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Gender Differences In Outcomes Of Coordinated Specialty Care For Early Psychosis

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GENDER DIFFERENCES IN OUTCOMES OF COORDINATED SPECIALTY CARE FOR EARLY PSYCHOSIS

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Abstract (250 words)

BACKGROUND
There has been growing interest in early intervention in psychotic disorders. However, gender differences in the outcomes of treatment have not been \studied in a clinical trial.

METHODS
Patients diagnosed with schizophrenia or schizoaffective disorder with less than 6 months exposure to antipsychotics entered a cluster randomized trial of coordinated specialty care in the Recovery After an Initial Schizophrenia Episode Early Treatment Program (RAISE-ETP). Secondary analyses examined gender differences in baseline characteristics as well as two-year gender outcomes, and the response to treatment controlling for baseline differences. Blinded evaluators assessed the Quality of Life Scale and the Positive and Negative Syndrome Scale (PANSS) every 6 months.

RESULTS
Altogether 404 individuals aged 15-40 entered the study, of whom 111 (27.4%) were female and 293 (72.5%) were male. At baseline, women were significantly more likely to have been married (p=0.007) and to be living independently (p=0.012) than men. Women were also more likely to be diagnosed with schizoaffective disorder, bipolar type (p=0.006) and scored higher on the depression subscale of the PANSS (p=0.0004). Women were less likely to use or abuse cannabis (p=0.0004), though no less likely to use or abuse alcohol. Controlling for these differences, there were no significant gender differences in outcomes or response to treatment.

CONCLUSION
Baseline gender differences in comorbid substance use and prevalence of mood symptoms in women with FEP are consistent with previous studies. The absence of significant gender differences in outcomes or response to treatment has not been previously established in a multi-site trial.

Acknowledgements

With infinite thanks to Dr. Rosenheck and his patient guidance.

Table of Contents

INTRODUCTION

Disease Presentation by Gender and Diagnosis

There has been increasing interest in biological and psychosocial differences between women and men in the clinical presentation, course of illness, and treatment outcomes of mental disorders and specifically in psychotic disorders such as schizophrenia. [1] Recent studies suggest that women with psychotic disorders are more likely to present with positive and affective symptoms while men have more prominent negative symptoms and cognitive impairments, [2 3 4] and are more likely to meet criteria for comorbid substance use disorders. [2] Female patients have been found to experience a pre-psychotic prodrome for twice as long as male patients, [5] and, perhaps as a result, experience full psychotic disorders at later age. [6] They also experience less impaired social functioning [7], while longitudinally, it has been suggested that women respond more quickly and completely to available treatments, with greater likelihood of remission and lower relapse rates. [6] While short-term studies suggest better quality of life among women with psychotic disorders than men, [7] longer term studies suggest these differences dissipate over time. [8]

Initial Treatment

The mainstay of treatment for psychotic spectrum disorder is symptomatic treatment with antipsychotics. There is a preference for second-generation antipsychotics due to fewer extrapyramidal symptoms associated with second-generation antipsychotics.[9] After initiating treatment, antipsychotics are titrated to therapeutic dose as tolerated.

Agent	**Initial oral dose range (mg/day)**	**Usual oral dose range (mg/day)**	**Usual maximum oral dose (mg/day)**
Aripiprazole	10 to 15	10 to 15	30
Clozapine	25 to 50	150 to 600	900
Olanzapine	5 to 10	10 to 20	30
Quetiapine	50 (immediate release) 300 (extended release)	400 to 800	800
Risperidone	1 to 2	2 to 6	8

Supplemental Table 1: Initial Dosing and Titration of Selected Second-Generation Antipsychotics [10]

Maintenance Treatment

If patient has responded fully and is no longer psychotic, antipsychotics are continued for two to three years if there is high suspicion for schizophrenia. Weekly follow-up is recommended for first three months of treatment for clinical evaluation of medication efficacy as well as monitoring of possible adverse effects including extrapyramidal symptoms (e.g. akathisia, parkinsonism, tardive dyskinesia), orthostasis, metabolic dysregulation (e.g. insulin resistance, weight gain), and QT elongation.

If patient has a partial response or recurrence of symptoms, assessing for compliance is important. Antipsychotics have a range of side effects that may significantly impact quality of life and may lead to medication noncompliance. If patient has had an adequate trial of the antipsychotic at therapeutic range, a change in antipsychotic is indicated. The decision is usually patient-centered, considering side effect profiles.

If patient continues to be symptomatic after two or more antipsychotics, the patient is considered to have treatment-resistant schizophrenia, and clozapine is indicated.

Study Purpose and Goals

Among the most important recent developments in the treatment of schizophrenia has been growing evidence that comprehensive coordinated specialty care can have important positive impact on outcomes on when provided early in course of the illness. [11] However, only two studies have focused specifically on differences between women and men in their first episode of psychosis (FEP). [3] [4]These studies, one on an Italian and the other on a Swiss FEP sample, largely confirmed previous baseline findings showing that women showed higher levels of affective symptoms and men, more severe negative symptoms. Female patients also showed greater insight into their illness with higher levels of functioning but more unmet needs. To our knowledge, no studies have looked at gender differences in the delivery and outcomes of coordinated specialty care for FEP in the U.S..

The recent National Institute of Mental Health (NIMH)-funded Recovery After an Initial Schizophrenia Episode-Early Treatment Program (RAISE-ETP) study, a 34 site cluster randomized trial of early episode psychosis in real-world settings (n=404), found comprehensive coordinated care improved quality of life, reduced symptoms [12] and increased school and work involvement [13] as compared to usual community care. Interaction analyses have shown greater improvement in those with shorter duration of untreated psychosi life s (Kane 2016) or higher socio-economic status (Bennett and Rosenheck, 2020). However, a secondary analysis comparing female and male participants has yet to be conducted. In this paper, we use data available from the RAISE-ETP trial, to compare women and men on baseline characteristics, use of services, and two-year outcomes.

Hypothesis

Literature review suggest that men have worse baseline functioning, less insight, poorer quality of life and slower antipsychotic response than women. My hypothesis is that men will benefit more from early intervention given their lower baseline functioning at FEP.

STATEMENT OF PURPOSE

To determine gender differences in outcomes of the RAISE-ETP trial.

METHODS

Student Contributions

Student completed a thorough literature review on existing literature on the effect of gender on psychotic spectrum disorders and of outcomes in psychiatric and medical illnesses. This ad hoc analysis did not require generation of data. Statistical analysis of public access data, available from the National Institute of Mental Health was conducted by collaborator Dr. Daniel Bennett and Dr. Robert Rosenheck. Student, with the help of Dr. Rosenheck, created relevant figures and tables, and interpreted the findings in context of larger literature on gender-specific outcomes in mental illness and other areas of medicine.

Ethics Statement

Previous studies have included details on the recruitment process including a CONSORT diagram of recruitment and disposition, [12] and an extensive description of the clinical intervention, called NAVIGATE [14].

Methods Description

Subjects and Sites

Inclusion criteria included: presenting for first episode of psychosis, exposure to antipsychotic medication for fewer than 6 months, and enrollment between July 2010 and July 2012. In total, 404 individuals aged 15-40 entered the study, of whom of whom 111 (27.4%) were female and 293 (72.5%) were male. Written informed consent was obtained from adult participants or from legal guardians for those under 18 years old. The Institutional Review Boards of the coordinating center and at each site approved the study. An NIMH Data and Safety Monitoring Board provided oversight to the original study. Thirty-four community mental health treatment centers across the United States were randomized to either to a specialized coordinated intervention called NAVIGATE or to usual community care.

Intervention

NAVIGATE coordinated care included: a) a web-based decision support system for assisting personalized medication management; b) family psycho-education; c) individual, resilience-focused training in illness self-management; and d) supported employment and education via remote training and consultation. [14] Participants without initial interest in work or school received continuing encouragement to participate in supported employment and education. At 13 of 17 NAVIGATE sites, patients received at least twice a month contact with employment and education specialists. The mean caseload was 10.72 clients for every employment and education specialist. The patient rating of support for employment and education across 9 fidelity items found that 4 sites

were rated between upper range of basic to good, 11 sites rated lower range of basic to good, and 2 sites were limited in fidelity. [12]

Assessments

Blinded evaluators remotely assessed quality of life and symptoms (see measures, below) at baseline and every 6 months for two years via videoconferencing. Self-report rating scale assessments were obtained at the same interval.

Self-report data on socio-demographic characteristics were recorded at baseline. Independent research assistants gathered additional data through monthly patient interviews. These interviews measured service use and employment on a monthly basis and self-reported well-being and sources of income (including disability payments) every three months.

Measures

Initial assessment included documentation of socio-demographic characteristics. A central team of blinded evaluators assessed quality of life using the Quality of Life Scale (QLS) [15] with 4 subscales of interpersonal relationships, instrumental role functioning, intrapsychic foundations (more recently re-conceptualized as "motivation"), and common objects and activities used in daily life. Psychiatric symptom severity was measured with the Positive and Negative Syndrome Scale (PANSS) [16] with five subscales [17] and the Calgary Depression Scale for Schizophrenia (CDSS). [18]

Patients self-reported well-being was assessed using a reduced versions of the perceived well-being scale [19], the Mental Health Recovery Measure, [20] the Autonomy Support Scale-Short Form, [21] the Brief Evaluation of Medication Influences and Beliefs, [22] and the Stigma Scale. [23]

Statistical Methods

Baseline characteristics were compared between genders using linear regression with interactions between round dummies and gender.

All standard errors in the longitudinal regressions were clustered by site to account for arbitrary error correlations within a site, including across individuals over time. All regressions controlled for baseline marital status, current residence, diagnosis, cannabis use, previous hospitalizations, age, and baseline depression symptoms because these variables were shown to be imbalanced by gender at baseline.

Longitudinal analyses of gender differences included terms representing gender, time in months since the baseline (a single continuous variable) and the interaction of gender by time.

Longitudinal analyses of gender differences in treatment effects included main effects for gender, time, and treatment; the interaction of gender by time and treatment by time; and the term of interest, the three-way interaction of gender by time by treatment. Subscales were examined only for the primary outcome, the QLS, to avoid artifactual results from multiple comparisons.

RESULTS

Baseline Characteristics

A total of 111 (27.4%) female patients and 293 (72.5%) male patients were included in the study. Mean age of female patients at first episode psychosis was significantly older at 24.33 ± 6.19 years compared to 22.68 ± 4.5 years of male patients ($p = 0.0067$) (Table 1).

Of the female patients, 89 (80.2%) were never married, compared to 269 (91.8%) of male patients ($p=0.007$) (Table 1). A total of 31 (27.9%) female patients lived independently and 72 (64.9%) lived with family members including parents, grandparents, and siblings. In comparison, only 41 (14.0%) of male patients lived independently and 215 (73.4%) lived with family. Females patients were significantly more likely to have been married ($p=0.007$) and significantly more likely to be living independently ($p=0.012$) compared to male patients.

A total of 44 female patients (40%) were covered by public insurance compared to 83 (28.5%) male patients ($p=0.03$).

There were no significant gender differences in race/ethnicity, patient education and employment status, or parental education status (Table 1).

In diagnosis across the psychotic disorder spectrum a great proportion of women than men (14 women, 12.6% and 10 (3.4%) men) were diagnosed with schizoaffective disorder, bipolar type ($p=0.006$).

Turning to substance abuse or dependence, women were overall less likely to use or abuse drugs of any type with only 24 (28.8%) female patients meeting abuse or dependence criteria for lifetime cannabis use, compared to 116 (39.6%) male patients

(p=0.0023). There were no significant gender differences in lifetime alcohol abuse or dependence. Recent use of illegal drugs including cannabis also was significantly different across genders with women using drugs on an average of 1.55 ± 5.33 days of the 30 days prior to enrollment, significantly few days than men who used drugs on an average of 3.74 ± 8.07 days (p=0.008).

There were also significant gender differences in number of hospitalizations prior to enrollment in the study. Among female patients 5 (6.2%) were hospitalized twice and 6 (7.4%) were hospitalized three times or more prior to enrollment. In contrast, only 9 male patients (3.8%) were hospitalized twice and only 12 (5.0%) were hospitalized three or more times prior to enrollment. Overall, women were significantly more thus likely to have been hospitalized multiple times prior to FEP (p=0.0087) (Table 2).

There were no significant gender differences on measures of medication compliance or duration of untreated psychosis.

On the Heinrich Carpenter measure of Quality of Life Interview women scored significantly higher than men (p=0.02) (Table 3). Specifically, women averaged higher on on the interpersonal relations and the common objects and activities subscales (Table 3). There were no differences within the instrumental role subscale and intrapsychic foundations subscale.

On the PANSS symptom severity scale, women scored significantly higher (p=0.0004) on the depression subscale (Table 3). There were no significant gender differences on the total PANSS score or on other subscales of the PANSS (positive, negative, disorganized/concrete, and excited). There were also no significant differences

in CDSS, a specific depression symptom severity scale, although women had non-significantly higher scores (p=0.15).

There were no further gender differences in other self-reported social and well-being measures such perceived well-being scale, the Mental Health Recovery Measure, the Autonomy Support Scale-Short Form, the Brief Evaluation of Medication Influences and Beliefs score, and the Stigma Scale score.

Longitudinal Analyses

Longitudinal analyses examining differences in outcomes by gender (i.e. the interaction of gender by time) showed no significant differences on the primary outcomes of QLS or on total PANSS symptoms (Table 4, column 3) but did show a significantly greater improvement in the intrapsychic functioning sub-scale of the QOLI among women ($p<.05$).

Evaluation of differences in treatment effects by gender (interaction of gender by time and by treatment group) showed no significant differences on any measure of clinical outcome or NAVIGATE service use (Table 4, column 4).

DISCUSSION

Secondary analysis of RAISE-ETP data on patients with early episode psychosis revealed that at program entry women were older with higher QLS scores and better social functioning than men, characteristics that are consistent with previous literature. [6] They also had more severe mood symptoms, [2] more numerous psychiatric hospitalizations and reported less use of cannabis but not alcohol or other drugs. Longitudinal analyses, the primary focus of this study, showed that controlling for these admission differences, there were no significant gender differences in 2-year measures of quality of life, in schizophrenia or depressive symptoms; or in use of key components of the coordinated specialty care intervention. Furthermore, no gender differences were observed in response to treatment over follow-up of 2 years.

Previous research on gender and schizophrenia suggests that women fare better than men early in the disease course, possibly due to their older age at onset and better adherence and response to antipsychotic medications, [7] though one study showed this advantage fades over time. [8]

A review of the literature on the association of gender and treatment outcomes in other mental illnesses reveal mixed findings. A review of Post-Traumatic Stress Disorder (PTSD) treatment outcome studies found equivocal effects of gender. [24] More specifically, studies comparing outcomes of exposure-only therapy and exposure-therapy plus cognitive restructuring therapy for PTSD, also found no gender effects [25,26] as did a refugee population receiving cognitive restructuring therapy. [27] A longitudinal follow-up of hospitalized adult patients with a history of childhood abuse similarly found no gender differences in outcomes [28] but a large multi-site study from the Veterans Health

Administration reported greater reduction in PTSD symptom scores among female than male Veterans. [29] This finding of superior outcomes for women diagnosed with PTSD patients has been reported in both additional VA [30] a non-VA samples. [31,32]

In the realm of substance use disorders, a review of 126 efficacy and effectiveness trials for nicotine dependence found that only two trials showed women to be significantly more likely to quit smoking than men, while 59 found women were significantly less likely to quit smoking. In addition, when followed for longer duration of time, women were particularly less likely to quit smoking than men. [33]

In the treatment of opioid use disorder women appear to do better than men on measures of both retention in treatment and relapse to drug use. Weinstein and colleagues, for example, reported women were 55% more likely to remain in treatment than men [34] and a seven-year follow-up study found that women had both greater treatment retention and employment and lower relapse rates than men. [35] Hser and colleagues identified young men who are daily drug users, unemployed, and unmarried as the highest risk group for dropping out of methadone maintenance but did not explicitly compare women and men. [36] More simply, Levine and colleagues reported no association of gender with retention rate in medication assisted treatment for drug abuse although a sub-group of women who had negative first month cocaine and marijuana urine tests and no history of sexual victimization were more likely to remain in treatment. [37]

Looking at other psychiatric conditions, Cuijpers and colleagues reported no gender effect on depression outcome after CBT and pharmacotherapy [38] and a general review found no gender effect on short- and long-term outcome in anorexia nervosa. [39]

There are similarly mixed effects of gender on the few studies of outcomes of treatment for medical illnesses. Carcel and colleagues reported that, compared to men, women with ischemic but not hemorrhagic stroke had lower 3- to 6-month mortality when exposed to diverse treatments. However, women were more likely to be disabled and had worse quality of life on the EuroQOL 5-Dimension self-report questionnaire of quality of life. [40]

A pooled analysis of randomized, controlled trials evaluating effectiveness of insulin in diabetes found that women had smaller reductions in HbA1c and were less likely to reach glycemic goals despite higher insulin doses and had more hypoglycemic events than males. [41] A post hoc analysis of a randomized, controlled trial evaluating the effect of berberine and pioglitazone on glucose metabolism in nonalcoholic fatty liver disease also reported greater benefits for women than for men. [42]

This unsystematic overview of differences in gender outcomes in other mental health disorders and some medical conditions showed no consistent pattern of gender differences in outcomes in the published literature with many no-difference findings like those observed in this study of outcomes and response to treatment in early episode schizophrenia.

Future research should focus further on longitudinal outcomes of FEP patients using larger samples sizes in longitudinal analysis. In addition, special attention might be brought to perimenopausal women. Perimenopause is an established period of vulnerability in psychotic spectrum illnesses, and is speculated to be secondary to loss of protective effect of estrogen (CITATION).

Limitations

Several methodological limitations require comment. First gender comparisons inevitably require observational research designs since random assignment is not possible. As a result. there may be unmeasured factors that influence outcomes differently among women and men. Since we found no evidence of gender differences in outcomes, after controlling for baseline differences that *were* measured, it seems unlikely that such factors would have altered our main findings. Second the study was not specifically designed to examine gender interactions affecting outcomes and may not have been adequately powered, especially in view of the fact that the sample of women was smaller than that of men. However, the fact that significant interactions have been found in other secondary analyses of the duration of untreated psychosis [12] and social class [43] suggests that the sample was adequate for identifying significant interactions if they existed. Third, although the study was conducted at 34 sites across the US the representativeness of the sample is unknown and thus the generalizability of the results is uncertain.

There is also larger limitation in medical science at large, which is the historical and current structural exclusion of women in research. In this thesis, women were the centered to be the main subject of interest. Historically, androcentrism in science has considered male bodies to be the "default" human body. This bias is visible in every aspect of medicine and medical education—from the regular practice of learning CPR on only male mannequins to the exclusion of pregnant or possibly pregnant women in pharmacological trials. Pregnant women are considered a vulnerable population, and excluding women of reproductive age might be seen as a solution to ethical challenges.

However, women are not smaller men.

Thorough review of literature shows that there are specific gender differences in epidemiological characteristics of psychiatric and medical illnesses. In limited incidences, specific drugs might be more efficacious in women. What might our healthcare look like if we regularly center women in making scientific advancements?

Another point of interest is the intersection of biological sex and socially influenced gender. RAISE-ETP trial only collected self-identified demographic data, thus limiting data on biological sex. As a result, we are unable to specifically comment on whether sex/gender incongruence and its effect on outcomes. We expect statistical analysis to be same with and without sex/gender data, as transgender and gender non-binary adults are a small minority. Thus, whatever differences that may have been can be considered outliers in statistical analysis.

However, this is an important learning point. As we gather data, routine practice of collecting both sex and gender will make gender analysis more inclusive of trans and gender non-conforming patients. In fact, given the high comorbidity of depression and other mental health illnesses in the transgender population, there might be a pressing need to collect more granular data to include transgender and gender non-conforming identity as a possible variable in analysis.

We must touch on the difference of biological sex and sociological experience of gender. Sex, or the biological differences in the continuum of male and female, does present real biochemical ramifications. The effect of sex hormones on human behavior, immune system, and manifestations of psychiatric illnesses are well established. Gender, or the social experience of men and women, is culturally specific. From an early age,

children are taught different gender roles, and girls are socialized very differently from boys. Given the well-established effect of chronic stress on health, we must consider the role of sexism in interpretation of gender differences.

The above, however, is less relevant for this paper, given findings of no differences.

CONCLUSION

Secondary analysis of the RAISE-ETP trial found at baseline women were older, less likely to use or abuse cannabis but not alcohol, had more mood-associated symptoms, higher quality of life, and more past hospital use. Adjusting for baseline differences, there were no significant effects of gender on the primary outcome of quality of life, total schizophrenia symptoms, or use of Coordinated Specialty Care services. Benefits of the NAVIGATE intervention as compared to usual community care also did not differ significantly by gender.

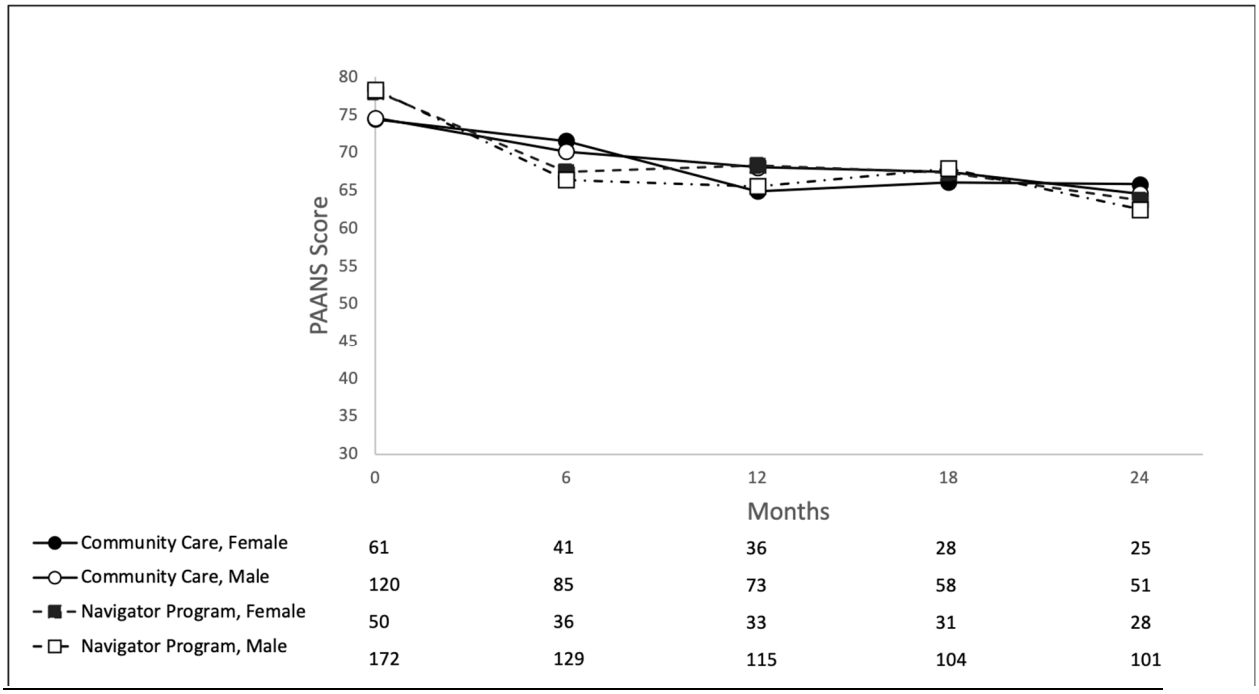

Figure 1: PAANS Score by Treatment Group and Gender.

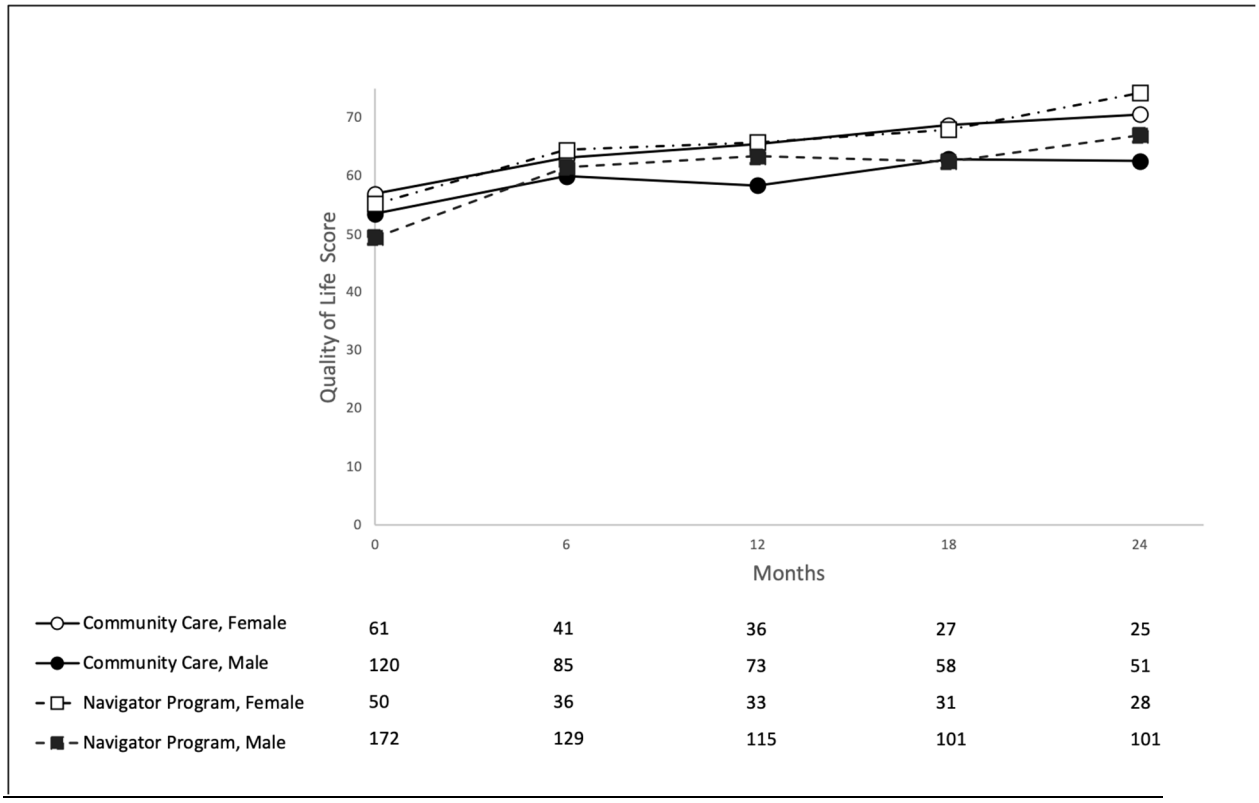

Figure 2: QoL Score by Treatment Group and Gender

Table 1. Sociodemographic Characteristics by Gender at program entry.

N (%)	Male (n=293)	Female (n=111)	F or t	df	p-value
Age^	22.68 (4.5)	24.33 (6.19)	t=2.73	1	0.0067
Race			F=1.37	2	0.16
White	166 (56.7%)	52 (46.9%)	F=1.99		
Non-white	127 (43.3%)	59 (53.2%)			
Hispanic ethnicity	59 (20.1%)	14 (12.6%)	F=1.24	1	0.27
Marital status			F=7.42	1	0.0068
Presently married	13 (4.4%)	11 (9.9%)			
Widowed/divorced/separated	11 (3.8%)	11 (9.9%)			
Never married	269 (91.8%)	89 (80.2%)		2	
Current residence			F=4.48	1	0.0119
Independent living	41 (14.0%)	31 (27.9%)			

Supported or structured	12 (4.1%)	2 (1.8%)			
Family, parents, grandparents, sibling	215 (73.4%)	72 (64.9%)			
Homeless, shelter, or other	25 (8.5%)	6 (5.4%)			
Patient's education			F=2.37	2	0.0945
Some college or higher	83 (28.3%)	42 (37.8%)			
Completed high school	102 (34.8%)	31 (27.9%)			
Some high school	93 (31.7%)	32 (28.8%)			
Some or completed grade school	15 (5.1%)	6 (5.4%)			
Mother's education			F=1.75	2	0.17
Some college or higher	130 (44.4%)	37 (33.3%)			
Completed high school	79 (27.0%)	32 (28.8%)			
Some high school or grade school	34 (11.6%)	25 (22.5%)			

No school or unknown	50 (17.1%)	1(15.3%)			
Type of insurance			F=3.41	2	0.0341
Private	68 (23.4%)	14 (12.7%)			
Public	83 (28.5%)	44 (40.0%)			
Uninsured	140 (48.1%)	52 (47.3%)			

^Continuous variable. Unmarked variables are categorical variables .

Table 2. Community Adjustment and Quality of Life by Gender at program entry.

N (%)	Male (n=293)	Female (n=111)	F or t	df	p-value
Current Student	56 (19.1%)	26 (23.4%)	F=0.78	1	
Currently working	42 (14.3%)	16 (14.4%)	F=0.09	1	0.76
Student or working	86 (29.6%)	36 (32.7%)	F=0.16	1	0.69
Quality of Life^			t=2.25	1	
Total score	51.25 (18.54)	56.28 (18.96)			0.0249
Interpersonal relations	19.26 (8.84)	21.08 (8.18)	t=1.94		0.0537
Instrumental role	5.14 (6.3)	6.69 (7)	t=0.15		0.15
Intrapsychic foundations	20.49 (6.92)	21.7 (7.08)	t=0.12		0.12
Common objects and activities	6.36 (2.37)	6.81 (2.12)	t=0.0487		0.0487
Autonomy support scale mean score^	5.53 (1.15)	5.58 (1.38)	t=0.3	1	0.77
BEMIB (medication influence and beliefs) mean score^	4.95 (1.01)	4.85 (1.05)	t=0.75	1	0.45
Mental health recovery measure mean score^	4.96 (1.16)	4.74 (1.42)	t=1.53	1	0.13
Stigma scale mean score^	3.95 (1.15)	4.09 (1.27)	t=0.94	1	0.35

Well-being scale mean score^	4.01 (0.77)	3.89 (0.86)	t=1.25	1	0.21
Current state of MH^	63.43 (23.21)	58.78 (24.53)	t=0.13	1	0.13
Life as a whole^	4.41 (1.41)	4.18 (1.45)	t=1.18	1	0.24
Intent to complete^	7.51 (1.68)	7.33 (2.02)	t=1.07	1	0.29
Intent to attend next visit^	7.98 (1.54)	7.97 (1.75)	t=0.26	1	0.80

^Continuous variable. Unmarked variables are categorical variables.

Table 3. Clinical Characteristics

N (%)	Male (n=293)	Female (n=111)	t or F	df	p-value
SCID diagnoses			F=3.58	4	0.0059
Schizophrenia	162 (55.3%)	52 (46.9%)			
Schizoaffective bipolar	10 (3.4%)	14 (12.6%)			
Schizoaffective depressive	36 (12.3%)	21 (18.9%)			
Schizophreniform provisional or definite	52 (17.8%)	15 (13.5%)			
Brief psychotic disorder	33 (11.3%)	9 (8.1%)			
Lifetime alcohol use disorder			F=3.36	1	0.0676
Did not meet criteria	178 (60.8%)	79 (71.2%)			
Met abuse or dependence criteria	115 (39.3%)	32 (28.8%)			
Lifetime cannabis use disorder			F=9.39	1	0.0023
Did not meet criteria	177 (60.4%)	87 (78.4%)			
Met abuse or dependence criteria	116 (39.6%)	24 (21.6%)			
Number of days of alcohol intoxication^	0.4 (2.08)	0.78 (2.87)		1	0.15

Number of days of illegal drugs^	3.74 (8.07)	1.55 (5.33)		1	0.0078
Duration of untreated psychosis (weeks)^	191.06 (254.96)	199.97 (281.48)	t=0.3	1	0.76
Number of prior hospitalizations			F=3.94	3	0.0087
0	200 (83.7%)	67 (82.7%)			
1	18 (7.5%)	3 (3.7%)			
2	9 (3.8%)	5 (6.2%)			
3 or more	12 (5.0%)	6 (7.4%)			
Prescribed one or more antipsychotics at consent	251 (85.7%)	86 (77.5%)	F=3.4	1	0.0661
Days not taking first antipsychotic			F=1.67	2	0.19
Few if any, <7	200 (68.7%)	67 (60.4%)			
7 or more	39 (13.4%)	14 (12.6%)			
Not prescribed antipsychotic	52 (17.9%)	30 (27.0%)			
Days taking less than prescribed number of pills			F=0.62	1	0.43
Never or almost never, 0 to 25%	202 (69.4%)	64 (57.7%)			
Sometimes to always, 26 to 100%	37 (12.7%)	17 (15.3%)			
Not prescribed antipsychotic	52 (17.9%)	30 (27.0%)			

Duration of lifetime anti-psychotic medication at consent (days)^	43.95 (43.95)	44.54 (50.6)			0.89
PANSS Symptom severity^				1	
Total score	76.82 (14.72)	76.1 (15.82)	t=0.76		0.76
Factor scores					
Positive	12.25 (3.91)	12.2 (3.64)	t=0.5		0.96
Negative	16.98 (5.14)	15.94 (5.22)	t=1.72		0.09
Disorganized/concrete	7.96 (2.68)	7.41 (2.99)	t=1.57		0.12
Excited	6.77 (2.83)	6.68 (2.58)	t=0.24		0.81
Depressed	7.69 (3.22)	9.01 (3.37)	t=3.57		0.0004
CDSS^	4.46 (4.35)	5.16 (4.06)	t=1.44	1	0.15
CGI^	4.04 (0.81)	4.06 (0.85)	t=0.28	1	0.78

^Continuous variable. Unmarked variables are categorical variables.

Table 4. Longitudinal outcomes of women and men in the RAISE-ETP program and differential response to NAVIGATE treatment

Outcome or Treatment Measure	N	Interaction of Female by time^	Interaction of Female by time by treatment group #
Quality of Life Scale (Total Score)	1373	0.0842	-0.0171
(se)		(0.1080)	(0.2400)
Interpersonal Relations	1376	0.0289	-0.0175
(se)		(0.0507)	(0.1180)
Intrapsychic functioning	1374	0.0721*	-0.0238
(se)		(0.0322)	(0.0659)
Instrumental Role Functioning	1375	-0.0237	0.0396
(se)		(0.0472)	(0.0846)
Common objects and Activities	1374	0.0077	-0.0070
(se)		(0.0139)	(0.0243)
PANSS total score	1377	0.0462	0.1200
(se)		(0.0914)	(0.2100)
Calgary Depression Score	1377	0.0216	-0.0397
(se)		(0.0201)	(0.0343)

Decision support for medications	1329	0.0048	-0.0035
(se)		0.0385	0.0058
Supported employment/education	1324	0.0024	-0.0003
(se)		(0.00241)	(0.0052)
Family psychoeducation	1331	-0.0002	0.0005
(se)		(0.00251)	(0.0036)
Individual resiliency training participation	1331	0.0012	0.0075
(se)		**(0.0034)**	(0.0049)

+Adjusted for age, marital status, living situation, psychotic diagnoses, use of cannabis, use of drugs, number of lifetime psychiatric hospitalizations, depressive symptoms and clustering of observations between sites.

* $p<.05$

^ model includes terms for main effects of gender and time in addition to the interaction term.

model includes terms for main effects of gender, time and treatment, interactions of time and gender and time and treatment as well as the final three-way interaction term

References

1. Riecher-Rössler A. Sex and gender differences in mental disorders. The Lancet Psychiatry 2017;4:8-9.
2. Irving J, Colling C, Shetty H, et al. Gender differences in clinical presentation and illicit substance use during first episode psychosis: a natural language processing, electronic case register study. BMJ Open 2021;11:e042949.
3. Heitz U, Studerus E, Menghini-Muller S, et al. Gender differences in first self-perceived signs and symptoms in patients with an at-risk mental state and first-episode psychosis. Early Interv Psychiatry 2019;13:582-8.
4. Comacchio C, Lasalvia A, Bonetto C, et al. Gender and 5-years course of psychosis patients: focus on clinical and social variables. Arch Womens Ment Health 2020;23:63-70.
5. Seeman MV. Women who suffer from schizophrenia: Critical issues. World J Psychiatry 2018;8:125-36.
6. Seeman MV. Does Gender Influence Outcome in Schizophrenia? Psychiatr Q 2019;90:173-84.
7. Dubreucq M, Plasse J, Gabayet F, et al. Sex Differences in Recovery-Related Outcomes and Needs for Psychiatric Rehabilitation in People With Schizophrenia Spectrum Disorder. J Clin Psychiatry 2021;82.
8. Thara R, Kamath S. Women and schizophrenia. Indian J Psychiatry 2015;57:S246-51.
9. Zhang J, Gallego J, Robinson D, Malhotra A, Kane J, Correkk C. Efficacy and safety of individual second-generation vs. first-generation antipsychotics in first-episode psychosis: a systematic review and meta-analysis. Int J Neuropsychopharmacol 2013;16:1205.
10. Marder S. Psychosis in adults: Initial management. UpToDate: UpToDate; 2022.
11. Correll CU, Galling B, Pawar A, et al. Comparison of Early Intervention Services vs Treatment as Usual for Early-Phase Psychosis: A Systematic Review, Meta-analysis, and Meta-regression. JAMA Psychiatry 2018;75:555-65.
12. Kane JM, Robinson DG, Schooler NR, et al. Comprehensive Versus Usual Community Care for First-Episode Psychosis: 2-Year Outcomes From the NIMH RAISE Early Treatment Program. Am J Psychiatry 2016;173:362-72.
13. Rosenheck R, Mueser KT, Sint K, et al. Supported employment and education in comprehensive, integrated care for first episode psychosis: Effects on work, school, and disability income. Schizophr Res 2017;182:120-8.
14. Mueser KT PD, Addington J, Brunette MF, Gingerich S, Glynn SM, Lynde DW, Gottlieb JD, Meyer-Kalos P, McGurk SR, Cather C, Saade S, Robinson DG, Schooler NR, Rosenheck RA, Kane JM. The NAVIGATE Program for First-Episode Psychosis: Rationale, Overview, and Description of Psychosocial Components. Psychiatr Serv 2015;66:680-90.
15. Heinrichs DW HT, Carpenter WT, Jr. The Quality of Life Scale: an instrument for rating the schizophrenic deficit syndrome. Schizophr Bull 1984;10:388-98.
16. Kay SR FA, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 1987;13:261-76.

17. Wallwork RS FR, Hashimoto R, Weinberger DR, Dickinson D. Searching for a consensus five-factor model of the Positive and Negative Syndrome Scale for schizophrenia. . Schizophr Res 2012;137:246-50.
18. Addington D AJ, Maticka-Tyndale E. Assessing depression in schizophrenia: the Calgary Depression Scale. Br J Psychiatry Suppl 1993:39-44.
19. Ryff C. Happiness is everything, or is it? Explorations on the meaning of psychological well-being. Journal of Personality and Social Psychology 1989;57:1069-81.
20. Young SL BW. The mental Health Recovery Measure. In: Toledo Uo, ed. Toledo, OH2003.
21. Williams GC RG, Ryan RM, Grolnick WS, Deci EL. Autonomous regulation and long-term medication adherence in adult outpatients. Health Psychol 1998;17:269-76.
22. Dolder CR LJ, Warren KA, Golshan S, Perkins DO, Jeste DV. Brief evaluation of medication influences and beliefs: development and testing of a brief scale for medication adherence. J Clin Psychopharmacol 2004;24:404-9.
23. King M DS, Shaw J, Watson R, Stevens S, Passetti F, Weich S, Serfaty M. The Stigma Scale: development of a standardised measure of the stigma of mental illness. Br J Psychiatry 2007;190:248-54.
24. Blain LM, Galovski TE, Robinson T. Gender differences in recovery from posttraumatic stress disorder: A critical review. Aggression and Violent Behavior 2010;15:463-74.
25. Bryant RA, Moulds ML, Guthrie RM, et al. A randomized controlled trial of exposure therapy and cognitive restructuring for posttraumatic stress disorder. Journal of Consulting and Clinical Psychology, 2008;76:695.
26. Felmingham KL, Bryant RA. Gender differences in the maintenance of response to cognitive behavior therapy for posttraumatic stress disorder. Journal of Consulting and Clinical Psychology, 2012;80:196.
27. Schulz PM, Resick PA, Huber LC, Griffin MG. The Effectiveness of Cognitive Processing Therapy for PTSD With Refugees in a Community Setting. Cognitive and Behavioral Practice 2006;15:522-51.
28. Stalker CA, Palmer SE, Wright DC, Gebotys R. Specialized Inpatient Trauma Treatment for Adults Abused as Children: A Follow-Up Study. The American Journal of Psychiatry, 2005;162:552-9.
29. Stefanovics EA, Rosenheck RA. Gender differences in outcomes following specialized intensive PTSD treatment in the Veterans Health Administration. Psychological Trauma: Theory, Research, Practice, and Policy 2020;12:272-80.
30. Eftekhari AR, J; Crowley, J; Rosen, C; Greenbaum, M; Karlin, B. Effectiveness of National Implementation of Prolonged Exposure Therapy in Veterans Affairs Care. JAMA Psychiatry 2013;70.
31. Galovski TE, Blain LM, Chappuis C, Fletcher T. Sex differences in recovery from PTSD in male and female interpersonal assault survivors. Behaviour Research and Therapy 2013;51:247-55.
32. Bekes V, Beaulieu-Prevost D, Guay S, Belleville G. Women With PTSD Benefit More From Psychotherapy Than Men. Psychological Trauma: Theory, Research, Practice, and Policy 2016;8:720-7.

33. Smith PH, Bessette AJ, Weinberger AH, Sheffer CE, McKee SA. Sex/gender differences in smoking cessation: A review. Preventive medicine 2016;92:135–40.
34. Weinstein Z, Kim H, Cheng D. Long-term retention in office based opioid treatment with buprenorphine. J Subst Abuse Treat 2017;74:65-70.
35. Ohlin L, Fridell M, Nyhlén A. Buprenorphine maintenance program with contracted work/education and low tolerance for non-prescribed drug use: a cohort study of outcome for women and men after seven years. BMC Psychiatry 2015;15:56.
36. Hser Y, Anglin M, Liu Y. A survival analysis of gender and ethnic differences in responsiveness to methadone maintenance treatmen. Int J Addict;25:1295-315.
37. Levine A, Lundahl L, Ledgerwood D. Gender-specific predictors of retention and opioid abstinence during methadone maintenance treatment. J Subst Abuse Treat 2015;54:37-43.
38. Cuijpers P, Weitz E, Twisk J, et al. Gender as predictor and moderator of outcome in cognitive behavior therapy and pharmacotherapy for adult depression: an "individual patient data" meta-analysis. Depression Anxiety 2014;31.
39. Strobel C, Quadflieg N, Voderholzer U. Short- and long-term outcome of males treated for anorexia nervosa: a review of the literature. Eat Weight Disord 2018;23:541–52.
40. Carcel C, Wang X, Sandset E, et al. Sex differences in treatment and outcome after stroke: pooled analysis including 19,000 participants. Neurology 2019;93:e2170–e80.
41. McGill JB, Vlajnic A, Knutsen PG, Recklein C, Rimler M, Fisher SJ. Effect of gender on treatment outcomes in type 2 diabetes mellitus. Diabetes Res Clin Pract 2013;102:167-74.
42. Yan H, Wu W, Chang X, et al. Gender differences in the efficacy of pioglitazone treatment in nonalcoholic fatty liver disease patients with abnormal glucose metabolism. Biology of Sex Differences 2021;12.
43. Bennett D, Rosenheck R. Socioeconomic Status and the Effectiveness of Coordinated Specialty Care for First Episode Psychosis. Health Services Research 2020.