Supplemental Material for "Cost-Effectiveness of Second-Generation Antipsychotics and Perphenazine in a Randomized Trial of Treatment for Chronic Schizophrenia" by Rosenheck et al. (Am J Psychiatry 2006; 163:2080–2089)

Estimation of Service Costs

Costs in this study were estimated by multiplying the number of units of each type of health service received by the estimated local unit cost of each service, and then summing the products to reflect the total health care costs. Unit costs estimated for each type of service were specific to each of the 24 states in which CATIE sites were geographically located. Where only national unit cost estimates were available, they were adjusted for state wage rates (1). Cost estimates were derived from published sources documenting: inpatient costs in the various sectors in each state (2); nursing home costs (3); substance abuse treatment costs (4); and residential treatment costs (4). Unit costs of some services were estimated using claims data from the 2002 MarketScan® data set, a compilation of all mental health and medical insurance claims from over 500,000 private sector mental health service users, classified by diagnosis and CPT code. Some unit cost estimates were derived from VA administrative files (5–9).

Unit costs estimated from published reports and public databases, as described above, were not specific to the agencies delivering services at each site. In addition, estimates of service use were based on self-report data and could not be independently validated. Faulty recall of service use, however, was minimized by frequent assessments and by probing on many different types of service. Furthermore, the primary source of differences in costs was the price and dose of study medication, which were based on protocol implementation records, not self-report.

Costs were estimated from the perspective of total health care costs rather than society as a whole, and thus did not address the administrative cost of transfer (e.g. disability) payments (10), criminal justice costs (11) or productivity (employment earnings). Analysis of disability payments and incarceration showed some statistically significant differences between groups, but they were not large enough to have

affected our conclusions. Productivity was included as a benefit in the instrumental activity scale of the Quality of Life Scale, which was included in the Patient Preference Weighted Index (PPWI).

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Additional Outcome Measures

To complement the primary measure of effectiveness, based as it is on health state preferences of the general public, we also constructed a secondary measure based on the *individual* preferences of each CATIE participant at the time of each assessment, using methods that have been described in greater detail previously (1). To construct this Patient Preference Weighted Index (PPWI), patients first ranked the importance of improvement to them in six domains: social life, work, energy, symptoms, confusion, and side effects from 1 (most important) to 6 (least important). They then indicated how many times more important each domain was, to them personally, than the least important domain, with a possible range

from 1-99. The weight for each domain was then standardized by dividing each score by the largest of the six scores for that person (possible range 0.01 to 1.0).

These personal patient domain preferences were then used to weight actual outcome data addressing each of the six domains. Measures of patient status in each domain were converted to standardized scores (z scores) and averaged if there were more than one component measure. These scores were re-standardized, and then multiplied by the patient preference weights. Resulting measures for each of the six domains were themselves converted to standardized scores and averaged.

Specific domain measures were calculated as follows. Individual patient importance weights for social life were multiplied by the standardized score of the social activities subscale of the Quality of Life Scale (QOLS) (2). Individual patient importance weights for work were multiplied by the instrumental activities subscale of the QOLS. Individual patient importance weights for energy were multiplied by the average of three standardized measures: the intra-psychic activity subscale of the QOLS, the negative symptom factor from the PANSS, and the Calgary Depression scale (3). Individual patient importance weights for symptoms were applied to a standardized version of Lenert's positive symptom factor from the PANSS. Individual patient importance weights for confusion were applied to Lenert's standardized cognitive symptom factor. Individual patient importance weights for side effects were applied to the average of three standardized measures of extrapyramidal symptoms (4–6) and of the body mass index, a measure of obesity. Measures of symptoms and side effects were multiplied by –1 so that larger PPWI scores uniformly reflect better health. As noted above, the six patient-preference weighted domain scores were standardized (i.e., converted to z scores) and averaged to yield a final PPWI that reflected the clinical status in six domains weighted by their importance to each patient at the time of each particular assessment.

Quality of life was also evaluated with two self-rated global measures, the Visual Analog Scale, on which patients rate their health on a scale from 0 (worst state of health) to 100 (perfect health) and the Lehman global quality of life item (7), on which patients rate their overall quality of life on a scale from 1 (terrible) to 7 (delighted).

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Paired Comparisons of Individual Agents

The original report identified an overall group-by-time interaction for the PANSS total score—suggesting improvement was greatest with olanzapine but diminished over time—but did not present specific pairwise treatment comparisons. This report presents further details of paired comparisons between individual agents. Consistent with the original report, the paired comparisons on the PANSS reported here showed significant superiority of olanzapine over two other SGAs, risperidone and quetiapine (online supplement figure D). However, no significant difference was observed between olanzapine and perphenazine, the drugs with the lowest PANSS scores at each time point in the original report. On average olanzapine scored an estimated 2.0 PANSS points lower than perphenazine, with a 95% confidence interval of the difference in least square means in mixed model analysis of –3.7 to -0.02 (p=0.03, not significant after adjustment for multiple comparisons). Excluding all observations after the first medication change (i.e., the Phase 1 only analysis), the estimated mean difference was 1.5 points lower for olanzapine than perphenazine (95% CI=–3.3 to 0.03, p=0.11). Thus, we can be 97.5% confident (one-tailed test) that the differences in mean PANSS scores between olanzapine and perphenazine in this study was less than 3.7 points (5% of the baseline value). Previous research suggests that a clinically significant improvement is typically associated with a 20% difference in the PANSS (1).

After the inclusion of data on side effects, weight gain, and symptoms in the measure of QALYS, perphenazine scored 0.003 higher than the next best drug (olanzapine), although the differences were not statistically significant (95% CI 0.014 to –0.009). There were also no significant differences between any drugs on a complementary measure based on patient health state preferences (as contrasted with societal

preferences) or on two patient-rated global measures of quality of life (online supplemental figures E, F, and G).

The data presented in the initial CATIE report suggesting lower rates of hospitalization for schizophrenia associated with olanzapine, differ from those presented here, which show no differences in hospitalization between groups. While the earlier report was based exclusively on "serious adverse event" reporting of hospitalization, specifically for schizophrenia, data reported here were based on monthly, systematic questioning of patients about all types of hospitalization from each of several providers, and were specifically intended for cost purposes. The data presented in the earlier paper were thus neither as detailed nor as inclusive as the hospital utilization and related cost data presented here, which show no differences in inpatient utilization (online supplemental figure A) or cost (online supplemental figure B). There were no statistically significant differences among any pair of the four SGAs on either total costs, QALYs, or the other measures of effectiveness, with the exception of symptoms, on which olanzapine was superior to both risperidone and quetiapine.

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Re-analysis of Primary Outcomes Using Multiple Imputation to Address Missing Data

Because there was substantial missing data in CATIE, especially in the latter months of the 18 month trial, we conducted a re-analysis of central economic and effectiveness outcomes using multiple imputation (1–4), a statistical technique that uses available data to simulate missing data iteratively in multiple data sets and then replicates the analyses of these data sets adjusting standard errors for variability across the imputed data sets. As in the critical facet of the original analysis, we compare outcomes across patients randomly assigned to treatment with olanzapine (O), perphenazine (P), quetiapine (Q), and risperidone (R), with the exclusion of patients with TD at baseline, or those assigned to ziprasidone on two primary outcome measures: total health costs and QALYs, as well as on several subcomponents of cost and

secondary effectiveness measures such as the PANSS. The follow-up periods for the analysis of cost data were monthly from 1 to 18 months and all interviews conducted during each interval were included. The follow-up periods selected for analysis of QALYs included month 1 and quarterly time points from 3 to18 months, with all interviews conducted during each interval included. Because we planned to compare the three SGAs, O, Q and R, to P during the intervals following the baseline assessment we used generalized linear models for repeated measures.

Due to the fact that some participants had missing observations at various time intervals, we first used the multiple imputation method developed by Rubin (1–3) to impute missing responses. To impute a missing outcome of type *k* at time interval *j* for subject *i* (where *i*=1, 2, …, n represents a participant *i*; *j*=1,2,3..18 represents a time point *j*; and *k* represents an outcome measure *k*), we used linear and quadratic terms to represent time for each intervention group (i.e. interaction terms between time and group were created) and the most recent non-missing type *k* outcome measure from subject *i* was included as a covariate. The minimum number of imputed outcomes is 1 (in the cases for which only one follow-up visit is missing) and the maximum number of imputed cost outcomes was 17 in cases for which only one follow-up interview was available. Specifically, we use the following imputation model for $j > 0$ since there are no missing observations at baseline:

$$Y_{ijk} = \alpha_0 + \alpha_{1Z_i} t_j + \alpha_{2Z_i} t_j^2 + \alpha_3^T X_i + \alpha_4 Y_{ik,j-1} + e_{ijk},$$

where Y_{ijk} denotes the outcome type *k* response measure for subject *i* at time point *j*. Nominal variable Z_i represents the intervention group assignment for subject *i*; i.e. Z_i=1-4, indicating whether subject *i* was assigned to olanzapine, perphenazine, quetiapine or risperidone; α_0 is a common intercept; $(\alpha_{1Z_i}, \alpha_{2Z_i})$ are group-specific linear and quadratic terms representing time for the intervention group to which subject *i* belongs; while α_3 is a vector of regression coefficients associated with baseline covariates vector X_i; and α_4 is the coefficient associated with $Y_{ik,j-1}$ which is the most recent outcome measure of type *k* observed for subject *i*. The error term e_{ijk} is normally distributed with a mean value of 0 and variance θ_k^2. Covariates *X* are selected among those that significantly predict the outcome in question using general estimation equations (Proc Genmod in SAS ®) with a step-down approach. Based on the fitted regression coefficients from the above imputation model, a new regression model is simulated from the posterior predictive distribution of the

parameters and is used to impute the missing values for each variable (5). The imputation is implemented using monotone regression method (Proc MI in SAS®). Twenty imputed data sets were generated for the analysis of each outcome described below.

After imputation, general linear models for repeated measures (5) were used to model the trajectory of each outcome. The time points were treated as discrete variables and the specific trajectory over time was modeled for each intervention group. Specifically we use the following repeated measures analysis model:

$$Y_{ijk} = \beta_{0Z_i} + \beta_1 t_j + \beta_2 t_j^2 + \beta_3^T \boldsymbol{x}_i + \varepsilon_{ijk},$$

where Y_{ijk} denotes the outcome type *k* response measure for subject *i* at time point *j* (*j*=0); the intervention group effect is modeled in β_{0Z_i}; (β_1, β_2) are common linear and quadratic terms representing trajectories for Y_{ijk}, β_3 is a vector of regression coefficients associated with baseline covariates vector $\boldsymbol{x}_i$. The error term ε_{ijk} is normally distributed with a mean value of 0, variance σ_k^2 and the correlation between the errors term at different time points within a same subject is assumed to be AR (1). The model was fitted with SAS ® Proc Mixed using the Model and Repeated statements. Since β_{0Z_i} is estimated twenty times from twenty complete imputed data sets, standard errors for the final β_{0Z_i} are estimated by incorporating the variability associated with estimating β_{0Z_i} in a single imputed data set and the variability across the twenty imputed data sets. This is achieved by SAS Proc MIanalyze ®.

Pairwise difference in the response between two intervention groups *g* and *h* is estimated as $\hat{\beta}_{0g} - \hat{\beta}_{0h}$ and the group difference is declared significant if the p value for the Wald test $(\hat{\beta}_{0g} - \hat{\beta}_{0h}) / \sqrt{Var(\hat{\beta}_{0g} - \hat{\beta}_{0h})}$ is less than 0.05 using Fisher's protected test after the overall group effect β_{0Z_i} is found to be significant by the likelihood ratio test with 3 degrees of freedom.

Multiple Imputation Results

The results of multiple imputation analyses were consistent with those of the original primary analysis (the numbers in parentheses, below, are the mean values of the dependent variables collapsed over

time points and with adjustment for baseline covariates) even after adjusting for multiple comparisons (largest $p<0.05$).

Total medication costs were significantly lower for patients randomly assigned to initiate treatment on perphenazine as compared to each of the other groups: P (314)< O (605), Q (522) and R (541). The log-costs for total health care costs (outpatient, inpatient and residential) excluding medications were also significantly lower for perphenazine than for each of the other groups: P (4.26)< Q (4.72), O (4.56) or R (4.63), in the multiple imputation analysis, as were log-costs for total health costs (i.e. including medications): P (6.07) < O (6.82), Q (6.80), R (6.75).

On the gold-standard symptom measure (the PANSS total score) patients randomly assigned to both olanzapine and perphenazine were significantly less symptomatic that those assigned to either quetiapine or risperidone: O (66.1), P (65.9) < R (71.0),Q (70.3). On QALYS, the primary measure of effectiveness in this study, patients randomly assigned to perphenazine scored significantly higher on quality of life than those assigned to each of the SGAs: P (0.721) > Q (0.705), O (0.704), and R (0.694).

Thus re-analysis of the primary analyses using multiple imputation to address missing data showed initial assignment to perphenazine to be both significantly less costly and significantly more effective on the primary outcomes, total health costs including medications, and QALYs. These results, while favoring perphenazine somewhat more strongly than the original analysis, are taken as a confirmation, rather than revision, of the original results, and as support for the conclusion that there were lower costs and no less effectiveness for perphenazine treatment as compared to each of the involved SGAs.

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The CATIE Study Investigators Group

Lawrence Adler, M.D., Clinical Insights, Glen Burnie, Md.

Mohammed Bari, M.D., Synergy Clinical Research, Chula Vista, Calif.

Irving Belz, M.D., Tri-County/ MHMR, Conroe, Texas

Raymond Bland, M.D., Southern Illinois University School of Medicine, Springfield, Ill.

Thomas Blocher, M.D., MHMRA of Harris County, Houston, Texas

Brent Bolyard, M.D., Cox North Hospital, Springfield, Mo.

Alan Buffenstein, M.D., The Queen's Medical Center, Honolulu, Hawaii

John Burruss, M.D., Baylor College of Medicine, Houston, Texas

Matthew Byerly, M.D., University of Texas Southwestern Medical Center, Dallas, Texas

Jose Canive, M.D., Albuquerque VA Medical Center, Albuquerque, N.Mex.

Stanley Caroff, M.D., Veterans Affairs Medical Center and the University of Pennsylvania, Philadelphia

Charles Casat, M.D., Behavioral Health Center, Charlotte, N.C.

Eugenio Chavez-Rice, M.D., El Paso Community MHMR Center, El Paso, Texas

John Csernansky, M.D., Washington University School of Medicine, St. Louis, Mo.

Pedro Delgado, M.D., University Hospitals of Cleveland, Cleveland, Ohio

Richard Douyon, M.D., VA Medical Center, Miami, Fla.

Cyril D'Souza, M.D., Connecticut Mental Health Center, New Haven, Conn.

Ira Glick, M.D., Stanford University School of Medicine, Stanford, Calif.

Donald Goff, M.D., Massachusetts General Hospital, Boston, Mass.

Silvia Gratz, M.D., Eastern Pennsylvania Psychiatric Institute, Philadelphia, Pa.

George T. Grossberg, M.D., St. Louis University School of Medicine-Wohl Institute, St. Louis, Mo.

Mahlon Hale, M.D., New Britain General Hospital, New Britain, Conn.

Mark Hamner, M.D., Medical University of South Carolina and VA Medical Center, Charleston, S.C.

Richard Jaffe, M.D., Belmont Center for Comprehensive Treatment, Philadelphia, Pa.

Dilip Jeste, M.D., University of California San Diego, VA Medical Center, San Diego, Calif.

Anita Kablinger, M.D., Louisiana State University Health Sciences Center, Shreveport, La.

Ahsan Khan, M.D., Psychiatric Research Institute, Wichita, Kan.

Steven Lamberti, M.D., University of Rochester Medical Center, Rochester, N.Y.

Michael T. Levy, M.D., PC, Staten Island University Hospital, Staten Island, N.Y.

Jeffrey Lieberman, M.D., University of North Carolina School of Medicine, Chapel Hill, N.C.

Gerald Maguire, M.D., University of California Irvine, Orange, Calif.

Theo Manschreck, M.D., Corrigan Mental Health Center, Fall River, Mass.

Joseph McEvoy, M.D., Duke University Medical Center, Durham, N.C.

Mark McGee, M.D., Appalachian Psychiatric Healthcare System, Athens, Ohio

Herbert Meltzer, M.D., Vanderbilt University Medical Center, Nashville, Tenn.

Alexander Miller, M.D., University of Texas Health Science Center, San Antonio, Texas

Del D. Miller, M.D., University of Iowa, Iowa City, Iowa

Henry Nasrallah, M.D., University of Cincinnati Medical Center, Cincinnati, Ohio

Charles Nemeroff, M.D., Ph.D., Emory University School of Medicine, Atlanta, Ga.

Stephen Olson, M.D., University of Minnesota Medical School, Minneapolis, Minn.

Gregory F. Oxenkrug, M.D., St. Elizabeth's Medical Center, Boston, Mass.

Jayendra Patel, M.D., University of Mass Health Care, Worcester, Mass.

Frederick Reimher, M.D., University of Utah Medical Center, Salt Lake City, Utah

Silvana Riggio, M.D., Mount Sinai Medical Center-Bronx VA Medical Center, Bronx, N.Y.

Samuel Risch, M.D., University of California San Francisco, San Francisco, Calif.

Bruce Saltz, M.D., Henderson Mental Health Center, Boca Raton, Fla.

Thomas Simpatico, M.D., Northwestern University, Chicago, Ill.

George Simpson, M.D., University of Southern California Medical Center, Los Angeles, Calif.

Michael Smith, M.D., Harbor-UCLA Medical Center, Torrance, Calif.

Roger Sommi, Pharm.D., University of Missouri, Kansas City, Mo.

Richard M. Steinbook, M.D., University of Miami School of Medicine, Miami, Fla.

Michael Stevens, M.D., Valley Mental Health, Salt Lake City, Utah

Andre Tapp, M.D., VA Puget Sound Health Care System, Tacoma, Wash.

Rafael Torres, M.D., University of Mississippi, Jackson, Miss.

Peter Weiden, M.D., SUNY Downstate Medical Center, Brooklyn, N.Y.

James Wolberg, M.D., Mount Sinai Medical Center, New York, N.Y.

Supplemental table A. Patient characteristics at the time of random assignment by initial treatment.

	Total Sample		Olanzapine		Perphenazine		Quetiapine		Risperidone		Ziprasidone		Chi sq/F	df	p
	Mean/N	%/SD	Mean/N	%/SD	Mean/N	%/SD	Mean/N	%/SD	Mean/N	%/SD	Mean/N	%/SD			
	N=1424		N=328		N=256		N=326		N=332		N=182				
Age	40.57	11.09	40.92	10.77	39.97	11.06	41	11.27	40.5	11.29	40.11	11.04	0.48	4	0.75
Male	1,057	74.18%	237	72.6%	196	76.6%	249	76.4%	247	74.4%	128	70.0%	3.93	4	0.41
Race/Ethnicity															
White	860	60.4%	192	58.5%	151	59.0%	211	64.7%	197	59.3%	109	60.2%	3.39	4	0.49
Black	494	34.7%	115	35.1%	90	35.2%	105	32.2%	121	36.5%	63	34.8%	1.38	4	0.84
Other	69	4.8%	21	6.4%	15	5.8%	10	3.0%	14	4.2%	9	5.0%	4.8	4	0.31
Hispanic	165	11.6%	41	12.5%	24	9.4%	48	14.7%	34	10.2%	18	9.8%	5.75	4	0.22
Marital Status															
Married	166	11.7%	36	11.0%	43	16.8%	34	10.4%	37	11.1%	16	8.7%	8.79	4	0.06
Separated/Divorces	382	26.8%	93	28.4%	65	25.4%	76	23.3%	91	27.4%	57	31.1%	4.5	4	0.34
Never Married	843	59.2%	188	57.3%	146	57.0%	206	63.1%	197	59.3%	106	57.9%	3.25	4	0.51
Widowed	34	2.4%	11	3.4%	2	7.8%	10	3.0%	7	2.1%	4	2.2%	4.9	4	0.29
PANSS Total	75.6	17.6	76.0	18.2	74.2	10.0	75.7	17.0	76.4	16.6	75.4	0.2	0.63	4	0.64
Positive	18.5	5.6	18.6	5.4	17.9	5.9	18.7	5.5	18.6	5.6	18.4	5.9	0.79	4	0.53
Negative	20.2	6.4	20.3	6.6	20.3	6.3	19.9	6.5	20.3	6.3	19.9	6.4	0.31	4	0.87
General	37.0	9.3	37.1	9.7	36.0	9.5	37.1	9.2	37.6	8.7	37.0	9.7	1.02	4	0.40
Depression (Calgary Scale)	14.1	5.0	14.0	5.1	14.2	5.1	13.8	4.9	14.5	5.1	14.0	4.9	0.8	4	0.52
Current Co-morbidity															
Alcohol Abuse/Dependence	109	7.6%	22	6.7%	27	10.5%	26	7.9%	23	6.9%	11	6.0%	4.42	4	0.35
Drug Abuse/Dependence	163	11.4%	36	10.9%	39	15.2%	29	8.8%	40	,1201	19	10.4%	6.2	4	0.19
Major Depression	156	10.9%	31	9.4%	29	11.3%	26	7.9%	42	12.6%	28	15.3%	8.5	4	0.07
Obsessive Compulsive Disorder	64	4.5%	9	2.7%	9	3.5%	18	5.5%	20	6.0%	8	4.4%	5.5	4	0.24
Other Anxiety Disorder	164	11.5%	36	11.0%	25	9.8%	34	10.4%	46	13.9%	23	12.6%	3.2	4	0.52
Side Effects															
EPS mean (Simpson Angus)	0.22	0.33	0.21	0.32	0.19	0.32	0.23	0.33	0.23	0.30	0.23	0.36	0.65	4	0.63
Barnes Akathesia Scale (1)	0.54	0.88	0.64	1.01	0.44	0.79	0.48	0.81	0.58	0.88	0.55	0.83	2.48	4	0.04
AIMS Severity Score (TD)(1)	1.62	3.07	1.85	3.35	0.71	1.64	1.88	3.35	1.79	3.17	1.77	3.20	7.05	4	p<.0001
TD (>1 on AIMS Severity)(1)	227	15.9%	65	19.8%	3	1.7%	67	20.6%	59	17.8%	33	18.0%	51.97	4	p<.0001
Body Mass Index	29.8	6.9	29.4	6.8	29.6	6.9	30.0	6.9	30.0	7.4	30.2	7.1	0.6	4	0.7
Quality of Life Scale	2.7	1.1	2.7	1.1	2.7	1.1	2.7	1.1	2.6	1.0	2.6	1.1	0.31	4	0.87
Social Interaction	2.5	1.3	2.5	1.2	2.6	1.4	2.5	1.4	2.5	1.3	2.5	1.3	0.91	4	0.45
Instrumental activity	2.0	1.6	2.0	1.7	2.0	1.6	1.9	1.7	2.0	1.5	2.1	1.7	0.46	4	0.77
Intrapsychic activity	3.0	1.1	3.0	1.2	3.0	1.2	3.0	1.2	2.9	1.0	2.9	1.2	0.36	4	0.83
Visual Analogue Scale (0-100)	60.1	26.9	62.0	25.0	62.0	27.5	60.8	27.2	57.0	28.1	58.5	26.2	1.94	4	1.02
Lehman Quality if Life Interview	4.3	1.4	4.4	1.4	4.4	1.4	4.4	1.4	4.3	1.4	4.2	1.4	0.75	4	0.55
Quality Adjusted life Years	0.672	0.130	0.665	0.138	0.689	0.122	0.673	0.129	0.662	0.125	0.671	0.142	1.78	4	0.13
Patient Weighted Health Index	-1.12	3.70	-1.45	4.03	-0.75	3.67	-0.88	3.58	-1.28	3.34	-1.21	3.91	1.59	4	0.17
Health costs (previous month)															
All medications	$417	$327	$418	$341	$420	$314	$409	$356	$431	$315	$400	$331	0.32	4	0.86
Inpatient/Residential/Nsg. home	$1,568	$714	$1,869	$4,209	$1,127	$2,530	$1,526	$3,775	$1,595	$4,317	$1,671	$3,756	1.4	4	0.23
Outpatient	$393	$972	$407	$896	$392	$1,173	$410	$1,024	$356	$842	$405	$928	0.16	4	0.96
Total	$2,378	$3,947	$2,693	$4,289	$1,940	$2,811	$2,346	$3,919	$2,383	$4,376	$2,476	$3,882	1.35	4	0.25

(1) No significant difference were observed on these measures for the subsample from which Tardive Dyskinesia was excluded (see Online supplemental table 2).

Supplemental table B. Patient characteristics at the time of random assignment by initial treatment, excluding patients with TD or those assigned to ziprasidone.

	Total Sample		**Olanzapine**		**Perphenazine**		**Quetiapine**		**Risperidone**		**Chi sq/F**	**df**	**p**
	Mean/N	%/SD	Mean/N	%/SD	Mean/N	%/SD	Mean/N	%/SD	Mean/N	%/SD			
	N=1049		N=263		N=256		N=261		N=269				
Age	39.3	10.9	39.36	10.56	39.97	11.06	39.15	10.88	38.78	11.05	0.55	3	0.65
Male	777	74.0%	190	72.2%	196	76.6%	192	73.5%	199	74.0%	1.3	3	0.72
Race/Ethnicity													
White	631	60.1%	153	58.2%	151	59.0%	167	64.0%	160	59.5%	2.22	3	0.52
Black	368	35.1%	96	36.5%	90	35.1%	84	32.1%	98	36.4%	1.4	3	0.70
Other	50	4.8%	14	5.3%	15	5.9%	10	3.8%	11	4.1%	1.62	3	0.65
Hispanic	129	12.3%	37	14.1%	24	9.3%	39	14.9%	29	10.8%	5.05	3	0.17
Marital Status											16.7	12	0.16
Married	131	12.5%	30	11.4%	43	16.8%	27	10.3%	31	11.5%			
Separated/Divorces	219	20.8%	61	23.2%	50	19.4%	55	20.9%	53	19.8%			
Never Married	636	60.6%	159	60.4%	146	57.0%	167	64.0%	164	61.0%			
Widowed													
PANSS Total	75.5	17.5	75.7	18.2	74.2	18.0	74.8	17.0	77.2	16.5	1.48	3	0.21
Positive	18.4	5.6	18.4	5.5	17.9	5.9	18.3	5.4	19.0	5.6	1.8	3	0.15
Negative	20.2	6.5	20.3	6.7	20.3	6.3	19.8	6.5	20.4	6.4	0.43	3	0.72
General	36.9	9.3	37.0	9.8	36.0	9.5	36.7	9.2	37.8	8.6	1.68	3	0.17
Depression (Calgary Scale)	1.6	0.6	1.6	0.6	1.6	0.6	1.6	0.6	1.6	0.6	0.84	3	0.47
Current Co-morbidity													
Alcohol Abuse/Dependence	86	8.2%	20	7.6%	27	10.5%	21	8.0%	18	6.7%	2.83	3	0.41
Drug Abuse/Dependence	126	11.9%	30	11.3%	39	15.2%	23	8.8%	34	12.6%	5.31	3	0.15
Major Depression	114	10.8%	25	9.4%	29	11.3%	23	8.8%	37	13.7%	4.08	3	0.25
Obsessive Compulsive Disorder	57	5.4%	8	3.0%	11	4.3%	20	7.7%	18	6.7%	6.9	3	0.07
Side Effects												3	
EPS mean (Simpson Angus)	0.18	0.29	0.16	0.27	0.19	0.32	0.16	0.25	0.20	0.29	1.35	3	0.26
Barnes Akathesia Scale (1)	0.47	0.84	0.58	0.97	0.43	0.79	0.46	0.76	0.47	0.81	2.17	3	0.09
AIMS Severity Score (TD)(1)	0.12	0.27	0.15	0.31	0.12	0.27	0.11	0.24	0.12	0.23	1.13	3	0.34
TD (>1 on AIMS Severity)(1)	7	67.0%	1	0.4%	3	1.2%	2	0.8%	1	0.4%	1.7	3	0.63
Quality of Life Scale	2.7	1.1	2.7	1.1	2.7	1.1	2.7	1.1	2.6	1.0	0.73	3	0.53
Social Interaction	2.6	1.3	2.5	1.2	2.6	1.4	2.6	1.4	2.5	1.3	1.21	3	0.30
Instrumental activity	2.0	1.6	2.0	1.7	2.0	1.6	2.0	1.7	1.9	1.5	0.19	3	0.91
Intrapsychic activity	3.0	1.2	3.1	1.2	3.0	1.2	3.1	1.2	2.9	1.0	1.35	3	0.26
Visual Analogue Scale (0-100)	60.0	27.3	62.4	25.3	61.9	27.5	60.3	27.1	55.5	28.6	3.53	3	0.014
Lehman Quality if Life Interview	4.3	1.4	4.4	1.4	4.4	1.3	4.4	1.4	4.2	1.5	0.83	3	0.47
Quality Adjusted life Years	0.686	0.126	0.682	0.132	0.689	0.120	0.695	0.123	0.676	0.127	1.11	3	0.34
Patient Weighted Health Index	-0.94	3.64	-1.12	3.98	-0.75	3.67	-0.59	3.43	-1.29	3.41	1.86	3	0.13
Body Mass Index	29.80	7.09	29.24	6.86	29.63	6.93	30.22	7.05	30.09	7.48	1.04	3	0.37
Health costs (previous month)													
All medications	$422	$325	$419	$344	$420	$314	$418	$331	$433	$313	0.14	3	0.94
Inpatient/Residential/Nsg. home	$1,512	$3,715	$1,828	$3,988	$1,127	$2,530	$1,442	$3,642	$1,636	$4,381	1.68	3	0.17
Outpatient	$365	$935	$379	$864	$392	$1,173	$410	$1,066	$281	$513	1.02	3	0.38
Total	$2,299	$3,831	$2,628	$4,078	$1,940	$2,811	$2,271	$3,813	$2,352	$4,389	1.42	3	0.23

Supplemental table C. Average monthly costs (including drug disounts and rebates) by treatment group over 18 months (1,2).

	Olanzapine (O)	Perphenazine (P)	Quetiapine (Q)	Risperidone (R)	Ziprasidone (Z)	F (3,4)	overall	Paired comparisons (6)
Total N=	328	256	326	332	182	Chi square (5)	p<	
Data set I (df=3): P vs. O, Q, and R								
Excluding patients with TD and patients on ziprasidone (N=)	263	256	261	269				
Monthly Drug Costs (3)	$595	**$288**	$523	$526	---	117.2	p<.0001	P<O,Q,R (all p<.0001*)
Experimental medications (3)	493	**196**	415	440	---	190.9	p<.0001	P<O,Q,R (all p<.0001*)
Concomitant medications (3)	103	**93**	108	86	---	1.1	0.34	ns
Monthly health service costs (4)	837	**851**	1134	1007	---	1.6	0.18	ns
median (5)	121	**89**	132	129	---	5.1	0.16	ns
Inpatient and residential treatment costs (4)	556	**531**	753	692	---	2.1	0.09	ns
Outpatient, mental health/ medica surgical svs. (4)	281	**321**	381	316	---	1.3	0.28	ns
Monthly total health costs (drugs and services) (4)	1428	**1139**	1657	1529	---	47.6	p<.0001	P<O,Q,R (all p<.0001*)
median (5)	783	**439**	752	743	---	55.0	p<.0001	P<O,Q,R (all p<.0001*)
Data Set II (df=2) O vs. Q vs. R								
Including Patients with TD but excluding those on zipr. or perph. (N=)	328		326	332				
Monthly Drug Costs (3)	**616**	---	**518**	**540**	---	23.2	p<.0001	O>Q,R (both p<.0001*)
Experimental medications (3)	**506**	---	**410**	**437**	---	36.0	p<.0001	O>Q,R (both p<.0001*);R>Q (p=.014*)
Concomitant medications (3)	**111**	---	**109**	**104**		0.4	0.64	ns
Monthly health service costs (4)	**902**	---	**1230**	**1095**	---	1.7	0.19	ns
median (5)	**140**	---	**160**	**147**	---	2.5	0.290	ns
Inpatient and residential treatment costs (4)	**580**	---	**809**	**709**	---	3.7	0.024	ns
Outpatient, mental health/ medica surgical svs. (4)	**322**	---	**421**	**386**	---	0.1	0.87	ns
Monthly total health costs (drugs and services) (4)	**1515**	---	**1749**	**1631**	---	0.8	0.45	ns
median (5)	**825**	---	**775**	**800**	---	0.5	0.80	ns
Data Set III: Z vs. P								
Excluding Patients with TD but including those on Ziprasidone (N=)		146			150			
Monthly Drug Costs (3)	---	311	---	---	516	Not applicable		P<Z (p<.0001*)
Experimental medications (3)	---	214	---	---	389	Not applicable		P<Z (p<.0001*); Z<R (p<.0002*)
Concomitant medications (3)	---	98	---	---	127	Not applicable		ns
Monthly health service costs (4)	---	947	---	---	1220	Not applicable		P<Z (p<.04)
median (5)	---	89	---	---	129	Not applicable		P<Z (p<.03)
Inpatient and residential treatment costs (4)	---	546	---	---	777	Not applicable		ns
Outpatient, mental health/ medica surgical svs. (4)	---	402	---	---	443	Not applicable		ns
Monthly total health costs (drugs and services) (4)	---	1258	---	---	1737	Not applicable		P<Z (p<.0001*)
median (5)	---	475	---	---	715	Not applicable		P<Z (p<.0001*)
Data Set IV: Z vs. O, Q, and R								
Including Patients with TD and those on Ziprasidone (N=)	177		181	174	178			
Monthly Drug Costs (3)	641	---	530	554	**521**	Not applicable		Z<O (p<.0001*)
Experimental medications (3)	505	---	415	453	**393**	Not applicable		Z<O (p<.0001*)
Concomitant medications (3)	137	---	115	102	**128**	Not applicable		ns
Monthly health service costs (4)	907	---	1233	1008	**1330**	Not applicable		Z>O (p=.049); Z>R (p=.038)
median (5)	132	---	165	121	**147**	Not applicable		Z>O (p=.024); Z>R (p=.015)
Inpatient and residential treatment costs (4)	584	---	798	603	**839**	Not applicable		ns
Outpatient, mental health/ medica surgical svs. (4)	322	---	435	405	**491**	Not applicable		ns
Monthly total health costs (drugs and services) (4)	1546	---	1763	1562	**1851**	Not applicable		ns
median (5)	931	---	819	770	**771**	Not applicable		ns

(1) Bolded values highlight treatment conditions of primary interest in each data set.

(2) All pairwise p-values < .05 are presented. "*" = statistically significant using criteria for multiple comparisons.

(3) Statistical analysis of drug costs based on un-transformed data from months 1-18 where each patient has the data from each month they participated in data collection (N= 12,163 patient-month observations for Data Set I; 11,308 for Data Set II; 3,241 for Data Set 3; and 7,732 for Data Set IV). Appropriate discounts and rebates applied to VA patients and patients whose care is funded by medicaid.

(4) Statistical analysis of health service and total costs based on log transformed data from months 1-18 where each patient has the data from each month they participated in data collection (N= 12,163 patient-month observations for Data Set I; 11,308 for Data Set II; 3,241 for Data Set 3; and 7,732 for Data Set IV).

(5) Kruskal-Wallis test.

(6) ns = paired comparisons examined with this datra set were not significantly different.

Supplemental table D. Average monthly costs during CATIE Phase 1 (i.e. with treatment crossovers excluded)(including drug disounts and rebates) by treatment group over 18 months (1,2).

	Olanzapine (O)	Perphenazine (P	Quetiapine (Q)	Risperidone (R)	Ziprasidone (Z)	F	overall	Paired comparisons (5)
Total N=	328	256	326	332	182		p<	
Data set I (df=3): P vs. O, Q, and R								
Excluding patients with TD and patients on ziprasidone (N=)	243	235	241	244				
Monthly Drug Costs (3)	$646	**$136**	$516	$562	---	357.3	p<.0001	P< O, Q, R (all p<.0001*)
Experimental medications (3)	545	**50**	412	474	---	561.0	p<.0001	P< O, Q, R (all p<.0001*)
Concomitant medications (3)	101	**87**	104	88	---	0.3	0.79	ns
Monthly health service costs (4)	758	**822**	962	970	---	1.3	0.26	ns
Inpatient and residential treatment costs (4)	493	**485**	634	651	---	1.2	0.32	ns
Outpatient, mental health/ medica surgical svs. (4)	265	**337**	328	320	---	0.6	0.60	ns
Monthly total health costs (drugs and services) (4)	1404	**960**	1478	1532	---	83.0	p<.0001	P< O, Q, R (all p<.0001*)
Data Set II (df=2) O vs. Q vs. R								
Including Patients with TD but excluding those on zipr. or perph. (N=)	303		298	300				
Monthly Drug Costs (3)	**666**	---	**515**	**564**	---	43.1	p<.0001	O>Q, R (both p<.0001*)
Experimental medications (3)	**559**	---	**410**	**466**	---	57.6	p<.0001	O>Q, R (both p<.0001*), R>Q (p<.0004
Concomitant medications (3)	**106**	---	**105**	**97**	---	0.9	0.41	ns
Monthly health service costs (4)	**835**	---	**1070**	**992**	---	1.9	0.16	ns
Inpatient and residential treatment costs (4)	**526**	---	**672**	**640**	---	0.9	0.4	ns
Outpatient, mental health/ medica surgical svs. (4)	**309**	---	**397**	**351**	---	0.8	0.78	ns
Monthly total health costs (drugs and services) (4)	**1501**	---	**1584**	**1555**	---	1.5	0.22	ns
Data Set III: Z vs. P								
Excluding Patients with TD but including those on Ziprasidone (N=)		132			132			
Monthly Drug Costs (3)	---	146	---	---	471	Not applicable		P<Z (p.0001*)
Experimental medications (3)	---	54	---	---	354	Not applicable		P< Z (p<.0001*)
Concomitant medications (3)	---	91	---	---	117	Not applicable		ns
Monthly health service costs (4)	---	962	---	---	1299	Not applicable		ns
Inpatient and residential treatment costs (4)	---	488	---	---	875	Not applicable		ns
Outpatient, mental health/ medica surgical svs. (4)	---	474	---	---	424	Not applicable		ns
Monthly total health costs (drugs and services) (4)	---	1109	---	---	1770	Not applicable		P< Z (p<.0001*)
Data Set IV: Z vs. O, Q, and R								
Including Patients with TD and those on Ziprasidone (N=)	162		166	159	158			
Monthly Drug Costs (3)	704	---	525	573	**471**	Not applicable		Z<O, R (p<.0001*)< Q (p=.0006*)
Experimental medications (3)	575	---	409	488	**358**	Not applicable		Z<O, R (p<.0001*)< Q (p=.0003*)
Concomitant medications (3)	129	---	117	84	**113**	Not applicable		ns
Monthly health service costs (4)	869	---	1040	914	**1492**	Not applicable		ns
Inpatient and residential treatment costs (4)	577	---	612	587	**967**	Not applicable		ns
Outpatient, mental health/ medica surgical svs. (4)	292	---	429	327	**524**	Not applicable		ns
Monthly total health costs (drugs and services) (4)	1573	---	1566	1487	**1962**	Not applicable		ns

(1) Bolded values highlight treatment conditions of primary interest in each data set.

(2) All pairwise p-values < .05 are presented. "*" = statistically significant using criteria for multiple comparisons.

(3) Statistical analysis of drug costs based on un-transformed data from months 1-18 where each patient has the data from each month they participated in data collection (N= 8,175 patient-month observations for Data Set I; 7,722 for Data Set II; 5,146 for Data Set 3; and 5,042 for Data Set IV). Appropriate discounts and rebates applied to VA patients and patients whose care is funded by medicaid.

(4) Statistical analysis of health service and total costs based on log transformed data from months 1-18 where each patient has the data from each month they participated in data collection (N= 8,175 patient-month observations for Data Set I; 7,722 for Data Set II; 5,146 for Data Set 3; and 5,042 for Data Set IV).

(5) ns = paired comparisons examined with this datra set were not significantly different.

Supplemental table E. Adjusted average total monthly costs (health care and drug costs) by treatment group, based on retransformed adjusted log costs, derived using the "smearing estimation" metho

ALL PHASE DATA INCLUDED	Olanzapine (O)	Perphenazine (P	Quetiapine (Q)	Risperidone (R)	Ziprasidone (Z)	F	overall	Paired comparisons (5)
Total N=	328	256	326	332	182		p<	
Data set I (df=3): P vs. O, Q, and R								
Excluding patients with TD and patients on ziprasidone (N=)	263	256	261	269				
` Monthly total health costs (drugs and services) (3)	1619	**817**	1680	1635	---	47.6	p<.0001	P<O,Q,R (all p<.0001*)
(standard error)	1442	**728**	1497	1457	---			
Data Set II (df=2) O vs. Q vs. R								
Including Patients with TD but excluding those on zipr. or perph. (N=)	328		326	332				
Monthly total health costs (drugs and services) (3)	**1433**	---	**1495**	**1446**	---	0.5	0.80	ns
(standard error)	**1167**	---	**1217**	**1177**	slo			
Data Set III: Z vs. P								
Excluding Patients with TD but including those on Ziprasidone (N=)		146			150			
Monthly total health costs (drugs and services) (3)	---	850	---	---	1709	Not applicable		P<Z (p<.0001*)
(standard error)	---	705	---	---	1417			
Data Set IV: Z vs. O, Q, and R								
Including Patients with TD and those on Ziprasidone (N=)	177		181	174	178			
Monthly total health costs (drugs and services) (3)	1560	---	1689	1512	**1664**	Not applicable		ns
(standard error)	1176	---	1274	1140	**1255**			
PHASE 1 ONLY DATA (CROSSOVERS EXCLUDED)	Olanzapine (O)	Perphenazine (P	Quetiapine (Q)	Risperidone (R)	Ziprasidone (Z)	F (3)	overall	Paired comparisons
Total N=	328	256	326	332	182	Chi squre (4)	p<	
Data set I (df=3): P vs. O, Q, and R								
Excluding patients with TD and patients on ziprasidone (N=)	243	235	241	244				
` Monthly total health costs (drugs and services) (4)	1725	**547**	1612	1690	---	83.0	p<.0001	P<O,Q,R (all p<.0001*)
(standard error)	1466	**464**	1370	1436	---			
Data Set II (df=2) O vs. Q vs. R								
Including Patients with TD but excluding those on zipr. or perph. (N=)	303		298	300				
Monthly total health costs (drugs and services) (4)	**1443**	---	**1350**	**1429**	---	0.14	0.87	ns
(standard error)	**1116**	---	**1044**	**1106**	---			
Data Set III: Z vs. P								
Excluding Patients with TD but including those on Ziprasidone (N=)		132			132			
Monthly total health costs (drugs and services) (4)	---	543	---	---	1761	Not applicable		P<Z (p<.0001*)
(standard error)	---	423	---	---	1373			
Data Set IV: Z vs. O, Q, and R								
Including Patients with TD and those on Ziprasidone (N=)	162		166	159	158			
Monthly total health costs (drugs and services) (4)	1617	---	1620	1511	**1637**	Not applicable		ns
(standard error)	1181	---	1183	1103	**1196**			

(1) Bolded values highlight treatment conditions of primary interest in each data set.

(2) All pairwise p-values < .05 are presented. "*" = statistically significant using criteria for multiple comparisons.

(3) Statistical analysis of health service and total costs based on log transformed data from months 1-18 where each patient has the data from each month they participated in data collection (N= 12,163 patient-month observations for Data Set I; 11,308 for Data Set II; 3,241 for Data Set 3; and 7,732 for Data Set IV).

(4) Statistical analysis of health service and total costs based on log transformed data from months 1-18 where each patient has the data from each month they participated in data collection (N= 8,175 patient-month observations for Data Set I; 7,722 for Data Set II; 5,146 for Data Set 3; and 5,042 for Data Set IV).

(5) ns = paired comparisons examined with this datra set were not significantly different.

Supplemental table F. Comparison of effectiveness: mixed model analyses of monthly values by group (1,2).

	Olanzapine (O)	Perphenazine (P	Quetiapine (Q)	Risperidone (R)	Ziprasidone (Z)	F	p	Paired comparisons (6)
Total N=	328	256	326	332	182			
Data set I (df=3): P vs. O, Q and R								
Excluding patients with TD and patients on ziprasidone (N=)	263	256	261	269				
PANSS Total Score (3)	64.8	**66.8**	67.3	68.8	---	6.46	p<.0002	O<P (.03), P<R (.03)
Quality Adjusted life Years (4)	0.717	**0.720**	0.718	0.704	---	3.1	0.03	P>R (.005*)
Patient Preference Weighted Index (PPWI)(5)	0.124	**0.075**	0.050	0.062	---	1.11	0.34	ns
Data Set II (df=2)O vs. Q vs. R								
Including Patients with TD but excluding those on zipr. or perph. (N=)	328		326	332				
PANSS Total Score (3)	**65.8**	---	**68.0**	**69.1**	---	8.99	p<.0001	O< R (p<.0001*), O<Q (p<.005*)
Quality Adjusted life Years (4)	**0.705**	---	**0.705**	**0.698**	---	1.1	0.33	ns
Patient Preference Weighted Index (PPWI)(5)	**0.071**	---	**-0.005**	**0.022**	---	2.05	0.13	ns
Data Set III: Z vs. P								
Excluding Patients with TD but including those on Ziprasidone (N=)		146			150			
PANSS Total Score (3)	---	67.2	---	---	68.0	Not applicable		ns
Quality Adjusted life Years (4)	---	0.722	---	---	0.716	Not applicable		ns
Patient Preference Weighted Index (PPWI)(5)	---	0.120	---	---	0.124	Not applicable		ns
Data Set IV: Z vs. O, Q and R								
Including Patients with TD and those on Ziprasidone (N=)	177		181	174	178			
PANSS Total Score (3)	63.2	---	67.1	68.4	**67.2**	Not applicable		ns
Quality Adjusted life Years (4)	0.721	---	0.709	0.702	**0.710**	Not applicable		ns
Patient Preference Weighted Index (PPWI)(5)	0.100	---	0.060	0.062	**0.113**	Not applicable		ns

(1) Bolded values highlight treatment conditions of primary interest in each data set.

(2) All pairwise p-values < .05 are presented. "*" = statistically significant using criteria for multiple comparisons.

(3) Least square means of PANSS scores from months 1, 3, 6, 9, 12, 15, 18 (N= 4,816 patient-month observations for Data Set I; 4,480 for Data Set II; 1,285 for Data Set III, and 3,802 for Data Set IV).

(4) Least squared means of QALYs (range 0-1): statistical analysis based on inverse transformation from month 1, 3, 6, 9, 12, 15, 18 (N= 4,777 patient-month observations for Data Set I; 4,454 for Data Set II; 1,270 for Data Set III; and 3,063 for Data Set IV).

(5) Least square means of PPWI (average z-scores weighted for patient preferences: interquartile range = -0.64 to + 0.64) from months 6, 12, and 18. (N= 2,475 patient-month observations for Data Set I; 2,250 for Data Set II; 1,695 for Data Set III; and 1,613 for Data Set IV).

(6) ns = paired comparisons examined with this datra set were not significantly different.

Supplemental table G. Comparison of effectivenes during CATIE Phase 1 (i.e. with treatment crossovers excluded): mixed model analyses of monthly values by group (1,2).

	Olanzapine (O)	Perphenazine (P)	Quetiapine (Q)	Risperidone (R)	Ziprasidone (Z)	F	p	Paired comparisons (6)
Total N=	328	256	326	332	182			
Data set I (df=3): P vs. O, Q and R								
Excluding patients with TD and patients on ziprasidone (N=)	263	256	261	269				
PANSS Total Score (3)	64.5	**65.9**	66.8	68.0	--	5.42	p=.001	O<P (p=0.11) , P<R (p=.03)
Quality Adjusted life Years (4)	0.727	**0.731**	0.727	0.713	--	2.46	p=.06	ns
Patient Preference Weighted Index (PPWI)(5)	1.12	**0.926**	0.452	0.934	--	0.85	0.46	ns
Data Set II (df=2)O vs. Q vs. R								
Including Patients with TD but excluding those on zipr. or perph. (N=)	328		326	332				
PANSS Total Score (3)	**65.5**	--	**67.6**	**68.4**	--	6.53	p=0.0015	O< R (p<.0005*), O<Q (p<.017*)
Quality Adjusted life Years (4)	**0.714**	--	**0.714**	**0.707**	--	0.76	p=.47	ns
Patient Preference Weighted Index (PPWI)(5)	**0.404**	--	**0.207**	**0.274**	--	0.6	p=.22	ns
Data Set III: Z vs. P								
Excluding Patients with TD but including those on Ziprasidone (N=)		146			150			
PANSS Total Score (3)	--	65.4	--	--	68.3	Not applicable		P<Z (p=.02)
Quality Adjusted life Years (4)	--	0.732	--	--	0.720	Not applicable		ns
Patient Preference Weighted Index (PPWI)(5)	--	0.894	--	--	0.760	Not applicable		ns
Data Set IV: Z vs. O, Q and R								
Including Patients with TD and those on Ziprasidone (N=)	177		181	174	178			
PANSS Total Score (3)	65.0	--	67.1	67.8	**67.6**	Not applicable		O<Z (p=.027)
Quality Adjusted life Years (4)	0.721	--	0.718	0.714	**0.714**	Not applicable		ns
Patient Preference Weighted Index (PPWI)(5)	0.619	--	0.423	0.486	**0.533**	Not applicable		ns

(1) Bolded values highlight treatment conditions of primary interest in each data set.

(2) All pairwise p-values < .05 are presented. "*" = statistically significant using criteria for multiple comparisons.

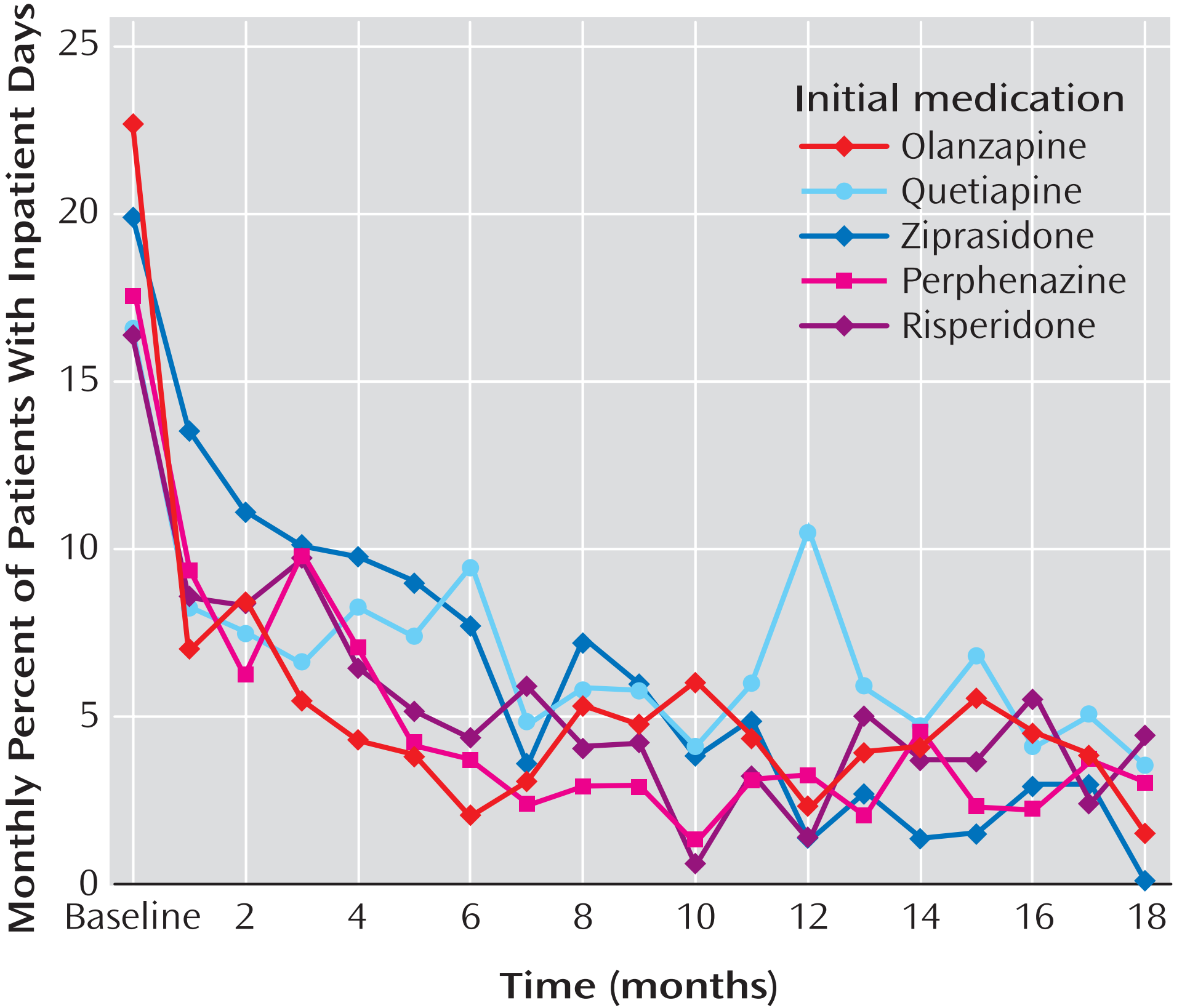
(3) Least square means of PANSS scores from months 1, 3, 6, 9, 12, 15, 18 (N= 3,411 patient-month observations for Data Set I; 3,221 for Data Set II; 2,192 for Data Set III, and 2,143 for Data Set IV).

(4) Least squared means of QALYs (range 0-1): statistical analysis based on inverse transformation from month 1, 3, 6, 9, 12, 15, 18 (N= 3,347 patient-month observations for Data Set I; 3,173 for Data Set II; 2,143 for Data Set III; and 2,109 for Data Set IV).

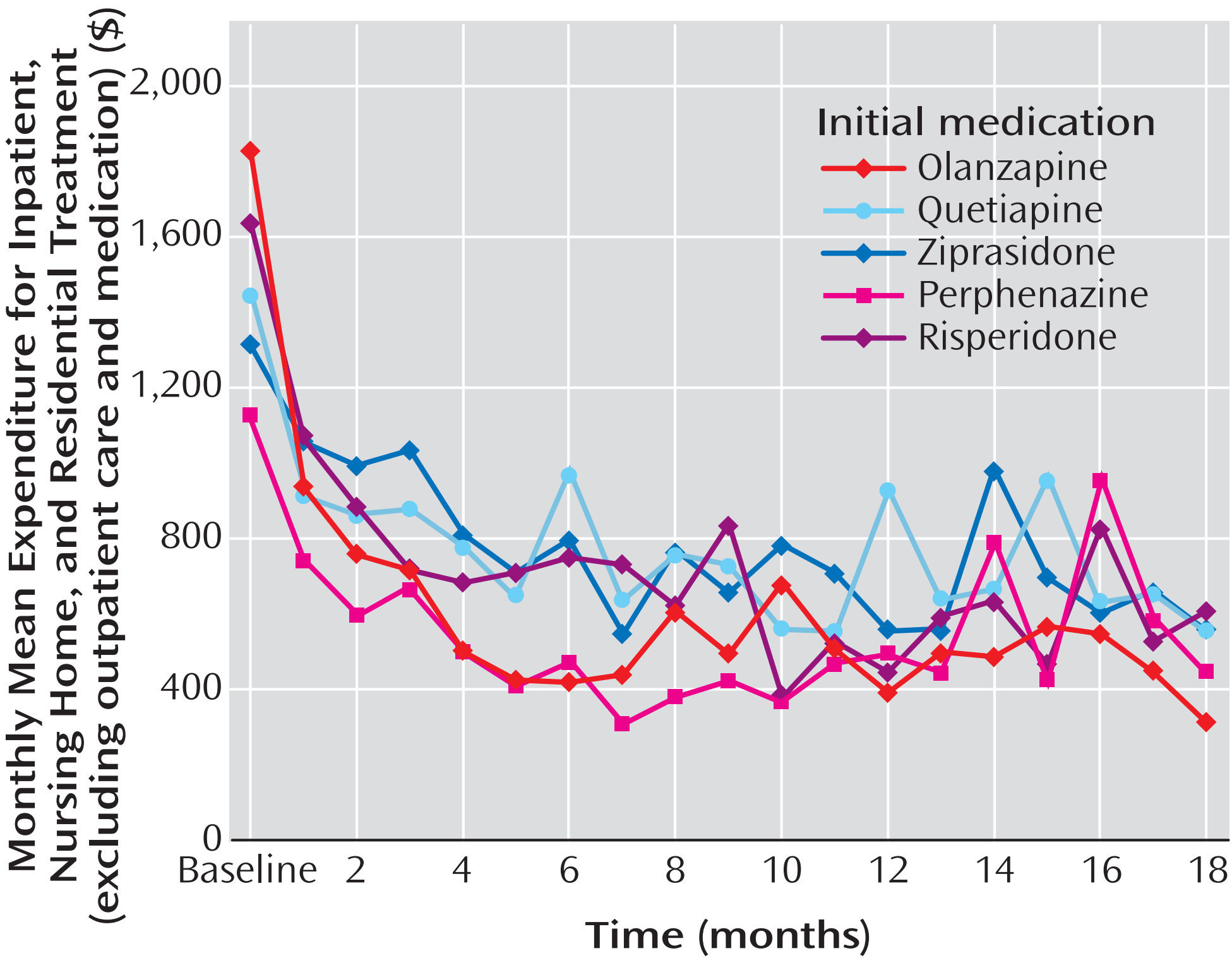
(5) Least square means of PPWI (average z-scores weighted for patient preferences: interquartile range = -0.64 to + 0.64) from months 6, 12, and 18. (N= 887 patient-month observations for Data Set I; 1,678 for Data Set II; 1,210 for Data Set III; and 1,171 for Data Set IV).

(6) ns = paired comparisons examined with this datra set were not significantly different.

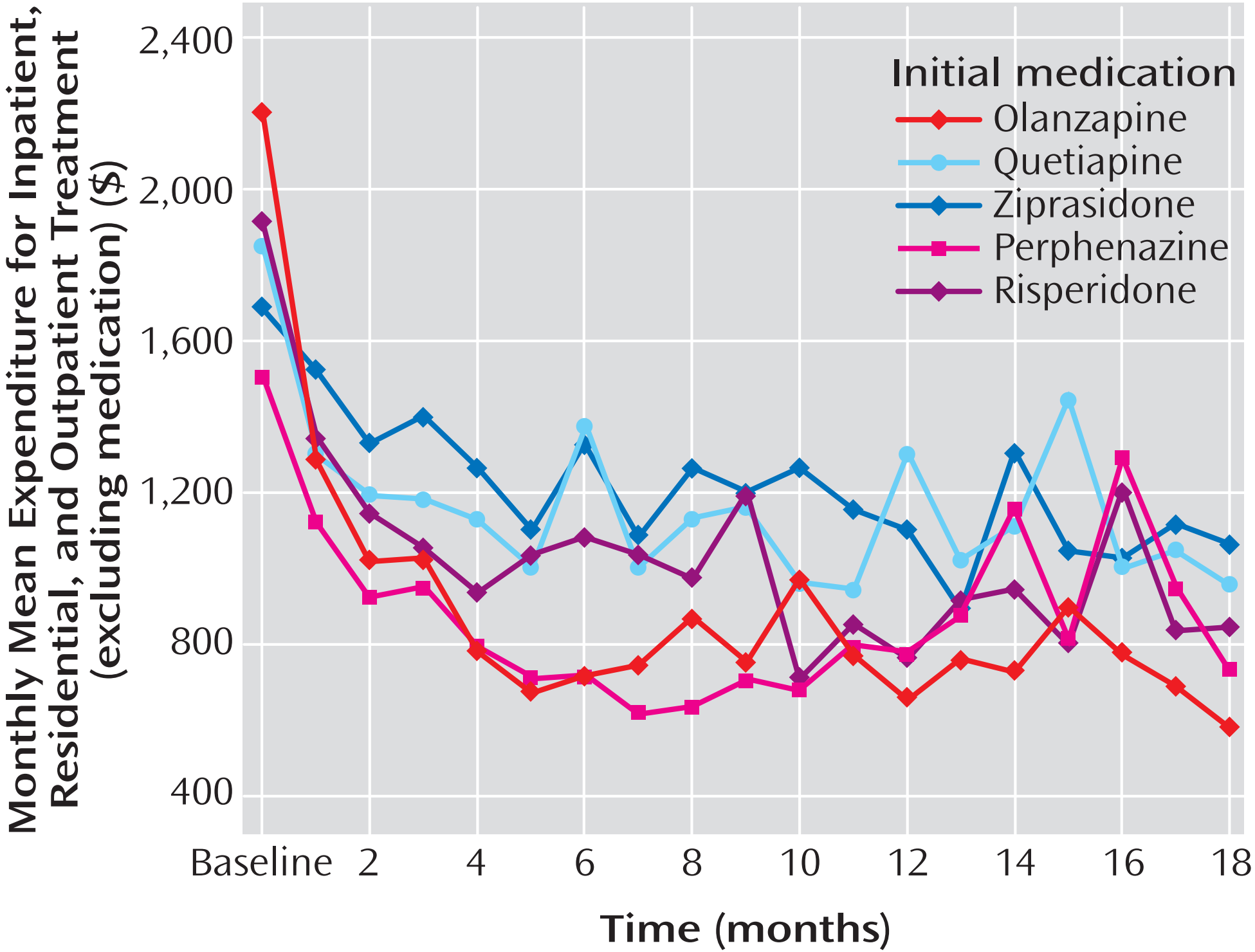
Supplemental Figure A. Percentage of Patients Hospitalized Each Month by Initial Assigned Medication



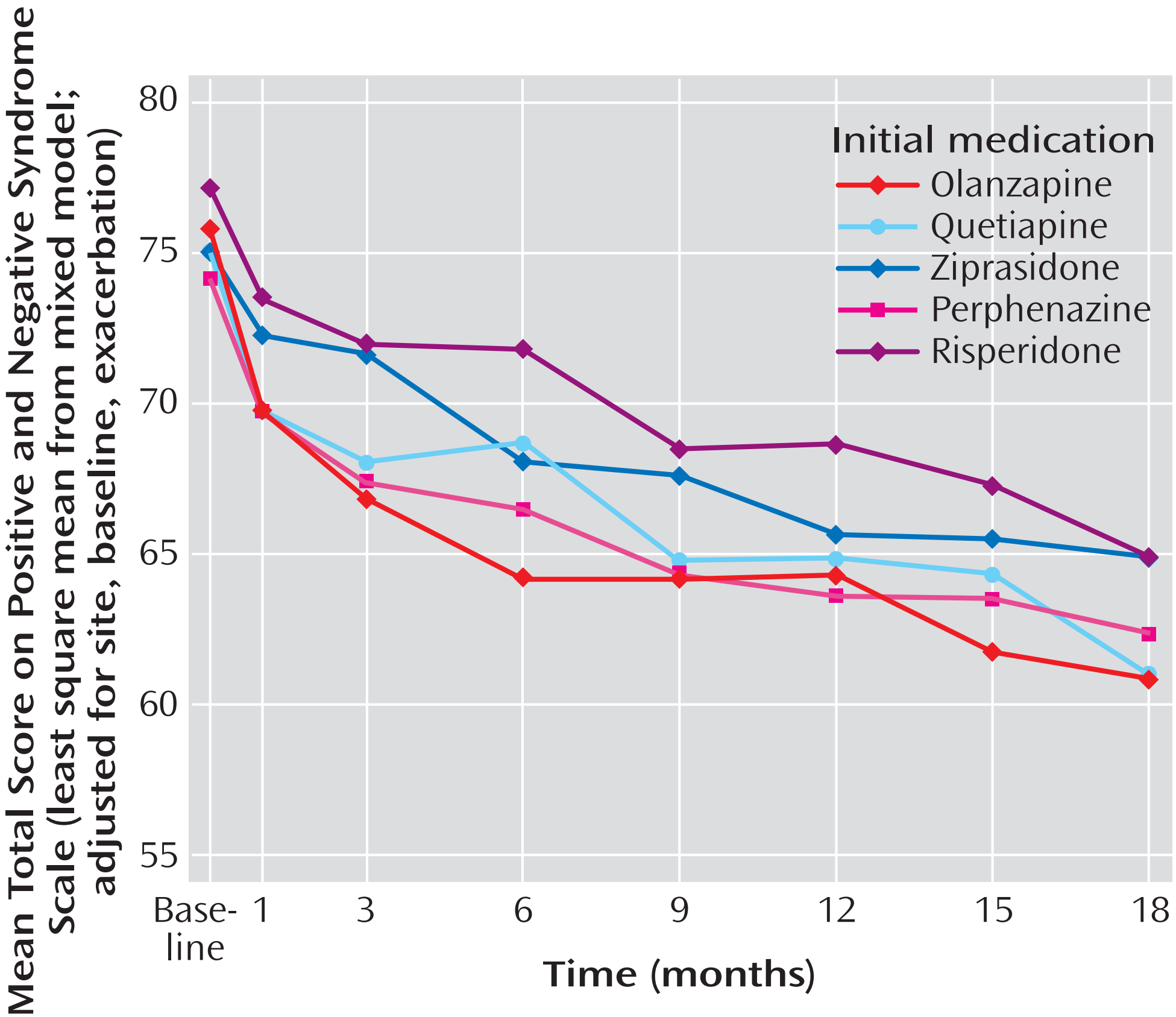
Supplemental Figure B. Total Costs of Average Monthly Inpatient, Nursing Home, and Residential Treatment by Initial Assigned Medication



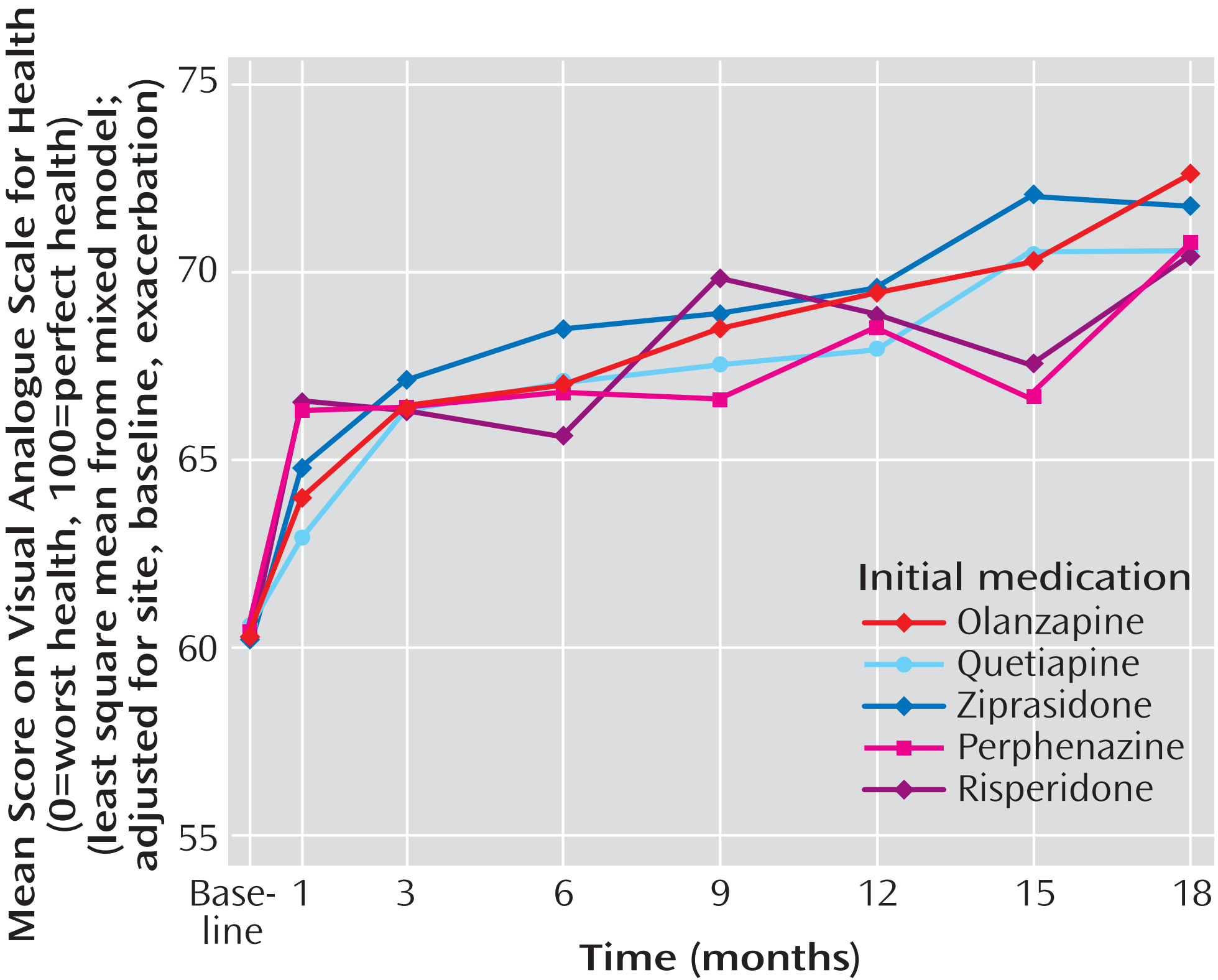
Supplemental Figure C. Total Costs of Average Monthly Health Care Including Outpatient Treatment by Initial Assigned Medication



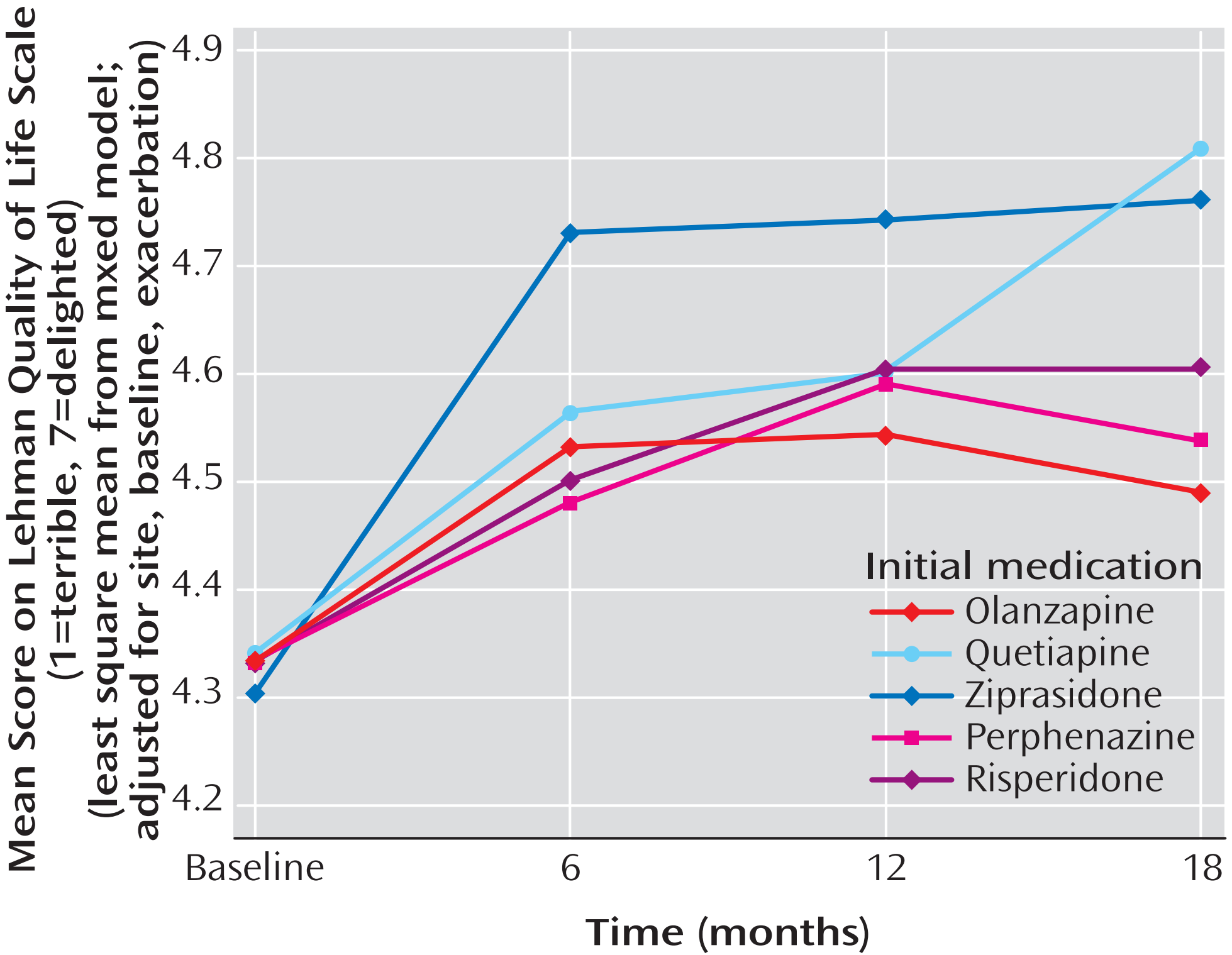
Supplemental Figure D. Average Monthly PANSS Total Symptom Score by Initial Assigned Medication



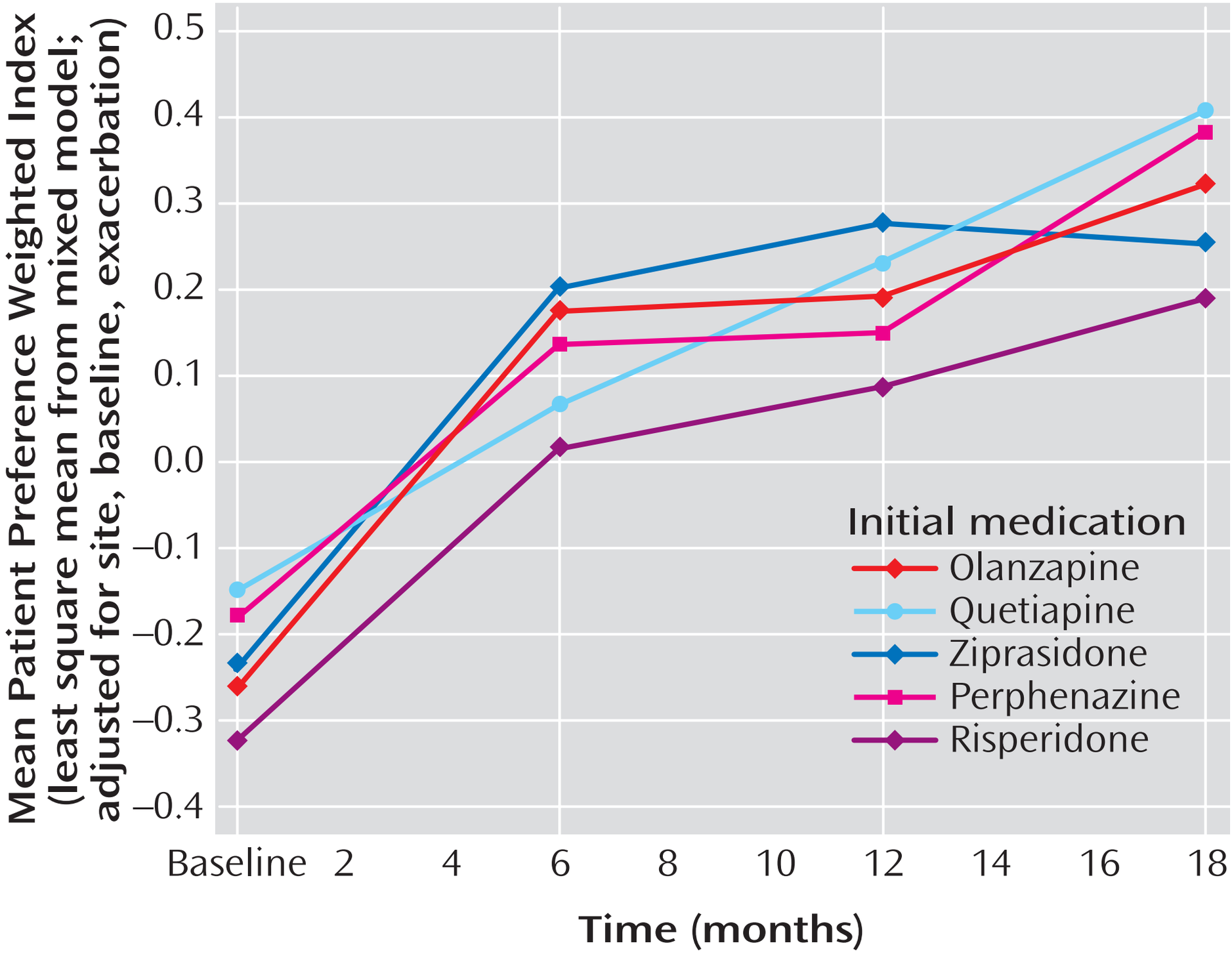
Supplemental Figure E. Average Monthly Patient Self-Rating of Health by Initial Assigned Medication



Supplemental Figure F. Average Monthly Quality of Life Ratings by Initial Assigned Medication



Supplemental Figure G. Average Monthly Patient Preference Weighted Index[a] by Initial Assigned Medication



[a] Outcome measure taking into account relative importance to patient of improvement in social life, work, energy, symptoms, confusion, and side effects.