Table S1. Baseline values and changes of each efficacy measure at weeks 1, 2, 3, 4, and 6 for patients with schizophrenia receiving polypharmacy (N = 138) vs. monotherapy (N = 132 )

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Baseline score | |  | Score change  at Week 1 | |  | Score change  at Week 2 | |  | Score change  at Week 3 | |  | Score change  at Week 4 | |  | Score change  at Week 6 | |
| Measure | Mean (SD) | p a |  | Mean (SD) | p b |  | Mean (SD) | p b |  | Mean (SD) | p b |  | Mean (SD) | p b |  | Mean (SD) | p b |
| CGI-Sc  Polypharmacy  Monotherapy | 5.4 (0.8)  5.5 (1.0) | 0.47 |  | -0.5 (0.6)  -0.5 (0.7) | 0.65 |  | -0.9 (0.9)  -0.9 (0.9) | 0.61 |  | -1.1 (1.0)  -1.1 (1.0) | 0.84 |  | -1.3 (1.0)  -1.3 (1.1) | 0.55 |  | -1.4 (1.1)  -1. 5 (1.1) | 0.86 |
| PANSSd-Total  Polypharmacy  Monotherapy | 88.2 (17.8)  87.7 (18.9) | 0.80 |  | -7.2 (8.9)  -7.8 (9.4) | 0.59 |  | -11. 7 (12.5)  -12.2 (12.3) | 0.69 |  | -14.5 (14.4)  -14.8 (14.0) | 0.79 |  | -16.5 (15.8)  -17.0 (15.1) | 0.70 |  | -19.5 (17.6)  -19.3 (17.3) | 0.93 |
| PANSS-Positive  Polypharmacy  Monotherapy | 23.9 (6.1)  24.0 (6.0) | 0.92 |  | -2.6 (3.2)  -2.7 (3.3) | 0.79 |  | -3.9 (4.5)  -4.4 (4.2) | 0.38 |  | -4.9 (4.7)  -5.4 (4.7) | 0.42 |  | -5.6 (5.2)  -6.1 (5.0) | 0.45 |  | -6.6 (5.9)  -6.8 (5.6) | 0.79 |
| PANSS-Negative  Polypharmacy  Monotherapy | 19.9 (6.1)  19.6 (6.0) | 0.66 |  | -1.1 (2.1)  -1.2 (2.0) | 0.55 |  | -1.9 (3.1)  -2.1 (2.8) | 0.52 |  | -2.5 (3.7)  -2.4 (3.4) | 0.94 |  | -2. 9 (3.9)  -2.7 (3.8) | 0.85 |  | -3.4 (4.2)  -3.2 (4.4) | 0.78 |
| PANSS-General psychopathology  Polypharmacy  Monotherapy | 44.4 (8.5)  44.1 (10.0) | 0.78 |  | -3.5 (4.7)  -3.9 (5.4) | 0.55 |  | -5.9 (6.4)  -5.7 (6.8) | 0.94 |  | -7.1 (7.4)  -7.0 (7.5) | 0.99 |  | -8.0 (8.2)  -8.2 (8.1) | 0.70 |  | -9.5 (9.0)  -9.2 (9.0) | 0.84 |
| CDSS e  Polypharmacy  Monotherapy | 2.0 (3.4)  2.5 (4.0) | 0.34 |  | -0.9 (2.1)  -1.0 (2.2) | 0.56 |  | -1.1 (2.5)  -1.0 (2.7) | 0.13 |  | -1.3 (2.9)  -1.1 (2.6) | 0.05 |  | -1.3 (2.9)  -1.2 (2.9) | 0.10 |  | -1.4 (3.1)  -1.3 (3.0) | 0.06 |
| GAF f  Polypharmacy  Monotherapy | 32.8 (7.5)  33.8 (7.8) | 0.29 |  | 5.2 (5.4)  6.2 (6.5) | 0.18 |  | 9.0 (7.6)  9.9 (8.1) | 0.34 |  | 12.1 (9.0)  12.2 (9.3) | 0.85 |  | 14.5 (10.5)  14.8 (10.6) | 0.80 |  | 17.3 (11.6)  16.9 (12.6) | 0.85 |

aIndependent t-test; bp values were determined by analysis of covariance (ANCOVA), with sex, age, age at onset, and baseline value as covariate;

cCGI-S = Clinical Global Impression-Severity of Illness; dPANSS = Positive and Negative Syndrome Scale; eCDSS = Calgary Depression Scale for Schizophrenia; fGAF = Global Assessment of Functioning

Table S2. Baseline values and changes of AIM, SAS, BAS, body weight, BMI, pulse rate, systolic BP, and diastolic BP at weeks 1, 2, 3, 4, and 6 for patients with schizophrenia receiving

polypharmacy (N = 138) vs. monotherapy (N = 132 ) (cont’s)

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Baseline score | |  | Score change  at Week 1 | |  | Score change  at Week 2 | |  | Score change  at Week 3 | |  | Score change  at Week 4 | |  | Score change  at Week 6 | |
| Measure | Mean (SD) | p a |  | Mean (SD) | p b |  | Mean (SD) | p b |  | Mean (SD) | p b |  | Mean (SD) | p b |  | Mean (SD) | p b |
| AIMSc  Polypharmacy  Monotherapy | 0.5 (2.0)  0.4 (1.4) | 0.67 |  | 0.1 (0.8)  -0.001 (0.5) | 0.30 |  | 0.01 (1.1)  0.03 (1.0) | 0.96 |  | 0.03 (1.2)  0.1 (1.1) | 0.94 |  | 0.1 (1.2)  0.1 (1.1) | 0.85 |  | 0.1 (1.2)  -0.03 (1.3) | 0.42 |
| SASd  Polypharmacy  Monotherapy | 1.4 (2.4)  1.4 (2.1) | 0.86 |  | 0.3 (1.9)  0.4 (1.9) | 0.66 |  | -0.1 (1.8)  0.7 (2.8) | **0.01** |  | 0.03 (2.1)  0.9 (3.0) | **0.01** |  | 0.1 (1.8)  0.8 (2.9) | **0.01** |  | 0.1 (2.2)  0.7 (3.0) | 0.07 |
| BASe  Polypharmacy  Monotherapy | 0.8 (1.4)  0.8 (1.3) | 0.95 |  | 0.1 (1.1)  0.1 (1.4) | 0.86 |  | 0.1 (1.4)  0.3 (1.7) | 0.25 |  | 0.1 (1.5)  0.2 (1.7) | 0.37 |  | 0.1 (1.7)  0.1 (1.6) | 0.94 |  | -0.04 (1.6)  0.03 (1.6) | 0.72 |
| Body weight (kg)  Polypharmacy  Monotherapy | 67.7 (15.1)  67.6 (14.8) | 0.96 |  | -0.1 (1.6)  -0.1 (1.4) | 0.64 |  | 0.1 (2.1)  0.2 (2.2) | 0.79 |  | 0.1 (2.4)  0.1 (2.2) | 0.97 |  | 0.3 (2.7)  0.1 (2.5) | 0.59 |  | 0.4 (3.0)  0.2 (2.7) | 0.59 |
| BMIf (kg/m2)  Polypharmacy  Monotherapy | 25.0 (4.8)  25.2 (5.2) | 0.72 |  | -0.05 (0.6)  -0.02 (0.5) | 0.66 |  | 0.1 (0.8)  0.1 (0.8) | 0.77 |  | 0.04 (0.9)  0.04 (0.9) | 0.94 |  | 0.1 (1.0)  0.1 (0.9) | 0.70 |  | 0.2 (1.1)  0.1 (1.0) | 0.68 |
| Pulse rate (beat/min)  Polypharmacy  Monotherapy | 84.1 (13.7)  83.3 (13.3) | 0.64 |  | -1.6 (13.4)  0.2 (13.7) | 0.47 |  | -3.1 (14.8)  -1.5 (13.7) | 0.47 |  | -3.5 (14.7)  -2.6 (13.7) | 0.80 |  | -3.5 (15.1)  -2.4 (14.1) | 0.68 |  | -4.6 (15.1)  -3.3 (14.3) | 0.52 |
| Systolic BPg (mm Hg) Polypharmacy  Monotherapy | 113.4 (15.8)  113.7 (17.3) | 0.87 |  | -1.2 (14.7)  -0.7 (15.8) | 0.67 |  | -1.1 (16.7)  -3.0 (15.9) | 0.29 |  | -2.3 (16.6)  -2.6 (15.4) | 0.94 |  | -1.3 (17.4)  -3.9 (14.2) | 0.14 |  | 0.1 (15.6)  -2.5 (16.5) | 0.15 |
| Diastolic BP (mm Hg)  Polypharmacy  Monotherapy | 75.9 (12.6)  76.2 (11.5) | 0.82 |  | -1.9 (12.4)  -1.6 (10.8) | 0.69 |  | -3.1 (13.8)  -2.9 (12.2) | 0.77 |  | -2.7 (12.5)  -2.0 (10.5) | 0.50 |  | -1.9 (13.0)  -3.0 (11.1) | 0.45 |  | -1.5 (12.4)  -0.6 (11.4) | 0.34 |

aIndependent t-test; bp values were determined by analysis of covariance (ANCOVA), with sex, age, age at onset, and baseline value as covariates

cAIMS = Abnormal Involuntary Movement Scale; dSAS = Simpson-Angus Rating Scale; eBAS = Barnes Akathisia Scale; fBMI = body mass index; gBP = blood pressure

Table S3. Baseline values and changes of safety measure and quality of life between week 0 and week 6 for patients treated with

polypharmacy vs. those treated with monotherapy

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Measure | Baseline value | |  |  | Value change at week 6 | |  |
| n | Mean (SD) | pa | n | Mean (SD) | pb |
| QTc c interval (ms)  Polypharmacy  Monotherapy | 138  130 | 408.9 (22.4)  407.9 (25.3) | 0.75 |  | 95  88 | -2.2 (22.9)  0.6 (29.2) | 0.35 |
| Fasting glucose level (mg/dL)  Polypharmacy  Monotherapy | 138  132 | 82.6 (20.4)  82.9 (19.0) | 0.90 |  | 96  90 | 2.7 (19.7)  1.6 (25.4) | 0.56 |
| ALT e (GPT) (U/L)  Polypharmacy  Monotherapy | 138  132 | 28.8 (18.4)  29.6 (19.4) | 0.74 |  | 94  89 | 3.4 (29.9)  -0.8 (15.6) | 0.37 |
| AST f (GOT) (U/L)  Polypharmacy  Monotherapy | 138  132 | 25.5 (12.0)  25.8 (11.8) | 0.87 |  | 94  89 | 1.1 (20.9)  -1.8 (11.5) | 0.30 |
| BUN g (mg/dL)  Polypharmacy  Monotherapy | 138  132 | 9.9 (3.1)  10.5 (3.7) | 0.14 |  | 94  89 | -0.5 (3.3)  -0.6 (4.1) | 0.87 |
| Creatinine (mg/dL)  Polypharmacy  Monotherapy | 138  132 | 0.8 (0.2)  0.9 (0.2) | 0.45 |  | 94  89 | -0.01 (0.1)  0.01 (0.2) | 0.37 |
| Cholesterol (mg/dL)  Polypharmacy  Monotherapy | 134  126 | 174.8 (38.9)  174.3 (37.9) | 0.92 |  | 93  83 | 6.2 (36.4)  9.6 (41.9) | 0.94 |
| Triglycerides (mg/dL)  Polypharmacy  Monotherapy | 134  127 | 124.2 (58.6)  129.1 (75.2) | 0.55 |  | 90  84 | 27.4 (71.3)  15.8 (69.9) | 0.29 |
| HDL h (mg/dL)  Polypharmacy  Monotherapy | 132  125 | 48.0 (18.5)  49.1 (17.6) | 0.62 |  | 93  82 | 1.0 (9.0)  1.5 (9.3) | 0.62 |
| LDL i (mg/dL)  Polypharmacy  Monotherapy | 132  123 | 103.9 (33.9)  104.4 (29.7) | 0.90 |  | 93  80 | -1.3 (31.6)  1.6 (27.8) | 0.62 |
| Prolactin (ng/ml)  Polypharmacy  Monotherapy | 134  128 | 35.4 (46.8)  37.5 (45.0) | 0.71 |  | 94  88 | 21.2 (56.1)  36.5 (55.9) | 0.07 |
| PCS j  Polypharmacy  Monotherapy | 137  132 | 51.1 (7.4)  49.9 (6.8) | 0.18 |  | 99  91 | 1.5 (6.1)  1.6 (6.2) | 0.69 |
| MCS k  Polypharmacy  Monotherapy | 137  132 | 40.2 (11.0)  39.4 (11.0) | 0.56 |  | 99  91 | 2.6 (9.3)  2.4 (9.1) | 0.59 |

aIndependent t-test; bp values were determined by analysis of covariance (ANCOVA), with sex, age, age at onset, and baseline value as covariates

cQTc interval = Bazett’s correction of QT interval; eALT (GPT) = alanine aminotransferase; f AST (GOT) = aspartate aminotransferase; gBUN = blood urea nitrogen; hHDL = high density lipoprotein; iLDL = low density lipoprotein; jPCS = physical component summary of SF-36; kMCS = mental component summary of SF-36

Table S4. Side effects (determined by individual item of UKU Scale) occurring in at least 10% of the patients in either group, N (%)

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | Polypharmacy (N = 138) | |  | Monotherapy (N = 132) | |  |  |
| Adverse event |  | N | % |  | N | % |  | *p* |
| At least one adverse event |  | 118 | 85.5 |  | 118 | 89.4 |  | 0.34 a |
| Concentration difficulties |  | 18 | 13.0 |  | 16 | 12.1 |  | 0.82 a |
| Asthenia/increased fatiguability |  | 30 | 21.7 |  | 34 | 25.8 |  | 0.44 a |
| Sleepiness/sedation |  | 21 | 15.2 |  | 20 | 15.2 |  | 0.99 a |
| Failing memory |  | 20 | 14.5 |  | 22 | 16.7 |  | 0.62 a |
| Depression |  | 16 | 11.6 |  | 16 | 12.1 |  | 0.89 a |
| Tension /inner unrest |  | 28 | 20.3 |  | 26 | 19.7 |  | 0.90 a |
| Increased duration of sleep |  | 13 | 9.4 |  | 20 | 15.2 |  | 0.15 a |
| Reduced duration of sleep |  | 32 | 23.2 |  | 30 | 22.7 |  | 0.93 a |
| Increased dream activity |  | 17 | 12.3 |  | 26 | 19.7 |  | 0.10 a |
| Rigidity |  | 16 | 11.6 |  | 16 | 12.1 |  | 0.89 a |
| Hypokinesia /akinesia |  | 12 | 8.7 |  | 15 | 11.4 |  | 0.47 a |
| Tremor |  | 26 | 18.8 |  | 31 | 23.5 |  | 0.35 a |
| Akathisia |  | 26 | 18.8 |  | 20 | 15.2 |  | 0.42 a |
| Increased salivation |  | 23 | 16.7 |  | 24 | 18.2 |  | 0.74 a |
| Reduced salivation |  | 28 | 20.3 |  | 29 | 22.0 |  | 0.74 a |
| Constipation |  | 18 | 13.0 |  | 23 | 17.4 |  | 0.32 a |
| Polyuria/polydipsia |  | 21 | 15.2 |  | 24 | 18.2 |  | 0.51 a |
| Orthostatic dizziness |  | 11 | 8.0 |  | 17 | 12.9 |  | 0.19 a |
| Pruritus |  | 18 | 13.0 |  | 16 | 12.1 |  | 0.82 a |
| Weight gain |  | 44 | 31.9 |  | 39 | 29.5 |  | 0.68 a |
| Weight loss |  | 32 | 23.2 |  | 42 | 31.8 |  | 0.11 a |
| Headache |  | 15 | 10.9 |  | 16 | 12..1 |  | 0.75 a |

aPearson χ2 test