Supplementary material

Metabolomics approach revealed robust changes in amino acid and biogenic amine signatures in patients with schizophrenia in the early course of the disease

Madis Parksepp, Liisa Leppik, Kadri Koch, Kärt Uppin, Raul Kangro, Liina Haring*, Eero Vasar, Mihkel Zilmer (Corresponding author* Liina.Haring@kliinikum.ee)

Table S1. Serum mean levels, standard deviations (SD), and range of amino acids (micromoles) for control subjects (CSs, n=37), first-episode psychosis (FEP) patients at baseline (before treatment with antipsychotics, $FEP_{b,}$ n=52), after 0.6-year treatment ($FEP_{0.6\text{-year,}}$ n=44), and after 5.1-year treatment ($FEP_{5.1\text{-year,}}$ n=37) with antipsychotics. Comparison between reduced and unrestricted models, *p*-values have been multiple test corrected according to false discovery rate (FDR) method. The unrestricted regression model is designated as True (i.e. more complex set of predictor variables explained more effectively biomarker level alterations over time) or False (i.e. unrestricted model did not provide more explanatory power than a simple one).

Regression equations for estimating biomarker level or biomarkers ratio alterations.	
Reduced model	log(biomarker)~Age+BMI+Gender+Smoking+(1|Patient)
Unrestricted model	log(biomarker)~Age+BMI+Gender+Smoking+Visit+Time1+Time2+(1|Patient)

BMI = body mass index, Visit = biomarker measurements at three time points in patients' group, Time1 = time difference between FEP_b and $FEP_{0.6\text{-year}}$, Time2 = time difference between $FEP_{0.6\text{-year}}$ and $FEP_{5.1\text{-year}}$, (1|Patient) = random effects of patients.

Amino acids	**CSs**	**FEP_b**	**$FEP_{(0.6\text{-year})}$**	**$FEP_{(5.1\text{-year})}$**	**Comparison between models**	
	Mean ± SD (range)	**Mean ± SD (range)**	**Mean ± SD (range)**	**Mean ± SD (range)**	**Adjusted *p*-value**	**True (T) or false (F)**
Alanine	425 ± 118 (232 – 716)	387 ± 112 (206 – 673)	462 ± 134 (290 – 750)	520 ± 171 (289 – 953)	0.03	T
Arginine	163 ± 36.1 (94.1 – 225)	144 ± 32.6 (75.9 – 216)	155 ± 35.5 (93.0 – 263)	143 ± 49.8 (72.5 – 327)	0.08	F
Asparagine	37.2 ± 13.0 (15.0 – 65.2)	33.8 ± 12.6 (4.80 – 83.3)	35.7 ± 14.1 (8.06 – 75.5)	53.2 ± 17.4 (30.2 – 87.4)	2e-07	T
Aspartate	35.3 ± 10.7 (15.9 – 65.2)	33.8 ± 14.3 (10.6 – 62.9)	29.9 ± 11.5 (7.86 – 57.4)	19.0 ± 7.14 (5.11 – 39.6)	7e-06	T
Citrulline	27.8 ± 8.37 (11.0 – 48.9)	22.5 ± 5.77 (12.1 – 38.1)	25.0 ± 6.66 (11.5 – 39.4)	29.1 ± 13.7 (14.1 – 76.7)	9e-03	T
Glutamine	342 ± 153 (76.5 – 683)	328 ± 148 (80.4 – 813)	365 ± 176 (103 – 810)	854 ± 308 (495 – 1760)	4e-18	T
Glutamate	216 ± 99.2 (114 – 550)	250 ± 116 (59.6 – 627)	241 ± 121 (57.2 – 529)	74.1 ± 40.1 (18.7 – 172)	1e-25	T
Glycine	257 ± 72.1 (123 – 443)	278 ± 65.1 (153 – 474)	287 ± 81.9 (149 – 597)	297 ± 81.5 (187 – 518)	0.41	F
Histidine	94.0 ± 20.9 (58.3 – 138)	86.4 ± 14.8 (61.5 – 135)	97.7 ± 16.1 (73.3 – 136)	107 ± 21.1 (66.4 – 157)	9e-03	T
Isoleucine	92.2 ± 30.2 (50.1 – 179)	86.8 ± 22.7 (42.7 – 158)	95.4 ± 29.5 (43.9 – 190)	96.1 ± 28.0 (46.4 – 164)	0.95	F
Leucine	176 ± 68.9 (79.6 – 409)	166 ± 47.6 (73.0 – 279)	174 ± 56.8 (85.5 – 364)	200 ± 78.4 (77.0 – 443)	0.69	F
Lysine	203 ± 46.4 (107 – 309)	205 ± 51.8 (117 – 314)	217 ± 56.0 (103 – 399)	231 ± 55.6 (124 – 393)	0.69	F
Methionine	10.2 ± 6.37 (4.43 – 35.2)	9.89 ± 6.36 (3.95 – 26.3)	12.0 ± 7.38 (3.23 – 33.5)	27.7 ± 7.76 (13.2 – 43.0)	1e-18	T
Ornithine	55.8 ± 17.2 (23.4 – 91.4)	66.7 ± 25.2 (30.7 – 143)	63.3 ± 20.0 (28.4 – 125)	81.5 ± 22.1 (39.9 – 136)	8e-03	T
Phenylalanine	71.0 ± 19.7 (38.2 – 115)	70.7 ± 12.5 (41.8 – 101)	68.9 ± 15.2 (38.2 – 108)	77.0 ± 20.1 (43.6 – 134)	0.44	F
Proline	229 ± 79.2 (123 – 479)	184 ± 55.5 (83.3 – 381)	237 ± 55.4 (140 – 362)	261 ± 91.2 (111 – 459)	7e-05	T
Serine	170 ± 52.3 (69.3 – 363)	174 ± 43.9 (99.4 – 293)	168 ± 34.4 (115 – 253)	159 ± 55.2 (88.9 – 346)	0.69	F
Threonine	165 ± 60.2 (74.1 – 373)	144 ± 35.0 (71.6 – 214)	160 ± 38.1 (71.0 – 280)	151 ± 62.3 (82.7 – 430)	0.44	F
Tryptophan	74.2 ± 17.0 (32.8 – 120)	66.9 ± 16.7 (30.3 – 120)	71.7 ± 18.4 (34.2 – 121)	82.4 ± 25.9 (46.1 – 157)	0.02	T
Tyrosine	73.0 ± 27.9 (33.7 – 159)	60.7 ± 13.8 (35.8 – 99.8)	70.7 ± 19.4 (40.6 – 121)	77.2 ± 23.6 (40.4 – 138)	0.09	F
Valine	233 ± 62.1 (126 – 401)	219 ± 61.7 (112 – 413)	244 ± 67.0 (136 – 448)	305 ± 83.7 (155 – 490)	7e-03	T

Table S2. Serum mean levels, standard deviations (SD), and range of biogenic amines (micromoles) for control subjects (CSs, n=37), first-episode psychosis (FEP) patients at baseline (before treatment with antipsychotics, $FEP_{b,}$ n=52), after 0.6-year treatment ($FEP_{0.6\text{-year,}}$ n=44), and after 5.1-year treatment ($FEP_{5.1\text{-year,}}$ n=37) with antipsychotics. Comparison between reduced and unrestricted models, *p*-values have been multiple test corrected according to false discovery rate (FDR) method. The unrestricted regression model is designated as True (i.e. more complex set of predictor variables explained more effectively biomarker level alterations over time) or False (i.e. unrestricted model did not provide more explanatory power than a simple one).

Biogenic amines	**CSs**	**FEP_b**	**$FEP_{(0.6\text{-year})}$**	**$FEP_{(5.1\text{-year})}$**	**Comparison between models**	
	Mean ± SD (range)	**Mean ± SD (range)**	**Mean ± SD (range)**	**Mean ± SD (range)**	**Adjusted p-value**	**True (T) or false (F)**
Acetylornithine	0.68 ± 0.36 (0.18 – 2.03)	0.69 ± 1.24 (0.00 – 8.98)	0.67 ± 0.47 (0.00 – 2.63)	0.74 ± 0.68 (0.00 – 2.68)	0.95	F
Alpha-aminoadipic acid	0.90 ± 0.40 (0.45 – 1.98)	0.55 ± 0.34 (0.00 – 1.34)	0.75 ± 0.38 (0.00 – 1.54)	0.40 ± 0.45 (0.00 – 1.59)	1e-06	T
Asymmetric dimethylarginine	0.42 ± 0.08 (0.19 – 0.60)	0.44 ± 0.10 (0.28 – 0.67)	0.44 ± 0.09 (0.29 – 0.63)	0.58 ± 0.19 (0.26 – 1.19)	0.008	T
Creatinine	69.4 ± 18.4 (35.0 – 112)	68.3 ± 16.2 (39.1 – 123)	69.7 ± 17.6 (42.0 – 124)	79.9 ± 32.5 (33.2 – 187)	0.51	F
Histamine	0.41 ± 0.04 (0.37 – 0.46)	0.34 ± 0.14 (0.12 – 0.46)	0.36 ± 0.12 (0.12 – 0.45)	0.28 ± 0.21 (0.00 – 0.57)	0.27	F
Kynurenine	2.71 ± 0.52 (1.37 – 3.89)	2.47 ± 0.85 (1.39 – 5.42)	3.02 ± 0.74 (1.77 – 4.88)	3.50 ± 2.05 (1.86 – 14.9)	3e-04	T
Putrescine	0.09 ± 0.04 (0.03 – 0.20)	0.11 ± 0.06 (0.02 – 0.32)	0.09 ± 0.04 (0.03 – 0.21)	0.14 ± 0.04 (0.06 – 0.23)	5e-03	T
Serotonin	0.76 ± 0.35 (0.19 – 1.47)	0.70 ± 0.40 (0.08 – 1.82)	0.65 ± 0.38 (0.05 – 1.48)	0.79 ± 0.47 (0.02 – 1.84)	0.25	F
Symmetric dimethylarginine	0.55 ± 0.10 (0.39 – 0.81)	0.56 ± 0.13 (0.28 – 0.93)	0.53 ± 0.12 (0.25 – 0.80)	0.65 ± 0.25 (0.32 – 1.49)	0.21	F
Taurine	49.0 ± 18.1 (25.8 – 116)	90.1 ± 31.6 (32.4 – 172)	51.4 ± 17.4 (28.2 – 119)	85.4 ± 31.8 (38.4 – 159)	2e-15	T

Table S3. Serum mean levels, standard deviations (SD), and range of biomarker ratios for control subjects (CSs, n=37), first-episode psychosis (FEP) patients at baseline (before treatment with antipsychotics, $FEP_{b,}$ n=52), after 0.6-year treatment ($FEP_{0.6\text{-year,}}$ n=44), and after 5.1-year treatment ($FEP_{5.1\text{-year,}}$ n=37) with antipsychotics. Comparison between reduced and unrestricted models, *p*-values have been multiple test corrected according to false discovery rate (FDR) method. The unrestricted regression model is designated as True (i.e. more complex set of predictor variables explained more effectively biomarker level alterations over time) or False (i.e. unrestricted model did not provide more explanatory power than a simple one).

Biomarker ratios	**CSs**	**FEP_b**	**$FEP_{(0.6\text{-year})}$**	**$FEP_{(5.1\text{-year})}$**	**Comparison between models**	
	Mean ± SD (range)	**Mean ± SD (range)**	**Mean ± SD (range)**	**Mean ± SD (range)**	**Adjusted p-value**	**True (T) or false (F)**
Alpha-aminoadipic acid / Kynurenine	0.33 ±0.13 (0.15 – 0.70)	0.24 ± 0.15 (0.00 – 0.65)	0.25 ± 0.14 (0.00 – 0.79)	0.12 ± 0.15 (0.00 – 0.61)	4e-05	T
Aspartate / Asparagine	1.07 ± 0.54 (0.43 – 3.07)	1.11 ± 0.57 (0.36 – 2.71)	0.98 ± 0.54 (0.27 – 2.44)	0.38 ± 0.15 (0.15 – 0.77)	2e-15	T
Glutamate / Glutamine	1.01 ±1.35 (0.20 – 7.18)	1.18 ± 1.37 (0.09 – 7.80)	0.99 ± 0.98 (0.08 – 5.14)	0.09 ± 0.05 (0.02 – 0.25)	2e-26	T
Ornithine / Arginine	0.35 ± 0.11 (0.16 – 0.66)	0.48 ± 0.20 (0.22 – 1.24)	0.42 ± 0.13 (0.23 – 0.81)	0.61 ± 0.21 (0.30 – 1.14)	2e-06	T
Tyrosine / Phenylalanine	1.03 ±0.23 (0.49 – 1.57)	0.86 ± 0.16 (0.61 – 1.28)	0.95 ± 0.49 (0.37 – 2.36)	1.01 ± 0.18 (0.61 – 1.32)	6e-04	T

Table S4. Estimated effects of complex set of predictor variables on amino acids serum concenrations between control subjects (CSs, n=37), first-episode psychosis (FEP) patients at baseline (before treatment with antipsychotics, $FEP_{b,}$ n=52), after 0.6-year treatment ($FEP_{0.6\text{-year},}$ n=44), and after 5.1-year treatment ($FEP_{5.1\text{-year},}$ n=37) with antipsychotics: results from linear mixed-effects model.

Amino acids	Intercept	Age	Gender	Body mass index	Smoking status	Disease and treatment effect			Time between $FEP_{(b)}$ and $FEP_{(0.6\text{-year})}$	Time between $FEP_{(0.6\text{-year})}$ and $FEP_{(5.1\text{ year})}$
						FEP patients before treatment	FEP patients after 0.6-year treatment	FEP patients after 5.1-year treatment		
	Estimate (standard error), *p*-value									
Alanine	3.67 (0.24), *p*<1e-04	-0.001 (0.004), ns	-0.04 (0.05), ns	0.01 (0.007), ns	0.09 (0.06), ns	-0.11 (0.06), ns	0.04 (0.07), ns	0.10 (0.08), ns	0.18 (0.62), ns	0.06 (0.04), ns
Arginine	5.09 (0.16), *p*<1e-04	0.005 (0.004), ns	-0.07 (0.05), ns	-0.004 (0.006), ns	-0.02 (0.05), ns	-0.14 (0.06), *p*=0.01	-0.07 (0.06), ns	-0.18 (0.07), *p*=0.01	0.31 (0.56), ns	0.04 (0.03), ns
Asparagine	4.10 (0.26), *p*<1e-04	-0.01 (0.006), ns	-0.06 (0.08), ns	-0.008 (0.01), ns	-0.10 (0.09), ns	-0.07 (0.09), ns	-0.003 (0.10), ns	**0.53 (0.11), *p*<1e-04**	1.88 (0.71), *p*=0.01	0.04 (0.05), ns
Aspartate	5.09 (0.16), *p*<1e-04	-0.005 (0.006), ns	-0.04 (0.07), ns	0.001 (0.009), ns	-0.14 (0.08), ns	-0.07 (0.09), ns	-0.19 (0.10), ns	**-0.59 (0.11), *p*<1e-04**	-0.68 (0.89), ns	0.08 (0.05), ns
Citrulline	3.46 (0.21), *p*<1e-04	-0.0001 (0.005), ns	-0.03 (0.06), ns	-0.007 (0.008), ns	0.02 (0.06), ns	-0.20 (0.07), *p*=0.006	-0.06 (0.08), ns	0.02 (0.09), ns	1.21 (0.67), ns	0.05 (0.04), ns
Glutamine	6.37 (0.28), *p*<1e-04	-0.01 (0.01), *p*=0.03	0.06 (0.08), ns	-0.01 (0.01), ns	0.06 (0.08), ns	0.02 (0.10), ns	0.18 (0.11), ns	**1.16 (0.13), *p*<1e-04**	2.04 (0.80), *p*=0.01	0.10 (0.06), ns
Glutamate	4.42 (0.28), *p*<1e-04	0.02 (0.01), *p*=0.03	-0.43 (0.09), *p*<1e-04	0.03 (0.01), *p*=0.003	0.11 (0.09), ns	0.002 (0.10), ns	-0.17 (0.10), ns	**-1.50 (0.12), *p*<1e-04**	-1.13 (0.74), ns	-0.07 (0.06), ns
Glycine	5.53 (0.17), *p*<1e-04	0.003 (0.004), ns	0.03 (0.05), ns	-0.006 (0.006), ns	0.08 (0.05), ns	0.07 (0.06), ns	0.11 (0.06), ns	0.12 (0.07), ns	0.81 (0.54), ns	-0.005 (0.03), ns
Histidine	4.40 (0.12), *p*<1e-04	-0.003 (0.003), ns	-0.07 (0.03), *p*=0.04	0.01 (0.004), *p*=0.03	0.02 (0.04), ns	-0.08 (0.04), ns	0.02 (0.04), ns	0.09 (0.05), ns	0.07 (0.38), ns	-0.002 (0.03), ns

(continued)

Table S4. (continued)

Amino acids	Intercept	Age	Gender	Body mass index	Smoking status	Disease and treatment effect			Time between FEP(b) and FEP(0.6-year)	Time between FEP(0.6-year) and FEP(5.1 year)
						FEP patients before treatment	FEP patients after 0.6-year treatment	FEP patients after 5.1-year treatment		
	Estimate (standard error), *p*-value									
Isoleucine	4.34 (0.17), *p*<1e-04	-0.005 (0.004), ns	-0.25 (0.05), *p*<1e-04	0.02 (0.006), *p*=0.008	-0.07 (0.05), ns	-0.06 (0.06), ns	-0.03 (0.06), ns	-0.03 (0.07), ns	0.04 (0.56), ns	0.03 (0.03), ns
Leucine	5.31 (0.20), *p*<1e-04	-0.005 (0.004), ns	-0.32 (0.05), *p*<1e-04	0.02 (0.007), *p*=0.006	-0.09 (0.06), ns	-0.06 (0.07), ns	-0.07 (0.07), ns	0.03 (0.08), ns	-0.005 (0.66), ns	0.005 (0.04), ns
Lysine	5.13 (0.16), *p*<1e-04	0.0002 (0.004), ns	-0.07 (0.05), ns	0.008 (0.006), ns	0.003 (0.05), ns	-0.009 (0.06), ns	0.03 (0.06), ns	0.07 (0.07), ns	0.12 (0.52), ns	-0.03 (0.03), ns
Methionine	2.94 (0.31), *p*<1e-04	-0.03 (0.007), *p*=8e-04	-0.07 (0.09), ns	-0.002 (0.01), ns	-0.19 (0.10), ns	0.03 (0.11), ns	0.25 (0.12), *p*=0.04	**1.35 (0.14), *p*<1e-04**	2.37 (0.98), *p*=0.04	0.03 (0.07), ns
Ornithine	3.97 (0.21), *p*<1e-04	0.00004 (0.005), ns	-0.15 (0.06), *p*=0.04	0.004 (0.008), ns	0.05 (0.06), ns	0.13 (0.07), ns	0.09 (0.08), ns	**0.32 (0.09), *p*=9e-04**	0.65 (0.64), ns	0.01 (0.04), ns
Phenylalanine	4.21 (0.15), *p*<1e-04	-0.004 (0.003), ns	-0.10 (0.04), *p*=0.03	0.008 (0.005), ns	-0.02 (0.04), ns	0.02 (0.05), ns	-0.04 (0.06), ns	0.07 (0.06), ns	-0.21 (0.50), ns	-0.008 (0.03), ns
Proline	5.31 (0.19), *p*<1e-04	0.001 (0.005), ns	-0.17 (0.06), *p*=0.004	0.005 (0.007), ns	0.07 (0.06), ns	**-0.25 (0.07), *p*=2e-04**	0.01 (0.07), ns	0.01 (0.08), ns	0.52 (0.61), ns	0.06 (0.04), ns
Serine	5.19 (0.17), *p*<1e-04	0.005 (0.004), ns	-0.01 (0.006), ns	-0.01 (0.006), ns	-0.02 (0.03), ns	0.03 (0.06), ns	0.02 (0.06), ns	-0.05 (0.07), ns	0.29 (0.56), ns	0.03 (0.03), ns
Threonine	5.15 (0.19), *p*<1e-04	-0.002 (0.005), ns	0.005 (0.06), ns	-0.003 (0.007), ns	0.04 (0.06), ns	-0.12 (0.07), ns	-0.02 (0.07), ns	-0.08 (0.08), ns	0.22 (0.60), ns	-0.006 (0.04), ns
Tryptophan	4.55 (0.16), *p*<1e-04	-0.008 (0.004), ns	-0.17 (0.05), *p*=5e-04	0.001 (0.006), ns	-0.02 (0.05), ns	-0.12 (0.06), *p*=0.04	-0.04 (0.06), ns	0.11 (0.52), ns	0.09 (0.52), ns	0.002 (0.03), ns
Tyrosine	4.05 (0.18), *p*<1e-04	-0.003 (0.004), ns	-0.13 (0.05), *p*=0.01	0.01 (0.006), *p*=0.04	-0.02 (0.05), ns	-0.16 (0.06), *p*=0.01	-0.05 (0.07), ns	0.001 (0.08), ns	-0.03 (0.59), ns	0.04 (0.04), ns
Valine	5.19 (0.16), *p*<1e-04	-0.002 (0.004), ns	-0.20 (0.05), *p*=1e-04	0.02 (0.006), *p*=0.005	-0.04 (0.05), ns	-0.08 (0.06), ns	-0.02 (0.06), ns	0.16 (0.07), *p*=0.02	0.19 (0.51), ns	0.02 (0.03), ns

Significant differences in the biomarker levels over time in the patients group compared to CSs are marked in bold.
ns: $p \geq 0.05$.

Table S5. Estimated effects of complex set of predictor variables on biogenic amines serum concenrations between control subjects (CSs, n=37), first-episode psychosis (FEP) patients at baseline (before treatment with antipsychotics, $FEP_{b,}$ n=52), after 0.6-year treatment ($FEP_{0.6\text{-year},}$ n=44), and after 5.1-year treatment ($FEP_{5.1\text{-year},}$ n=37) with antipsychotics: results from linear mixed-effects model.

	Intercept	**Age**	**Gender**	**Body mass index**	**Smoking status**	**Disease and treatment effect**			**Time between $FEP_{(b)}$ and $FEP_{(0.6\text{-year})}$**	**Time between $FEP_{(0.6\text{-year})}$ and $FEP_{(5.1\text{ year})}$**
						FEP patients before treatment	**FEP patients after 0.6-year treatment**	**FEP patients after 5.1-year treatment**		
Biogenic amines	**Estimate (standard error), *p*-value**									
Acetylornithine	-0.05 (0.49), ns	0.01 (0.01), ns	-0.06 (0.14), ns	0.02 (0.02), ns	-0.36 (0.15), *p*=0.02	0.04 (0.17), ns	-0.01 (0.18), ns	-0.01 (0.21), ns	0.42 (1.69), ns	-0.09 (0.10), ns
Alpha- amino-adipic acid	0.46 (0.23), ns	0.002 (0.006), ns	-0.24 (0.07), *p*=4e-04	0.02 (0.009), *p*=0.01	-0.07 (0.07), ns	**-0.37 (0.08), *p*<1e-04**	-0.25 (0.09), *p*=0.006	**-0.65 (0.10), *p*<1e-04**	0.81 (0.71), ns	-0.01 (0.05), ns
Asymmetric dimethylarginine	-1.00 (0.16), *p*<1e-04	0.0004 (0.004), ns	-0.02 (0.05), ns	0.005 (0.006), ns	0.08 (0.05), ns	0.03 (0.06), ns	0.03 (0.06), ns	0.23 (0.07), *p*=0.002	0.24 (0.50), ns	0.02 (0.03), ns
Creatinine	4.45 (0.17), *p*<1e-04	-0.006 (0.004), ns	-0.27 (0.05), *p*<1e-04	0.003 (0.006), ns	-0.07 (0.05), ns	-0.02 (0.06), ns	-0.02 (0.06), ns	0.11 (0.07), ns	0.23 (0.48), ns	-0.005 (0.04), ns
Histamine	0.53 (0.09), *p*<1e-04	-0.002 (0.002), ns	-0.03 (0.03), ns	-0.002 (0.003), ns	-0.03 (0.03), ns	-0.06 (0.03), *p*=0.04	-0.06 (0.03), ns	-0.09 (0.04), *p*=0.03	0.19 (0.17), ns	-0.006 (0.02), ns
Kynurenine	0.73 (0.17), *p*=1e-04	-0.005 (0.004), ns	-0.14 (0.06), *p*=0.006	0.02 (0.006), *p*=0.003	0.04 (0.05), ns	-0.14 (0.06), *p*=0.02	0.04 (0.06), ns	0.11 (0.08), ns	0.44 (0.54), ns	-0.07 (0.04), ns
Putrescine	-2.59 (0.31), *p*<1e-04	-0.002 (0.008), ns	-0.17 (0.09), ns	0.01 (0.01), ns	0.09 (0.10), ns	-0.003 (0.11), ns	-0.10 (0.11), ns	0.33 (0.13), *p*=0.02	-0.26 (0.96), ns	-0.04 (0.06), ns
Serotonin	0.03 (0.45), ns	0.007 (0.01), ns	-0.13 (0.13), ns	-0.02 (0.02), ns	0.31 (0.14), *p*=0.03	-0.24 (0.15), ns	-0.32 (0.17), ns	-0.21 (0.19), ns	0.72 (1.54), ns	-0.16 (0.09), ns
Symmetric dimethylarginine	-0.67 (0.16), *p*=1e-04	-0.003 (0.004), ns	-0.06 (0.05), ns	0.007 (0.006), ns	-0.05 (0.05), ns	0.02 (0.06), ns	-0.04 (0.06), ns	0.12 (0.07), ns	0.20 (0.57), ns	-0.01 (0.03), ns
Taurine	3.79 (0.21), *p*<1e-04	0.0002 (0.005), ns	-0.03 (0.06), ns	0.002 (0.008), ns	0.06 (0.07), ns	**0.59 (0.08), *p*<1e-04**	0.02 (0.08), ns	**0.51 (0.10), *p*<1e-04**	-0.87 (0.77), ns	-0.03 (0.05), ns

Significant differences in the biomarker levels over time in the patients group compared to CSs are marked in bold.
ns: $p \geq 0.05$.

Table S6. Estimated effects of complex set of predictor variables on biomarker ratios between control subjects (CSs, n=37), first-episode psychosis (FEP) patients at baseline (before treatment with antipsychotics, $FEP_{b,}$ n=52), after 0.6-year treatment ($FEP_{0.6\text{-year,}}$ n=44), and after 5.1-year treatment ($FEP_{5.1\text{-year,}}$ n=37) with antipsychotics: results from linear mixed-effects model.

Ratios of amino acids and biogenic amines	**Intercept**	**Age**	**Gender**	**Body mass index**	**Smoking status**	**Disease and treatment effect**			**Time between $FEP_{(b)}$ and $FEP_{(0.6\text{-year})}$**	**Time between $FEP_{(0.6\text{-year})}$ and $FEP_{(5.1\text{ year})}$**
						FEP patients before treatment	**FEP patients after 0.6-year treatment**	**FEP patients after 5.1-year treatment**		
	Estimate (standard error), *p*-value									
Alpha-amino-adipic acid / Kynurenine	0.28 (0.09), *p*=0.002	0.001 (0.002), ns	-0.05 (0.03), ns	0.003 (0.003), ns	-0.03 (0.03), ns	-0.10 (0.03), *p*=0.003	-0.10 (0.04), *p*=0.007	**-0.23 (0.04), *p*<1e-04**	0.21 (0.30), ns	0.02 (0.02), ns
Aspartate / Asparagine	-0.37 (0.29), ns	0.008 (0.007), ns	0.02 (0.09), ns	0.006 (0.01), ns	-0.06 (0.09), ns	0.007 (0.10), ns	-0.20 (0.11), ns	**-1.09 (0.13), *p*<1e-04**	-2.13 (1.02), *p*=0.04	0.06 (0.06), ns
Glutamate / Glutamine	-1.95 (0.49), *p*=1e-04	0.03 (0.01), *p*=0.02	-0.50 (0.14), *p*=8e-04	0.05 (0.02), *p*=0.01	0.18 (0.15), ns	-0.01 (0.17), ns	-0.36 (0.18), ns	**-2.65 (0.22), *p*<1e-04**	-3.26 (1.30), *p*=0.01	-0.14 (0.10), ns
Ornithine / Arginine	-1.10 (0.22), *p*<1e-04	-0.005 (0.005), ns	-0.08 (0.06), ns	0.007 (0.008), ns	0.08 (0.07), ns	**0.27 (0.07), *p*=4e-04**	0.163 (0.08), *p*=0.04	**0.50 (0.09), *p*<1e-04**	0.36 (0.66), ns	-0.02 (0.04), ns
Tyrosine / Phenylalanine	-0.16 (0.12), ns	0.001 (0.003), ns	-0.04 (0.03), ns	0.04 (0.005), ns	0.007 (0.04), ns	**-0.18 (0.04), *p*=2e-04**	-0.01 (0.05), ns	-0.07 (0.05), ns	-0.008 (0.44), ns	0.04 (0.03), ns

Significant differences in the biomarker ratio levels over time in the patients group compared to CSs are marked in bold.
ns: $p \geq 0.05$.