.9$ $P = 0.81$
Aripiprazole	24 (13.6)	11 (14.6)	4 (10.0)	6 (17.6)	3 (12.0)	$\chi^2 = 9.5$ $P = 0.02$
Clozapine	6 (3.4)	2 (2.6)	0 (0.0)	3 (8.8)	0 (0.0)	$\chi^2 = 6.2$ $P = 0.100$
Haloperidol	3 (1.7)	1 (1.3)	0 (0.0)	2 (5.8)	0 (0.0)	$\chi^2 = 4.7$ $P = 0.19$
Olanzapine	32 (18.2)	30 (37.9)	11 (27.5)	10 (27.4)	10 (40.0)	$\chi^2 = 2.7$ $P = 0.44$
Paliperidone	13 (7.4)	8 (10.6)	1 (2.5)	3 (8.8)	1 (4.0)	$\chi^2 = 3.1$ $P = 0.380$
Quetiapine	12 (6.8)	8 (10.6)	2 (5.0)	1 (2.9)	1 (4.0)	$\chi^2 = 3.0$ $P = 0.383$
Risperidone	53 (30.1)	14 (18.6)	21 (52.5)	8 (23.5)	10 (40.0)	$\chi^2 = 12.8$ $P = 0.005$
AP combination, Yes, *N* (%)	45 (25.6)	14 (18.7)	10 (25.0)	11 (32.3)	9 (36.0)	$\chi^2 = 4.8$ $P = 0.312$
AP change, Yes *N* (%)	80 (43.9)	30 (39.5)	17 (41.4)	20 (50.0)	13 (50.0)	$\chi^2 = 2.24$ $P = 0.523$
CEDD, mean ± SD	603.0 ± 465.3	552.75 ± 456.6	538.40 ± 361.5	676.94 ± 555.0	761.60 ± 496.2	$F = 1.37$ $P = 0.245$
Non-Adherent, *N* (%)†	37 (33.6)	15 (35.7)	8 (27.5)	10 (41.6)	4 (26.6)	$\chi^2 = 1.6$ $P = 0.664$
Co-medications *N* (%)						
Mood stabilizers	12 (6.3)	9 (11.4)	1 (2.4)	1 (2.5)	1 (3.7)	$\chi^2 = 5.82$ $P = 0.213$
Antidepressants	33 (17.4)	10 (12.6)	9 (21.4)	8 (20.0)	6 (22.2)	$\chi^2 = 2.93$ $P = 0.664$
Anxiolytics	85 (44.7)	37 (46.8)	20 (47.6)	13 (32.5)	14 (51.8)	$\chi^2 = 1.76$ $P = 0.779$
Environmental factors						
Paternal Age (years), mean ± SD	32.77 ± 6.8	31.64 ± 5.4	35.35 ± 7.1	32.47 ± 7.8	31.9 ± 6.9	$F = 1.97$ $P = 0.101$

Table 1. (Continued)

	All	Clusters				Statistic‡
		A	B	C	D	
Maternal Age (years), mean ± SD	29.32 ± 5.6	28.83 ± 4.9	30.46 ± 5.4	28.57 ± 6.6	30.37 ± 6.3	$F = 0.96$ $P = 0.432$
Obstetric Complications, Yes *N* (%)	39 (24.4)	15 (23.4)	6 (15.7)	11 (30.5)	7 (30.4)	$\chi^2 = 3.14$ $P = 0.374$
Traumatic Experience, Yes *N* (%)	103 (56.6)	44 (57.9)	26 (63.4)	22 (55.0)	14 (53.8)	$\chi^2 = 0.82$ $P = 0.843$

AP, antipsychotic; CEDD, chlorpromazine equivalent daily dose; DTP, duration of treatment psychosis; DUP, duration of untreated psychosis; PANSS, Positive and Negative Syndrome Scale; PAS, premorbid adjustment scale; pIQ, premorbid intelligent quotient; UKU, Udvalg for Kliniske Undersøgelser side-effect rating scale.

*Assessed at two months.

†Assessed from plasma levels ($N = 110$).

‡Post hoc Bonferroni significant tests ($P < 0.05$): [1]A vs. B; [2]A vs. C; [3]A vs. D; [4]B vs. C; [5]B vs. D; [6]C vs. D.

and twelve months ($P < 0.001$). However, after two years, cluster C worsened until it was equal to cluster D. Significant differences could also be observed between cluster C and D regarding general symptoms after six ($P < 0.001$) and twelve months ($P = 0.021$).

As FEP could be heterogeneous in terms of final diagnostic, we explored differences at baseline in mood symptoms (items 1 and 2 of the PANSS negative subscale and item 6 of the PANSS general subscale) and impulsivity (item 14 of the PANSS general subscale) between clusters. Regarding mood symptoms, significant differences were observed for items 1 and 2 of the negative subscale ($P < 0.001$), with cluster C showing higher punctuations than cluster A and B (item 1 $P < 0.001$ vs. A and $P = 0.01$ vs. B; item 2 $P < 0.001$ vs. A and $P = 0.03$ vs. B) but not significantly different from cluster D. Clusters C and D had also higher scores in impulsivity than clusters A (C vs. A $P = 0.001$, D vs. A $P = 0.008$) and B (C vs. B $P < 0.001$, B vs. B $P = 0.001$). We also analyzed differences in the diagnosis at the end of the two-year follow-up period, but no significant differences were observed.

We also analyzed the trajectories of the main side-effects reported during the first year of the follow-up: EPS, hyperprolactinemia, and weight gain (Figure 2, Table S1). As it can be observed, differences between clusters in UKU trajectories seem to be related to the SAS score ($F_3 = 20.52$, $P < 0.001$). Following UKU scores, clusters B and D presented significantly higher rates of EPS than clusters A and C (B or D vs. A or C $P < 0.001$). Cluster D showed the most severe scores for EPS (D vs. B $P = 0.008$). Males from cluster B also showed higher levels of prolactin than cluster A after one year ($P = 0.05$). Interestingly, patients from cluster B were more often treated with risperidone than clusters A and C. No significant differences in the waist circumference increase trajectories were observed between clusters ($F_3 = 3.43$, $P > 0.01$). Cluster A showed less propensity to increase waist circumference after one year compared to clusters B ($P = 0.02$), C ($P = 0.04$) and D ($P = 0.05$).

Discussion

In the present study, we show that by using longitudinal data concerning overall efficacy and tolerability from FEP patients, four clusters of AP response can be identified. These clusters correspond to the classic pharmacogenetic phenotypes (32): cluster A, drug not toxic and beneficial; cluster B, drug beneficial but toxic; cluster C, drug neither toxic nor beneficial; and cluster D, drug toxic and not beneficial. We also demonstrated that baseline clinical characteristics could be useful in the field of personalized medicine to predict the response phenotype from these four and to apply individualized treatment. Our results are especially relevant if we take into account that they were obtained with FEP patients (33) and FEP recovery has come into focus as the main goal of any treatment strategy (34, 35).

Baseline patient and clinical characteristics of FEP individuals can be used to predict their response phenotype (17). The variables identified in our study have repeatedly been associated with poor adherence and risk of relapse (36, 37).

A lack of insight into the illness is the main cause of treatment non-adherence in patients with schizophrenia (38). In FEP patients, a negative attitude to medication predicts non-adherence (39). In our study, we found significant differences in insight between the four clusters, but none in the case of adherence. Insight deficit has been related to other symptoms in FEP patients: symptom severity (40), and more disorganized and negative symptoms, as well as to a lesser extent, impaired cognition (41). In our study, clusters with poorer insight suffered increased symptom severity and showed cognitive deficits.

Poor premorbid adjustment is considered a predictor of poor outcome and may be a non-specific

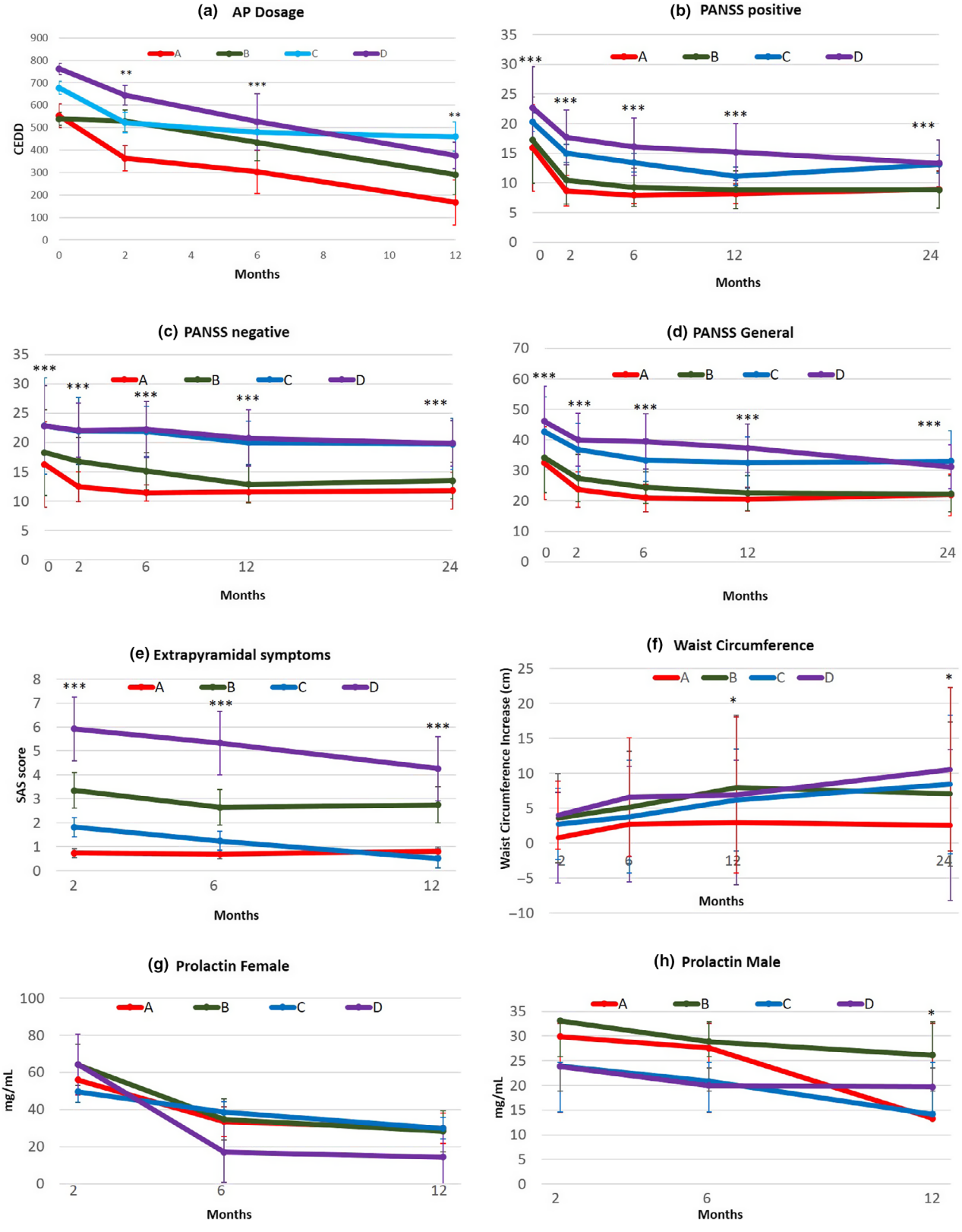

Fig. 2. Trajectories during the follow-up period for each cluster of: (a) the AP dosage; (b) the Positive PANSS scale; (c) the Negative PANSS scale; (d) the Generalized PANSS scale; (e) extrapyramidal symptoms; (f) waist circumference; (g) prolactin levels in female; and (h) prolactin levels in male (*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$).

marker of greater neurodevelopmental disturbances with a negative effect on the outcome (42). Accordingly, in our sample, clusters with poor PAS are related to increased symptom severity and received higher AP dosage. Other patient-related variables, such as family history of psychosis (in our study more frequent in cluster D), have been related to poor outcome in a large FEP cohort (43).

Among illness variables, longer DUP is the most common factor as a predictor of poor response to AP (37). DUP affects treatment response, remission, and relapse liability (44, 45). Earlier illness onset, especially during childhood and adolescence, has traditionally been seen as a negative prognostic factor, as confirmed by several studies. However, there is emerging evidence that the effect of earlier illness onset may, at least in part, be mediated by longer illness duration and more relapses (46); in our study with FEP, the clusters did not differ in illness duration. Greater severity of all aspects of psychopathology (positive, negative, and general) was correlated with impaired insight and functional status (37). Finally, substance abuse and dependence are comorbidities that interfere with treatment outcomes in schizophrenia, typically indicating higher disease burden and greater non-adherence (47). Among all the variables described above, in our study, poor premorbid adjustment and illness severity were related to efficacy as they allowed differentiation between clusters that could be considered responders to AP treatment (clusters A and B) from those with poor response (clusters C and D). DUP and insight could be useful to differentiate those clusters with significant side-effects than from those without in responders and no responders groups, as showed by the significant differences between clusters A and B and between clusters C and D.

Neurocognitive deficits have also been well established in FEP as independent disease characteristics in addition to symptomatology, but their effects on outcome parameters are less well understood (48). Better performance on baseline neurocognitive testing across multiple domains, particularly verbal memory, was strongly associated with the likelihood of remission, medication response, and continuation of antipsychotic treatment in the Clinical Antipsychotic Trial of Intervention Effectiveness (CATIE) trial (49). In our study with FEP, verbal memory was one of the factors significantly different between clusters that could be considered responders to AP treatment (clusters A and B) from those with poor response (clusters C and D). This result is in agreement with meta-analytic data suggesting verbal memory as a particularly good predictor of a variety of outcomes (50).

The phenotypes of AP response identified in our study open the door to applying personalized prescription. Each cluster could benefit from differences in the efficacy and toxicity of Aps (2, 51), and from other therapeutic approaches (52–54). Part of the reason for a lack of observed efficacy with several of these strategies (52–54) could be that they have been applied to the wrong patients. The response phenotypes reported herein could improve application of these therapeutic strategies. Clusters with poor response could also benefit from different strategies to improve response: improving patient communication, the use of psychoeducational interventions, cognitive-behavioral therapy (CBT), individual and family interventions, or long-acting injectable APs (55).

According to clinical guidelines (14), and taking into account the limitations of the present study in the interpretation of our results, we suggest the following recommendations for each cluster. Patients belonging to cluster A could be considered good responders, showing effective control of all symptoms after two months of AP treatment with few adverse effects. Therefore, they could be treated with any SGA recommended for FEP (risperidone, olanzapine, amisulpride). Cluster B patients showed appropriate control of positive symptoms after two months of AP treatment, but the control of negative and general symptoms required one year of treatment, associated with hyperprolactinemia and extrapyramidal symptoms. They should be treated with low doses of AP, avoiding AP with high incidence of EPS (ie, risperidone) and any strategy that may increase adverse reactions (ie, polypharmacy of PA). Cluster C patients showed partial response to AP, controlling the positive symptoms after one year, but persisting in the negative and general symptoms after two years of AP medication. The absence of hyperprolactinemia and EPS may allow the use of high doses and the search for other strategies to control their symptoms. Finally, cluster C patients could be considered non-responders, with persistent positive, negative, and general symptoms after two years of AP treatment and serious side-effects. These patients could be candidates for early clozapine trials.

Some limitations should be considered when interpreting our results. Firstly, although our sample comprised patients with FEP, representing a homogeneous clinical population, they are not antipsychotic-naïve patients. Taking into account that the mean duration of previous treatment was more than four weeks, differences in trajectories between clusters could be due to differences in the starting treatment implementation. However, days of treated psychosis did not show significant

differences between clusters; in fact, cluster D, that showed the highest symptom severity, had the lowest values of previous exposure to antipsychotic. Secondly, the sample size, although represents one of the largest cohorts of FEP patients with longitudinal data in the literature, limits its statistical power and did not allow the study of subgroups according to, for example, different antipsychotic drugs.

In conclusion, despite the limitations of our study, the results presented here allow phenotypes of AP response to be identified which can then be used to apply individualized treatment by using simple and classic clinical variables. Further studies are needed to establish the biological basis beyond these clusters, using both genetics and neuroimaging. If the results presented here are replicated in independent cohorts, and related to long-term response outcomes, they open the door to modifications of current clinical guidelines, adding more accurate recommendations on FEP AP treatment.

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Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Descriptive values, sample size and statistics of those variables (PANSS, UKU, SAS, Prolactin, Waist Circumference, CEDD) included in the present study.

Appendix 1

PEPs Group

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