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Psychopharmacological Treatment in the RAISE-ETP Study: Outcomes of a Manual and Computer Decision Support System Based Intervention

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Abstract

Objective—RAISE-ETP compared NAVIGATE, a comprehensive program for first-episode psychosis, to clinician-choice treatment over two years. Quality of life and psychosis and depressive symptom outcomes were better with NAVIGATE. Compared with prior comprehensive first-episode psychosis interventions, NAVIGATE medication prescription included unique elements of 1) detailed first-episode psychotropic medication guidelines and 2) a computerized decision support system to facilitate shared decision making regarding prescriptions. We present comparisons between the treatment conditions of the psychotropic medications prescribed, side effect experienced, metabolic outcomes and scores from the Adherence Estimator that assesses beliefs related to intentional non-adherence.

Methods—Prescription data were obtained monthly using the Service Use and Resource Form. At baseline, 3, 6, 12, 18 and 24 months, participants reported whether they were experiencing any of 21 common antipsychotic side effects, vital signs were obtained, fasting blood samples collected and the Adherence Estimator completed.

Results—Over the 2 years, the 223 NAVIGATE participants compared to the 181 clinician-choice participants had more medication visits, were more likely to be prescribed an antipsychotic and also an antipsychotic conforming to NAVIGATE prescribing principles and were less likely to be prescribed an antidepressant. NAVIGATE participants experienced fewer side effects and also gained less weight; other vital signs and cardiometabolic laboratory findings did not differ between treatments. Adherence Estimator scores decreased (fewer beliefs associated with non-adherence) with NAVIGATE but not clinician-choice care.

Conclusions—As part of comprehensive care services, medication prescription can be optimized for first-episode psychosis, contributing to better outcomes with less side effect burden than standard care.

Clinical Trials registration—NCT01321177: An Integrated Program for the Treatment of First Episode of Psychosis (RAISE-ETP), http://www.clinicaltrials.gov/ct2/show/NCT01321177

Introduction

Comprehensive specialty care treatment for early psychosis has been strongly advocated (e.g. (1)) and several randomized comparisons performed (2–8). Given the critical role of medication treatment, it is notable that comprehensive specialty care interventions varied widely in how much medication treatment was specified and that such limited information was provided on treatment goals and guidelines, prescriber training and treatment delivery. In published manuscripts, medication prescription was not mentioned for the GET UP PIANO TRIAL intervention (7); the STEP intervention (8) included “psychotropic prescription”; Grawe and colleagues (3) used antipsychotics “at the lowest effective dose”;

the LEO study (2) intervention employed “low dose atypical antipsychotic regimens” while COAST (6) used “optimum atypical medication”, and OPUS (4) used medication treatment “designed individually according to national guidelines”. In contrast, medication prescription in the NAVIGATE intervention of the *Recovery After an Initial Schizophrenia Episode - Early Treatment Program* (RAISE-ETP) included unique elements of 1) program-developed first-episode medication guidelines, 2) a computerized decision support system to support shared decision making regarding prescriptions and 3) training and ongoing support for prescribers throughout the study.

We examined NAVIGATE’s effects on prescription practices and measures of general side effects, vital signs and cardiometabolic outcomes using data from the RAISE-ETP study (5,9) comparing NAVIGATE treatment with clinician-choice Community Care. These analyses complement findings (5) of better symptom Positive and Negative Syndrome Scale (10) and Calgary Depression Scale for Schizophrenia (11) outcomes with NAVIGATE compared with Community Care.

Methods

NAVIGATE treatment (12) included coordinated medication management, psychoeducation, resilience-focused individual therapy and supported employment and education. NAVIGATE team members supported each other’s efforts including adherence to NAVIGATE medication guidelines. Individual resilience-focused therapy included modules about medications and health-promoting behaviors.

Medication procedures

Research data and treatment guidelines (13–17) support distinctive medication strategies for first-episode and multi-episode patients. Our approach to assisting busy clinicians at our non-academic “real world” sites to incorporate specialized first-episode treatment strategies into their work started by developing first-episode medication guidelines based upon review of the treatment literature. Medication recommendations were limited to marketed agents given the community facilities setting. NAVIGATE treatment used a shared decision making model (18). For medication selection, patients and prescribers chose among medications with equivalent evidence based upon patient factors and preferences. The shared decision making framework plus the failure of any antipsychotic to demonstrate superior efficacy for initial treatment of psychosis led to the decision to group recommended medications into treatment stages instead of a single medication algorithm. Medication grouping criteria included data from first-episode or adolescent patients with psychotic disorders and low side effect risk. Symptom remission rather than symptom improvement was the treatment goal. If satisfactory initial response was not obtained, medications were chosen from subsequent stage groups. The antipsychotics available in the United States during guideline development with data from contemporary studies with first-episode or adolescent populations were aripiprazole, chlorpromazine, clozapine, haloperidol, olanzapine, quetiapine, risperidone and ziprasidone. Because of concerns about side effects for chlorpromazine, clozapine, haloperidol and olanzapine and for less maintenance treatment efficacy for haloperidol (19,20), these medications were excluded from the stage 1 group (consisting of the

remaining studied agents aripiprazole, quetiapine, risperidone and ziprasidone). Stage 2 agents were the stage 1 agents plus chlorpromazine, haloperidol and olanzapine; clozapine was a stage 3 agent. For each medication, first-episode dosing guidelines were developed (e.g. for risperidone, starting dose of 1–2 mg/day, target dose of 3–4 mg/day and maximum dose of 8 mg/day). Over the two-year RAISE-ETP treatment duration, continuous antipsychotic treatment was recommended. Patients and prescribers evaluated the potential benefits and disadvantages of switching antipsychotics for participants who entered RAISE-ETP with prescriptions not conforming to NAVIGATE stage 1 principles. Participants who agreed to take antipsychotics but not a NAVIGATE-preferred medication were prescribed their preferred agent; participants who declined to take any antipsychotic had ongoing prescriber monitoring visits. Side effect management strategies (dose reduction being the usual initial strategy) and for monitoring and treatment of cardiometabolic abnormalities were also provided. Since the depressive symptoms of first-episode patients often remit with antipsychotic treatment alone (21), prescription of adjunctive antidepressants for all first-episode patients with depressive symptoms was not advised. Instead, consideration of the persistence and severity of depression was suggested when making decisions about adjunctive antidepressants. The detailed NAVIGATE medication manual is available at (22).

Participants and prescribers used COMPASS, a NAVIGATE-developed computer clinical decision making tool accessed via a secure web-based platform. COMPASS was designed to facilitate patient-prescriber communication. Participants entered information about symptoms, side effects, treatment preferences, medication adherence and attitudes, and substance use into COMPASS before meeting with prescribers. Vital signs data and laboratory test results were also entered. Using a measurement-based approach, the prescriber's assessments, also entered directly into COMPASS, were modified/informed based upon these prior entered data. Integrating participant treatment priorities and the prescriber's assessments, COMPASS provided suggested guideline treatments. Prescribers and participants then made medication decisions informed by these recommendations. NAVIGATE guidelines recommended a prescriber visit at least monthly for the first two years of treatment.

NAVIGATE prescriber training included an in-person group two-day session on NAVIGATE principles followed by individual training via teleconferencing on technical aspects of COMPASS. Monthly group prescriber teleconferences with the NAVIGATE Central Team included group feedback about clinical challenges and NAVIGATE treatment options for these and review of relevant psychosis literature.

RAISE-ETP study

This report focuses on the first two years of patient participation, the minimum by design for all participants. Patients aged 15 to 40 years receiving treatment for a first-episode of psychosis due to schizophrenia, schizoaffective disorder, schizophreniform disorder, brief psychotic disorder, or psychotic disorder not otherwise specified and who had taken ≤6 months of antipsychotics during their lifetime were recruited from 34 community mental health treatment facilities nationwide without preexisting first-episode specialty care programs. Written informed consent was obtained from adult participants; written consent

from guardians and written assent from participants younger than 18. RAISE-ETP was conducted under the guidance of the NIMH Data and Safety Monitoring Board and of Institutional Review Boards at the coordinating center and the sites.

RAISE-ETP employed cluster randomization. The 17 randomly-assigned NAVIGATE sites recruited 223 participants and the 17 Community Care sites 181 participants. Community Care clinicians were trained on recruitment, informed consent and study assessment procedures but received no guidance about treatment approaches. The study design and assessments have been previously described (9). Monthly, patient self-report data on prescription (medication and dose) and on number of medication management visits were obtained with the Service Use and Resource Form (23). At baseline, 3, 6, 12, 18 and 24 months, participants reported in a yes/no format whether they had experienced during the past 30 days 21 common side effects of antipsychotic medications (dizziness, blurred vision, excess saliva, nausea, constipation, increased appetite, weight gain, weight loss, restlessness, shaking, rigidity, fatigue, drowsiness, excess sleep, insomnia, decreased libido, other sexual problems, breast swelling or discharge, impaired sexual performance and amenorrhea). Concurrently, vital signs were obtained and fasting blood samples collected. Participants taking medications also completed the Adherence Estimator, a self-report scale (24) measuring beliefs related to intentional non-adherence that has been validated against pharmacy claims (25).

Statistical analyses

As RAISE-ETP participants had psychotic disorders, our paramount medication question was whether NAVIGATE compared with Community Care treatment was associated with greater likelihood of antipsychotic prescription. We also compared the likelihood of participants receiving a prescription that conformed to NAVIGATE stage 1 (“first-line”). By study month, we determined if participants were prescribed antipsychotic mono-therapy with a NAVIGATE stage 1 antipsychotic. We allowed a broad range of antipsychotic doses (instead of our targeted dose ranges) to qualify as first-line to allow for low doses for antipsychotic initiation and higher doses for management of treatment-resistance (e.g. the qualifying dose range for risperidone was 1–8 mg per day, based upon 1mg/day being the NAVIGATE recommended lowest starting dose and 8 mg/day the highest dose). Participants receiving concurrent stimulants were classified as not being prescribed first-line medications; participants prescribed antipsychotic mono-therapy with paliperidone at approved doses were classified as being prescribed a first-line medication (NAVIGATE training included review of the administration advantages of paliperidone palmitate over risperidone microspheres). Given that depression outcomes were better with NAVIGATE than Community Care, we also compared the likelihood of antidepressant prescription between conditions. Other medication explorations: Antipsychotic prescription involves choice of agent and dose. To characterize these, we examined the likelihood of the most commonly prescribed agents being prescribed (irrespective of dose or other medications prescribed) and the mean modal dose for oral formulations of each agent.

General side effects

The primary measure was the total number of side effects (excluding amenorrhea being not applicable to male participants). Secondary measures were amenorrhea and a priori side effect groupings (sedation, extrapyramidal symptoms, anticholinergic side effects, increased appetite or weight gain and sexual problems). A side effect group was considered present if any side effect within that group was present.

Longitudinal analyses of the any-antipsychotic-use (yes/no) outcome and other binary outcomes reported in Table 1 and Supplemental Table 2 were performed using a generalized linear mixed models analysis with a logit link. PROC GLIMMIX in SAS 9.4 was used. Each subject's modal dose was calculated and the mean modal dose was compared between conditions using a mixed models analysis with a random intercept for site. Longitudinal analysis of the cardiometabolic outcomes (Table 3) and total number of side effects (Table 4) was performed with mixed models using the PROC MIXED procedure in SAS 9.4. The mixed models approach takes into account the within subject correlation of the repeated measurements. The difference in the trajectories between the two treatment groups was assessed by including a time-by-treatment interaction term in the mixed models. Least square means which estimate the population marginal means for a balanced design are reported in Table 3 and 4. In all longitudinal analysis, cluster correlation within site was addressed by including a random intercept for subjects nested within sites. The limited number of clusters in clustered randomized trials can cause an imbalance between treatment groups on baseline measures, potentially confounding the relationship between treatments and outcomes. As per the overall RAISE-ETP statistical analysis plan (5,26), variables with significant baseline group imbalance were included as covariates in our analyses if they were correlated with the outcome of interest at a level of ≥.30.

Multiple comparisons adjustments were done by controlling the False Discovery Rate (FDR) using the Benjamini-Hochberg's procedure (27,28). The R 'multtest' package was used. FDR correction was applied to groups of analyses that addressed the same clinical question. The blocks were: medication classes (Table 1); specific agents (Table 1); daily dose (Table 2); vital signs (Table 3); laboratory findings (Table 3); number of side effects (Table 4) and specific side effects (Supplemental Table 2). Significance was declared for analyses with FDR-corrected p-values <0.05.

Odds ratios in Table 1 were converted to Cohen's d using the formula $d=\log(OR)\frac{\sqrt{3}}{\pi}$. Elsewhere, effect sizes of the difference between least square means were calculated using the formula: $ES=t\sqrt{2/df}$, where t = t-value and df = degrees of freedom.

Results

Participants

Supplemental Table 1 presents participant characteristics. Briefly, 73% were men, the most frequent racial backgrounds were Caucasian (54%) and African-American (37%), the mean age was 23 years and the most frequent diagnoses were schizophrenia (53%) and schizophreniform disorder (14%).

COMPASS implementation

Two hundred eleven of the 223 NAVIGATE participants (94.6%) completed one or more COMPASS visits. During their first 2 years of study participation, NAVIGATE participants completed 3004 COMPASS assessments.

Number of medication visits

As presented in Figure 1, NAVIGATE compared with Community Care participants had significantly more medication visits (treatment-by-time interaction $F=3.78$, $df=23, 9246$, $p<0.0001$; effect of treatment, $F=12.80$, $df=1, 9246$, $p=0.0003$). Over the 2 years, the least square means estimate of the number of medication visits per month was 0.292 (95% CI: 0.226, 0.357) for Community Care and 0.554 (95% CI: 0.423, 0.685) for NAVIGATE.

Medication prescription

As shown in Table 1, NAVIGATE compared with Community Care participants were significantly more likely to receive an antipsychotic prescription (odds ratio 3.734, 95% CI: 1.709, 8.162) and less likely (odds ratio 0.391, 95% CI: 0.162, 0.943) to receive an antidepressant prescription.

Over the trial, NAVIGATE participants were more likely to receive prescriptions conforming to NAVIGATE first-line principles (odds ratio 2.189, 95% CI:1.084, 4.421). Prescriptions at study entry for NAVIGATE and Community Care participants were equally likely to not conform with NAVIGATE first-line principles ($t=-0.49$, $df=744$, $p=0.6263$). In post hoc analyses of participants who were not receiving a NAVIGATE first-line prescription at baseline, 62.7% of the 110 NAVIGATE participants compared with 44.4% of the 90 Community Care participants later received a NAVIGATE first-line prescription (odds ratio = 2.065, 95% CI = 1.024, 4.164, $t=2.11$, $df=31$, $p=0.0432$).

As shown in Tables 1 and 2, the specific antipsychotics prescribed and mean modal dose did not significantly differ between conditions for any of the major antipsychotics. At a trend level, NAVIGATE compared with Community Care participants were more likely to be prescribed aripiprazole and less likely to be prescribed haloperidol.

Vital Sign and Cardiometabolic Outcomes

As presented in Table 3, both weight and BMI analyses revealed significant treatment-by-time interactions. The estimated mean increase in BMI from baseline to month 24 was 2.10 (95% CI:1.32, 2.89) for NAVIGATE and 2.44 (95% CI:1.90, 2.99) for Community Care participants; the corresponding estimated weight gain was 6.51 (95% CI:4.61, 8.41) kg for NAVIGATE and 7.31 (95% CI:5.62, 9.00) for Community Care participants. No significant treatment-by-time interactions or treatment effects were detected in analyses of other vital signs data or of lipid or carbohydrate metabolism measures.

General Side Effects

Analysis of the number of side effects revealed a significant treatment-by-time interaction. As shown in Table 4, NAVIGATE and Community Care participants reported equal number of side effects at baseline but NAVIGATE participants reported fewer side effects at

subsequent visits (significantly less at month 6 and 12 and at a trend level at months 3, 18 and 24). A secondary analysis controlling for antipsychotic prescription similarly revealed an advantage for NAVIGATE treatment (treatment- by-time interaction, F=2.88, df=5,1087, p=0.004). Supplemental Table 2 presents the analyses of side effect groups. NAVIGATE participants were significantly less likely to have sedation or anticholinergic side effects and at a trend level less extrapyramidal symptoms, appetite increase and sexual dysfunction.

Adherence Estimator

Scores did not differ at baseline and decreased (fewer beliefs associated with non-adherence) significantly among NAVIGATE but not Community Care participants (treatment-by-time interaction F=2.46, df=5,940, p=0.0316). Least square means estimates of baseline and 24 month scores were 8.3278 (SE=0.8577) and 6.0870 (SE=0.6855) with NAVIGATE (change decrease of 2.2408 (SE=1.0622)) and 7.1239 (SE=0.8015) and 7.8996 (SE=0.8052) with Community Care (change increase of 0.7757 (SE=0.9308)).

Discussion

The NAVIGATE model was developed to treat a specialized population, patients with first-episode schizophrenia and related disorders, in non-academic “real world” settings. An initial question was whether the COMPASS decision support system could be implemented and used in community settings. The 3,004 completed COMPASS visits provide an affirmative response to this question. Further, NAVIGATE participants had on average slightly less than twice as many monthly medication management visits (0.554 versus 0.292) as Community Care participants and the pattern of more NAVIGATE medication visits was present across all trial phases. These findings support the sustained feasibility and acceptability of the NAVIGATE treatment model in comparison with usual care. NAVIGATE prescribers had the support of a manual, training by the Central Team in treatment principles and COMPASS use, the guidance that was built into the COMPASS visits and access to monthly teleconferences.

The next key question was whether NAVIGATE recommendations and the COMPASS system influenced prescriptions? Regarding antipsychotics, prescriptions for any antipsychotic as well as prescriptions conforming to NAVIGATE first-line antipsychotic principles were significantly more likely with NAVIGATE compared with Community Care. Prescriptions for specific antipsychotics did not differ significantly. At a trend level, aripiprazole prescriptions were more likely and haloperidol prescriptions less likely for NAVIGATE participants, consistent with NAVIGATE-preferred medication stages. Clozapine was required only infrequently with our first-episode population. Rates were greater with NAVIGATE than Community Care (4.7% versus 1.8% of months with prescription data) but the difference was not significant. Given the NAVIGATE emphasis upon low dose strategies, we anticipated that NAVIGATE prescriptions would be for lower doses. Instead we found no differences, probably resulting from the finding that the mean modal doses for Community Care antipsychotic prescriptions overall were within recommended first-episode treatment ranges.

In a prior analysis of medication prescription at RAISE-ETP entry (29), 39.2% of participants were receiving problematic prescriptions. An important question is whether rates of problematic medication prescriptions change during extended treatment. Differences in data sources available at baseline and longitudinally precluded applying the prior baseline criteria to the current longitudinal analyses. Prescriptions that do not conform with NAVIGATE first-line principles may be clinically appropriate (e.g. for symptoms that do not improve with a first-line medication). Nevertheless, the extent that patients with baseline prescriptions not conforming to NAVIGATE first-line principles later receive a first-line prescription does provide one metric to evaluate whether prescription patterns improve over time. It is encouraging that substantial numbers of Community Care participants receiving prescriptions not conforming with NAVIGATE first-line principles eventually received a NAVIGATE first-line prescription and that NAVIGATE compared with Community Care treatment significantly increased the likelihood of this change.

We earlier reported that NAVIGATE participants had lower depressive symptoms (5). The present analysis shows that this was achieved with significantly less likelihood of antidepressant prescription. This may reflect the finding that the depressive symptoms of patients with first-episode psychosis often remit with antipsychotic treatment alone (21) and this information was included in NAVIGATE training. Further, the NAVIGATE psychosocial interventions (12) may have contributed to better depression symptom outcomes. A recent meta-analysis (30) found small beneficial effects for adjunctive antidepressants for depression and negative symptoms with people with schizophrenia. First-episode subgroup analyses did not detect effects but the number of first-episode studies included was small. Negative symptom outcomes in RAISE-ETP did not differ between conditions despite less antidepressant use. Further research is needed to determine 1) whether first-episode psychosis specialty care treatment consistently produces better depression outcomes with less antidepressant prescription and 2) antidepressant effects (if any) on negative symptoms among first-episode patients.

The lower number of side effects among NAVIGATE participants is notable given that NAVIGATE participants were more likely to be prescribed antipsychotics and the side effects assessed were ones specifically associated with antipsychotic treatment. NAVIGATE training emphasized side effect prevention and/or minimization and the COMPASS system included structured side effect assessments at each visit and decision support for side effect management. These may have contributed to less side effect burden from prevention efforts and better detection and treatment of antipsychotic-induced side effects when they occurred. The less frequent use of antidepressants at NAVIGATE sites may also have contributed to fewer side effects.

Although significant differences between NAVIGATE and Community Care outcomes were found for weight gain/BMI, the differences were small in magnitude. Nevertheless, given the likely future duration of antipsychotic exposure, such differences are potentially important. Given the potential adverse effects of antipsychotics on lipid and glucose metabolism, it is reassuring that NAVIGATE treatment enhanced antipsychotic prescription compared with Community Care while producing similar laboratory outcomes. Nevertheless, the mean 6.5

kg weight gain among NAVIGATE participants shows that additional tools for preventing adverse metabolic outcomes are needed.

Medication data from other comparisons of comprehensive first-episode specialty care with usual care are limited. Broadly, data from our and other trials (31,32) and from demonstration projects (33) suggest that comprehensive care treatment may be associated with better medication treatment. Intervention compared with control condition participants in the LEO trial were significantly less likely to stop prescribed medication (31) and in the OPUS trial more likely at a trend level of significance to be taking an antipsychotic at 1-year but not at 2-year follow-up (32).

A limitation of RAISE-ETP medication data is the reliance on patient self-report. Self-report was necessary as a source instead of clinic or pharmacy records to permit medication tracking for participants who discontinued treatment at their RAISE-ETP site. Patient self-report may have introduced inaccuracies in the overall data, but should have had limited impact on the NAVIGATE versus Community Care comparisons, as participants in both conditions should have had equivalent ability to report treatments prescribed. It should be noted that our data are for medications prescribed instead of medications taken. The Adherence Estimator data documented an advantage with NAVIGATE but not Community Care treatment for medication beliefs related to adherence. An important future research question is whether these belief changes translate into improved adherence.

In summary, we previously reported differential improvement with the comprehensive NAVIGATE treatment model compared to Community Care in quality of life and clinical psychopathology outcomes (5). We now add findings of greater frequency of antipsychotic prescription, reduced side effect burden, reduced antidepressant prescription, and some reduction of the consequences of antipsychotics on medical health. The NAVIGATE model of measurement-based care in the context of shared decision making provides a framework for incorporating future advances. As knowledge of first-episode medication treatment advances, future medication guideline improvements may produce even better outcomes than our current efforts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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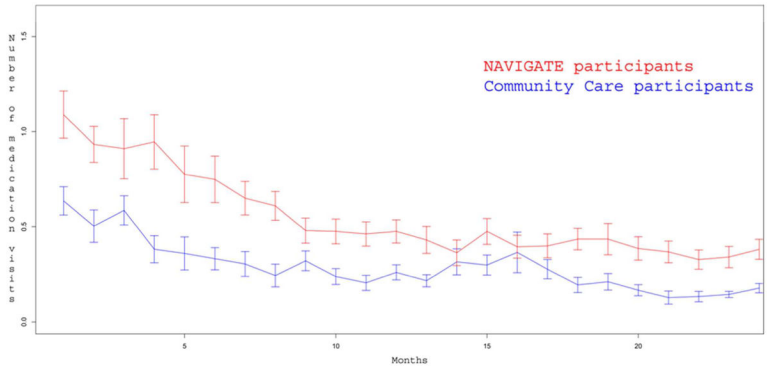

Figure 1.

Least Squares Mean Estimates of Number of Medication Visits by NAVIGATE and Community Care Participants

Bars present standard errors

Treatment-by-time interaction, F=3.78, df=23, 9246, p<0.0001; effect of time, F=41.85, df=23, 9246, p<0.0001; effect of treatment, F=12.80, df=1, 9246, p=0.0003

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Table 1

Odds ratios of specific prescriptions across conditions

Prescribed medication	Months of prescription		Comparison across treatment conditions, accounting for clustering[1]								
	Community Care (data available for 2548 months)	NAVIGATE (data available for 3686 months)	Odds ratio between conditions[2]	95% Confidence Interval of odds ratio		Effect size	F	Df		P-value unadjusted	P-value adjusted for multiple comparisons
Medication classes											
Any antipsychotic	1901 (74.6%)	3193 (86.6%)	3.734	1.709	8.162	0.73	11.78	1	32	0.0017	0.0051
Antipsychotic conforming to Navigate first-line principles	1065 (41.8%)	1873 (50.8%)	2.189	1.084	4.421	0.43	5.15	1	32	0.0301	0.0373
Any antidepressant	997 (39.1%)	1044 (28.3%)	0.391	0.162	0.943	−0.52	4.72	1	32	0.0373	0.0373
Specific agents											
Oral antipsychotics											
Aripiprazole	245 (9.6%)	839 (22.8%)	4.126	1.354	12.573	0.78	6.72	1	32	0.0143	0.0786
Clozapine	45 (1.8%)	174 (4.7%)	4.149	0.505	34.061	0.78	1.90	1	32	0.1782	0.3920
Haloperidol	169 (6.6%)	76 (2.1%)	0.164	0.043	0.627	−1.00	7.54	1	32	0.0098	0.0786
Olanzapine	196 (7.7%)	438 (11.9%)	1.899	0.776	4.648	0.35	2.13	1	32	0.1541	0.3920
Paliperidone	164 (6.4%)	153 (4.2%)	0.798	0.243	2.624	−0.12	0.15	1	32	0.7019	0.7019
Quetiapine	205 (8.0%)	307 (8.3%)	0.746	0.294	1.894	−0.16	0.41	1	32	0.5261	0.6452
Risperidone	516 (20.3%)	590 (16.0%)	0.559	0.201	1.557	−0.32	1.34	1	32	0.2564	0.4701
Ziprasidone	136 (5.3%)	174 (4.7%)	1.463	0.435	4.923	0.21	0.41	1	32	0.5279	0.6452
Long acting formulations											
Any long acting	328 (12.9%)	659 (17.9%)	1.447	0.486	4.310	0.20	0.48	1	32	0.4952	0.6452
Haloperidol decanoate	131 (5.1%)	91 (2.5%)	0.236	0.053	1.041	−0.80	3.93	1	32	0.0561	0.2057
Paliperidone palmitate	166 (6.5%)	376 (10.2%)	1.343	0.357	5.062	0.16	0.21	1	32	0.6533	0.7019
Risperidone microspheres[3]	18 (0.7%)	139 (3.8%)									

[1] the models included treatment condition, time and the treatment-by-time interaction; the treatment-by-time interaction was not significant for any analysis

[2] odds ratios less than 1.0 indicate more likelihood of being prescribed at Community Care sites; ratios greater than 1.0 indicate more likelihood of being prescribed at NAVIGATE sites

[3] a comparison across conditions using the methods employed for the other agents could not be performed due to risperidone microspheres not being prescribed during some months in the Community Care condition.

Table 2

Least Squares Means Estimates of Mean Modal Total Daily Dose of Oral Antipsychotics

	Community Care		NAVIGATE							
Medication	**Mean modal total daily dose (mgs)**	**Standard Error**	**Mean modal total daily dose (mgs)**	**Standard Error**	**Effect size of difference**	**F**	**DF**		**P-value unadjusted**	**P-value adjusted for multiple comparisons**
Aripiprazole	9.9001	1.4198	11.7947	1.0650	0.148	1.14	1	104	0.2882	0.5764
Clozapine[1]	433.08	116.64	330.05	51.1483	−0.462	0.64	1	6	0.4529	0.7246
Haloperidol[2]	6.3609	1.0007	7.4112	1.4649	0.174	0.35	1	23	0.5596	0.7461
Olanzapine	16.2874	2.3122	16.0956	1.8331	−0.010	0.00	1	71	0.9484	0.9484
Paliperidone[1,3]	6.4629	0.5292	6.1699	0.4912	−0.104	0.16	1	31	0.6882	0.7865
Quetiapine	252.72	33.1365	302.35	31.4412	0.227	1.18	1	46	0.2830	0.5764
Risperidone	3.3596	0.2334	2.8795	0.2233	−0.186	2.21	1	128	0.1396	0.5764
Ziprasidone	92.3507	15.1161	114.65	11.5487	0.297	1.37	1	31	0.2499	0.5764

[1] analysis included sex as a covariate

[2] analysis included covariate of baseline PANSS total score

[3] main effect of sex, F=5.0, DF=1, 31, p=0.0322

Table 3

Cardiometabolic Outcomes

		Community Care		NAVIGATE			Treatment-by-time interaction				
	Month	**Mean**	**SE**	**Mean**	**SE**	**Effect size of difference**	**F**	**df**	**df**	**P-value unadjusted**	**P-value adjusted for multiple comparisons**
Body Composition											
BMI							3.04	5	1215	0.0098	0.0245
	baseline	27.2427	0.7217	26.0958	0.4951						
	3	27.8401	0.6771	27.3082	0.485						
	6	28.3095	0.7156	27.7756	0.5306						
	12	28.5715	0.6235	27.894	0.5931						
	18	29.2651	0.6163	28.4123	0.6228						
	24	29.6877	0.6768	28.1995	0.7129						
	Change from baseline to 24 months	2.4450[c]	0.2741	2.1037[c]	0.3192	−0.033					
Weight (kg)							3.05	5	1215	0.0096	0.0245
	baseline	81.3760	1.9108	78.2802	1.7203						
	3	83.2126	1.8154	81.9948	1.6670						
	6	84.6799	1.9307	83.5032	1.6971						
	12	85.4158	1.5804	83.8114	1.9195						
	18	87.4738	1.5187	85.4652	2.1124						
	24	88.6817	1.7333	84.7894	2.3428						
	Change from baseline to 24 months	7.3057[c]	0.8451	6.5093[c]	0.9510	−0.026					
Waist Circumference (cm)[1]							1.92	5	1201	0.0885	0.1106
	baseline	92.7275	1.7704	89.9862	1.3025						
	3	93.6111	1.7098	92.0080	1.5107						
	6	94.2452	1.8743	92.8688	1.4867						
	12	94.7920	1.7671	93.6949	1.5890						
	18	96.3404	1.8852	95.1632	1.7295						

		Community Care		NAVIGATE			Treatment-by-time interaction				
	Month	**Mean**	**SE**	**Mean**	**SE**	**Effect size of difference**	**F**	**df**	**df**	**P-value unadjusted**	**P-value adjusted for multiple comparisons**
	24	97.7259	2.0378	94.3385	1.9641						
	Change from baseline to 24 months	4.9983[c]	1.2039	4.3523[c]	0.9794	−0.017					
Arterial Blood Pressure (sitting)											
Systolic (mm Hg)[2,3]							2.39	5	1226	0.0361	0.0602
	Baseline	116.35	0.6883	118.08	0.9782						
	3	117.64	1.2630	119.00	0.9406						
	6	120.22	1.3228	120.01	0.7244						
	12	120.36	1.1864	120.81	1.5657						
	18[*]	118.55	1.3222	122.13	1.1864						
	24	120.09	1.2620	119.33	1.3379						
	Change from baseline to 24 months	3.7398[b]	1.1792	1.2483	1.4352	−0.054					
Diastolic (mm Hg)[4]							1.17	5	1226	0.3218	0.3218
	baseline	74.6808	0.5214	76.2811	0.856						
	3	76.0545	1.0492	77.0225	0.8895						
	6	79.0419	1.1567	78.7375	0.6408						
	12	77.7743	0.8642	78.9512	1.258						
	18	78.2073	1.2558	79.6163	1.028						
	24	79.8126	1.3882	78.6973	1.3664						
	Change from baseline to 24 months	5.1319[c]	1.3175	2.4161	1.2531	−0.060					
Fasting Lipids											
Total Cholesterol (mg/dL)							1.97	5	891	0.0811	0.1825
	baseline	169.95	3.2728	174.64	1.9448						
	3	170.02	2.2383	177.16	2.6500						
	6	171.34	2.7588	173.65	3.2709						
	12	172.55	3.5069	169.47	3.0377						

		Community Care		NAVIGATE			Treatment-by-time interaction				
	Month	**Mean**	**SE**	**Mean**	**SE**	**Effect size of difference**	**F**	**df**	**df**	**P-value unadjusted**	**P-value adjusted for multiple comparisons**
	18	171.35	3.4717	173.11	4.1272						
	24	168.58	3.3068	170.62	3.4961						
	Change from baseline to 24 months	−1.3671	3.2445	−4.0195	2.3802	−0.031					
LDL Cholesterol (mg/dL)							0.28	5	881	0.9245[1]	0.9245
	baseline	99.9251	2.5774	101.42	1.6707						
	3	103.49	1.7704	106.23	2.2987						
	6	103.66	2.3027	103.65	2.2947						
	12	99.6132	3.0655	98.9614	2.1996						
	18	99.804	2.2549	100.53	3.3883						
	24	100.44	2.9749	100.39	2.7796						
	Change from baseline to 24 months	0.5183	3.6255	−1.0338	2.7292	−0.016					
HDL Cholesterol (mg/dL) fasting and non-fasting[5]							2.75	5	958	0.0179	0.0806
	baseline	48.0421	1.1452	49.7708	1.5056						
	3	46.853	1.2623	47.1032	1.3076						
	6	46.4682	1.3688	46.0938	1.4369						
	12	47.2537	1.3968	45.1386	1.0349						
	18	47.9065	1.2309	45.6219	1.1983						
	24	45.6067	1.0796	46.2947	1.1081						
	Change from baseline to 24 months	−2.4354[b]	0.8238	−3.4760[b]	1.1631	−0.033					
Triglycerides (mg/dL)							0.93	5	891	0.4583	0.6772
	baseline	115.93	10.3916	114.25	7.4903						
	3	114.38	11.0634	124.95	9.3386						
	6	117.45	10.31	120.1	7.0756						
	12	120.2	8.8019	127.37	10.4994						

		Community Care		NAVIGATE			Treatment-by-time interaction				
	Month	**Mean**	**SE**	**Mean**	**SE**	**Effect size of difference**	**F**	**df**	**df**	**P-value unadjusted**	**P-value adjusted for multiple comparisons**
	18	121.87	11.1891	135.95	6.5137						
	24	124.32	13.4618	123.06	8.8039						
	Change from baseline to 24 months	8.3893	12.6797	8.8121	3.7783	0.001					
Fasting Carbohydrate Metabolism											
Glucose (mg/dL)							0.83	5	862	0.5267	0.6772
	baseline	90.0145	3.6372	87.6624	2.2898						
	3	93.7213	2.9028	88.7429	2.2742						
	6	92.541	3.0156	88.8855	2.2706						
	12	92.0924	3.6772	91.5533	2.5357						
	18	93.0603	3.1043	94.4915	3.9186						
	24	95.3634	6.7115	92.0561	3.4818						
	Change from baseline to 24 months	5.3489	4.6509	4.3937	2.1333	−0.009					
Insulin (uU/mL)							2.54	5	742	0.0273	0.0819
	baseline	12.3547	1.4812	13.8299	2.3354						
	3	12.694	1.9596	13.0922	1.7490						
	6	11.9127	1.2836	16.2503	3.2596						
	12	14.1626	2.6064	14.8295	1.5054						
	18	14.7696	3.0439	19.8163	3.1310						
	24	18.6943	4.5002	16.4618	2.9418						
	Change from baseline to 24 months	6.3395	4.0985	2.6319	2.6781	−0.039					
HOMA-IR							1.70	5	720	0.1316	0.2369
	baseline	3.2013	0.6296	3.5299	0.7361						
	3	3.2995	0.6034	3.3740	0.5379						
	6	2.8749	0.4322	4.4203	1.0781						
	12	3.7653	0.9853	3.6526	0.4825						

		Community Care		NAVIGATE			Treatment-by-time interaction				
	Month	**Mean**	**SE**	**Mean**	**SE**	**Effect size of difference**	**F**	**df**	**df**	**P-value unadjusted**	**P-value adjusted for multiple comparisons**
	18	3.9467	0.8985	5.3059	1.0898						
	24	7.3170	3.8796	4.3619	0.9572						
	Change from baseline to 24 months	4.1157	3.4241	0.8320	0.9309	−0.049					
HbA1c (fasting and nonfasting)							2.80	5	920	0.0161	0.0806
	baseline	5.4281	0.09299	5.3029	0.05684						
	3	5.5872	0.2025	5.4064	0.03318						
	6	5.5056	0.1139	5.3887	0.04380						
	12	5.3687	0.1153	5.4239	0.06284						
	18	5.4571	0.1431	5.4716	0.07376						
	24	5.4195	0.09117	5.4591	0.06389						
	Change from baseline to 24 months	−0.008538	0.04769	0.1562[b]	0.05688	0.104					

Difference between conditions at each timepoint,

[*] p (adjusted) <0.05;

[**] p (adjusted) <0.01

Change from baseline,

[a] p (adjusted) <0.05;

[b] p (adjusted) <0.01,

[c] p (adjusted) <0.001

[1] main effect of time, F=8.44, DF=5,1201, p (adjusted) = 0.0001;

[2] analysis included sex as a covariate;

[3] main effect of time, F=3.82, DF=5,1226, p (adjusted) = 0.0001 and main effect of sex, F=68.98, DF=1,1226, p<0.0001;

[4] main effect of time, F=11.22, DF=5,1226, p (adjusted) = 0.0001;

[5] main effect of time, F=7.33, DF=5, 958, p (adjusted) = 0.000

Table 4

Least square means estimates of number of side effects[1]

	Community Care		NAVIGATE					
						Differences of means		
	mean	Standard error	mean	Standard error	Effect size of difference	t	P-value unadjusted	P-value adjusted for multiple comparisons
Baseline	7.0911	0.2472	6.8875	0.2734	−0.022	0.55	0.5808	0.5808
3	6.0332	0.3277	4.9624	0.4101	−0.094	2.04	0.0416	0.0832
6	6.1748	0.3597	4.3591	0.3109	−0.148	3.82	0.0001	0.0006
12	5.6097	0.2845	4.1927	0.4397	−0.118	2.71	0.0069	0.0207
18	5.0961	0.4325	4.1169	0.3399	−0.077	1.78	0.0753	0.0904
24	5.2029[2]	0.5263	4.0879[2]	0.2851	−0.079	1.86	0.0627	0.0904

[1] the model included treatment condition, time and the treatment-by-time interaction; treatment- by-time interaction, F=3.86, df=5,1143, p=0.0018

[2] the effect size for the decrease in the mean number of side effects from baseline to 24 months for the Community Care condition was −0.156 and −0.34 for Navigate