# Effectiveness of Switching From Long-Acting Injectable Fluphenazine or Haloperidol Decanoate to Long-Acting Injectable Risperidone Microspheres: An Open-Label, Randomized Controlled Trial

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**ABSTRACT**

***Objective:*** This multisite randomized trial addressed risks and benefits of staying on long-acting injectable haloperidol or fluphenazine versus switching to long-acting injectable risperidone microspheres.

***Method:*** From December 2004 through March 2008, adult outpatients with a Structured Clinical Interview for *DSM-IV* Axis I Disorders-Patient Edition diagnosis of schizophrenia or schizoaffective disorder who were taking haloperidol decanoate (n = 40) or fluphenazine decanoate (n = 22) were randomly assigned to stay on current long-acting injectable medication or switch to risperidone microspheres and followed for 6 months under study protocol and an additional 6 months naturalistic follow-up. Kaplan-Meier and Cox regression analyses were used to examine the primary outcome (time to treatment discontinuation), and random regression models were used to examine secondary outcomes.

***Results:*** Groups did not differ significantly in time to treatment discontinuation through 6 months of protocol-driven treatment. When the 6-month naturalistic follow-up period was included, time to treatment discontinuation was significantly shorter for individuals assigned to switch than for individuals assigned to stay (10% of stayers discontinued versus 31% of switchers; $P = .01$). Groups did not differ with respect to psychopathology, hospitalizations, sexual side effects, new-onset tardive dyskinesia, or new-onset extrapyramidal symptoms. However, those randomized to switch to long-acting injectable risperidone microspheres had greater increases in body mass (increase of 1.0 body mass index [BMI] versus decrease of −0.3 BMI; $P = .00$) and prolactin (maximum increase to 23.4 ng/mL versus decrease to 15.2 ng/mL, $P = .01$) compared to those randomized to stay.

***Conclusion:*** Switching from haloperidol decanoate or fluphenazine decanoate to risperidone microspheres resulted in more frequent treatment discontinuation as well as significant weight gain and increases in prolactin.

***Trial Registration:*** ClinicalTrials.gov identifier: NCT00044655

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Current outcomes for most people with schizophrenia are disappointing. Hence, a compelling clinical question regularly faced by people with schizophrenia and their prescribers is, Should I stay on my current antipsychotic regimen or switch to a different one? Schizophrenia Patient Outcomes Research Team guidelines[1] recommend long-acting injectable antipsychotic maintenance therapy for persons who have difficulty complying with oral medication or who prefer regimens of relatively widely spaced injections. An important open question for people taking first-generation long-acting injectable medications who are not symptom free is whether the benefits of changing to a second-generation long-acting injectable outweigh the relative risks and costs. Because the cost per day of risperidone microspheres is over 50 times that of first-generation long-acting injectable antipsychotic medications, this question is of particular interest to payers.

To date, risperidone microspheres has been compared to placebo[2] or to oral antipsychotic medications.[3,4] A randomized controlled trial (RCT) that compared risperidone microspheres (25 mg, 50 mg, or 75 mg) to placebo found that risperidone microspheres is more efficacious than placebo and is well tolerated, especially at lower dosages.[2] Further, risperidone microspheres continued to be well tolerated for a year or longer.[5] This study excluded those who received a long-acting injectable antipsychotic medication within 120 days.[5] More recent RCTs have compared risperidone microspheres to oral antipsychotics. Chue et al[3] found no significant differences between risperidone microspheres and oral risperidone. Keks et al[4] had similar results in comparison to olanzapine. A 2-year RCT comparing risperidone microspheres to quetiapine[6] found significantly longer time to relapse with risperidone microspheres, and most recently, Rosenheck et al[7] reported no significant differences between risperidone microspheres and psychiatrists' choice of oral antipsychotic. A nonrandomized prospective study examining a switch from first-generation depot antipsychotics to risperidone microspheres concluded that patients could be switched without compromising clinical stability.[8] However, this study did not include a comparison to individuals who remained on first-generation injectables.

We provide data from an RCT addressing relative risks and benefits of staying on a first-generation injectable antipsychotic versus switching to a second-generation injectable antipsychotic, risperidone microspheres, in patients currently taking fluphenazine decanoate or haloperidol decanoate. We studied risperidone microspheres because it was the first second-generation long-acting injectable available for clinical use.

**Clinical Points**

- People who switch from haloperidol decanoate or fluphenazine decanoate to risperidone microspheres can be expected to discontinue treatment more frequently than if they had stayed on the original medication.
- People who switch from haloperidol decanoate or fluphenazine decanoate to risperidone microspheres can be expected to experience significant weight gain and increases in prolactin.

## METHOD

### Study Participants

From December 2004 through March 2008, 15 study sites in the National Institute of Mental Health Schizophrenia Trials Network and 5 sites in Connecticut's public mental health system recruited individuals 18 years and older with a Structured Clinical Interview for *DSM-IV* Axis I Disorders-Patient Edition (SCID-I/P)[9] diagnosis of schizophrenia or schizoaffective disorder who were currently taking fluphenazine decanoate or haloperidol decanoate (defined by plasma level >0 ng/mL for the prescribed antipsychotic or chart documentation of a recent injection). Eligible patients were those who might benefit from a switch to risperidone microspheres—specifically, those with suboptimal response to treatment because of persistent psychopathology or significant side effects. However, we did not enroll anyone whose symptoms or side effects were so severe that a medication change was indicated immediately. Hence, we enrolled only individuals for whom a change in medication was a reasonable clinical option, but not required. Additional inclusion criteria were willingness to change antipsychotic medication, access to medications without financial burden, and at least 1 clinic visit every 3 months for the past 6 months. Additional exclusion criteria included exacerbation of psychiatric symptoms within prior 3 months resulting in significant intervention (eg, psychiatric hospitalization, services from crisis intervention or psychiatric emergency department), living in a skilled nursing facility due to physical condition or disability, pending criminal charges, currently pregnant or breastfeeding, and being prescribed more than 1 antipsychotic medication (oral risperidone was allowed). This research was conducted with approval from participating institutions' institutional review boards. The study is registered at ClinicalTrials.gov (identifier: NCT00044655).

After thorough description of the study to participants and assessment of understanding of consent materials, clinical interviewers obtained written informed consent to participate. (Supplementary eFigure 1 available at PSYCHIATRIST.COM includes a CONSORT diagram detailing recruitment flow.)

### Study Design and Treatment

Following baseline assessment, participants were randomly assigned to either stay on current injectable medication or switch to risperidone microspheres. Randomization was stratified by gender and by baseline decanoate. No exceptions were made to the predetermined randomization streams.

Participants who were assigned to switch to risperidone microspheres and who had not taken oral risperidone previously received oral risperidone for at least a week to identify and exclude anyone with an idiosyncratic, untoward reaction to risperidone. Those who had previously tolerated oral risperidone proceeded directly to risperidone microspheres. Participants receiving haloperidol decanoate injections every 4 weeks received their first dose of risperidone microspheres the same day they received their last dose of haloperidol decanoate and received risperidone microspheres every 2 weeks thereafter. Those receiving fluphenazine decanoate every 2 weeks received risperidone microspheres the same day that they received their last 2 fluphenazine decanoate injections and received risperidone microspheres every 2 weeks thereafter. Condition entry was defined as the date the participant was informed of and began the randomized treatment assignment.

The protocol specified that study participants continue their assigned treatment for 6 months unless clinically contraindicated. Medication dosing was unconstrained by study protocol; prescribers used clinical judgment to adjust dosages of assigned treatment if indicated. The protocol allowed use of adjunctive or concomitant psychotropic medications other than antipsychotic medications. After the 6-month study period, assessment continued for an additional 6 months of naturalistic follow-up. Treatment throughout was open label with assessment by blinded clinical raters. During both protocol-specified and naturalistic follow-up, study medications were not supplied by the study; participants were required to have access to study medications without financial burden (eg, through entitlements).

### Baseline Measures

The SCID-I/P[9] provided research diagnoses. Chart review and participant interview informed sociodemographic information and psychiatric history.

### Primary Outcome Measure

The primary outcome measure was time to all-cause medication discontinuation. Record reviews provided start and stop dates for each dosage of each medication prescribed and dates of each injection.

### Secondary Outcome Measures

Secondary outcomes included psychiatric symptoms, hospitalization, and medication adverse events assessed at baseline and 6 follow-up points: 2 weeks, 1 month, 3 months, 6 months, 9 months, and 12 months after condition entry.

We used the Positive and Negative Syndrome Scale (PANSS)[10] to assess psychiatric symptoms. Dates of inpatient hospitalization were obtained from a self-report calendar augmented by record review.

Other secondary measures included Abnormal Involuntary Movement Scale (AIMS)[11] and Simpson-Angus Scale[12] for extrapyramidal side effects, Arizona Sexual Experiences

**Table 1. Demographic and Other Characteristics of Outpatients With Schizophrenia-Spectrum Disorders Who Were Randomly Assigned at Baseline to Stay on a First-Generation Injectable Antipsychotic or Switch to Long-Acting Injectable Risperidone Microspheres**

| | Stay on First-Generation Injectable Antipsychotic (n = 30) | | Switch to Long-Acting Injectable Risperidone Microspheres (n = 32) | | | | |
|---|---|---|---|---|---|---|---|
| Characteristic | n | % | n | % | $\chi^2$ | *df* | *P* |
| Male gender | 22 | 73 | 22 | 69 | 0.2 | 1 | .69 |
| Haloperidol decanoate | 19 | 63 | 21 | 66 | 0.0 | 1 | .85 |
| Caucasian race | 11 | 37 | 12 | 38 | 0.0 | 1 | .95 |
| Latino ethnicity | 4 | 13 | 1 | 3 | 2.2 | 1 | .14 |
| Tardive dyskinesia present | 9 | 30 | 13 | 41 | 0.8 | 1 | .39 |
| EPS present | 8 | 27 | 14 | 44 | 2.0 | 1 | .16 |
| | Mean | SD | Mean | SD | *t* Test | *df* | *P* |
| Age, y | 47.3 | 9.1 | 48.5 | 12.2 | −0.4 | 60 | .66 |
| Haloperidol dosage (per every 4 wk), mg[a] | 114.7 | 56.9 | 119.9 | 43.5 | −0.3 | 35 | .78 |
| Fluphenazine dosage (per every 2 wk), mg[b] | 37.5 | 28.4 | 32.5 | 15.6 | 0.4 | 16 | .66 |
| PANSS total score | 69.9 | 17.9 | 65.4 | 14.0 | 1.1 | 60 | .28 |
| Body mass index | 31.3 | 8.7 | 31.0 | 9.8 | 0.1 | 60 | .90 |
| Arizona Sexual Experiences Scale total score | 15.2 | 5.0 | 15.9 | 5.6 | −0.4 | 54 | .66 |
| Prolactin, ng/mL | 18.5 | 13.8 | 16.7 | 9.8 | 0.5 | 47 | .59 |

[a]Stay, n = 19; switch, n = 18.
[b]Stay, n = 10; switch, n = 8.
Abbreviations: EPS = extrapyramidal symptoms, PANSS = Positive and Negative Syndrome Scale.

Scale[13] for sexual functioning, and Subjective Side Effect Rating Scale[14] for distress from common side effects of antipsychotic medications. We recorded participants' pulse, blood pressure, height, weight, waist and hip measurements, serum prolactin levels, lipid panels, and blood and urine glucose levels. Outcomes collected but not reported herein will be the subject of future reports.

We adapted the Schooler-Kane[15] research criteria for tardive dyskinesia (at least "moderate" movements in 1 or more body areas or at least "mild" movements in 2 or more body areas rated with the AIMS) to identify new-onset tardive dyskinesia. We defined possible new-onset extrapyramidal symptoms (EPS) as a mean score increase of > 0.3 across items on the Simpson-Angus Scale.

### Rater Training, Reliability, and Blinding

Clinicians with at least master's degrees and clinical experience with people with schizophrenia conducted all interviews. Randomization occurred centrally, and study sites followed procedures to maintain blinding. Raters participated in initial training, conducted by Schizophrenia Trials Network staff, for certification and annual retraining to maintain certification.

### Data Analysis

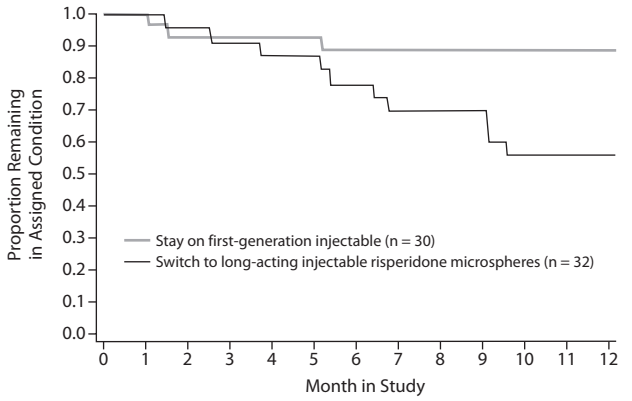
Paralleling the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) phase 1[16] and subsequent analyses of the impact of switching antipsychotic medications using CATIE data,[17] we used Kaplan-Meier and Cox regression to examine the effect of staying on a first-generation injectable antipsychotic compared to switching to risperidone microspheres on time to all-cause treatment discontinuation, including covariates of gender and baseline medication, our 2 prespecified stratification variables. We applied random regression models to examine secondary outcomes. Independent variables included group (stay or switch), time (linear and quadratic), and group by linear and quadratic time, with covariates of gender and baseline medication. We used intent-to-treat models for primary analyses in which a significant group-by-time interaction would support the hypothesized treatment effect. Secondarily, we examined 2 as-treated models, 1 that completely excluded individuals who discontinued their assigned treatment condition and 1 in which data from such individuals were excluded only from time of discontinuation of assigned treatment. For participants assigned to stay, discontinuation from assigned treatment was defined as discontinuing fluphenazine decanoate or haloperidol decanoate or adding 1 or more additional antipsychotics (addition of oral haloperidol to haloperidol decanoate or oral fluphenazine to fluphenazine decanoate did not count as discontinuation of assigned treatment). For participants assigned to switch, discontinuation from assigned treatment was defined as discontinuing risperidone microspheres or adding another antipsychotic (addition of oral risperidone or paliperidone did not count as discontinuation of assigned treatment).

## RESULTS

Sixty-two individuals were randomized, and 53 (29 stay, 24 switch) began their assigned treatment. Groups did not differ significantly at baseline on demographics, dosage of first-generation injectable, or secondary measures (Table 1).

Among those assigned to stay, 3 (10%) discontinued their assigned treatment within the first 6 study months (1 changed to the oral version of the injectable, 1 to a different oral antipsychotic, and 1 began antipsychotic polypharmacy with addition of a different oral agent). Reasons for discontinuation included increased psychiatric symptoms (n = 1), EPS concerns (n = 1), and participant report that he

**Figure 1. Time to Medication Change for Any Reason[a]**




[a]Groups did not differ at 6 months (Kaplan-Meier, Mantel-Cox $\chi^2_1 = 0.94$, $P = .33$). However, groups differed significantly at 12 months (Kaplan-Meier, Mantel-Cox $\chi^2_1 = 6.00$, $P = .01$). In Cox regression analyses, treatment group remained significant after controlling for gender and baseline decanoate (Wald $\chi^2_1 = 5.00$, $P = .03$).

was informed that he did not have to take the injectable form of the medication (n = 1). Among those assigned to switch, 5 (21%) discontinued their assigned treatment within the first 6 study months (all returned to their baseline first-generation injectable); reasons included increased psychiatric symptoms (n = 3), hypertension and weight gain (n = 1), and participant preference to "feel better" (n = 1).

Groups did not differ significantly in time to all-cause treatment discontinuation during the first 6 study months (Kaplan-Meier, Mantel-Cox $\chi^2_1 = 0.94$, $P = .33$), when treatment was defined by study protocol. When the additional 6 months of naturalistic follow-up were included, time to all-cause treatment discontinuation was significantly shorter for individuals assigned to switch to risperidone microspheres than for individuals assigned to stay on a first-generation injectable antipsychotic (Kaplan-Meier, Mantel-Cox $\chi^2_1 = 6.00$, $P = .01$; Figure 1), and switching from a first-generation injectable to risperidone microspheres resulted in treatment discontinuation more often (31% discontinued) than did continuation on a first-generation injectable antipsychotic (10% discontinued). This difference remained significant after controlling for gender and baseline antipsychotic (fluphenazine decanoate vs haloperidol decanoate) in Cox regression analyses (Wald $\chi^2_1 = 5.00$, $P = .03$), and neither gender nor baseline decanoate was significantly related to treatment discontinuation at 6 or 12 months.

Stay and switch groups did not differ significantly on psychopathology over time (Table 2), whether measured as total PANSS, total PANSS positive items, or the 5 factors defined by Marder and colleagues.[18] Groups did not differ with respect to likelihood of being hospitalized for psychiatric reasons, which was uncommon in both groups. Three (10%) and 2 individuals (6%) were hospitalized at least once during the 6 months under study protocol for stay and switch groups, respectively ($\chi^2_1 = 0.3$, $P = .59$), while 4 (13%) and 3 individuals (9%) were hospitalized at least once during the full 12 months for stay and switch groups, respectively ($\chi^2_1 = 0.2$, $P = .62$). Nor did groups differ with respect to time to first hospitalization for psychiatric reasons. Neither group experienced hospitalizations for medical reasons during the 6 months under study protocol; 3 participants assigned to switch were hospitalized for medical reasons in months 6–12.

Groups did not differ with respect to incidence of sexual side effects (Table 2), new-onset EPS within 6 months (n = 2 of 21 [10%] without EPS at baseline who were assigned to stay and n = 2 of 13 [15%] without EPS at baseline who were assigned to switch [$\chi^2_1 = 0.3$, $P = .61$]) or within 12 months (n = 3 of 21 [14%] without EPS at baseline who were assigned to stay and n = 2 of 13 [15%] without EPS at baseline who were assigned to switch [$\chi^2_1 = 0.0$, $P = .93$]), or new-onset tardive dyskinesia within 6 months (n = 5 of 21 [24%] without tardive dyskinesia at baseline who were assigned to stay and n = 6 of 14 [43%] without tardive dyskinesia at baseline who were assigned to switch ($\chi^2_1 = 1.4$, $P = .23$) or 12 months (n = 7 of 21 [33%] without tardive dyskinesia at baseline who were assigned to stay and n = 7 of 14 [50%] without tardive dyskinesia at baseline who were assigned to switch, [$\chi^2_1 = 1.0$, $P = .32$]).

Those assigned to risperidone microspheres significantly increased their body mass index (BMI) compared to those assigned to stay (Table 2; Figure 2). Individuals assigned to switch gained a mean of 1.5 BMI (SD = 2.2, n = 22) at 6 months and 1.0 BMI (SD = 2.0, n = 17) at 12 months, and individuals assigned to stay gained or lost little (0.5 BMI [SD = 1.3, n = 24] at 6 months and −0.3 BMI [SD = 1.7, n = 24] at 12 months).

Risperidone microspheres also resulted in a significant increase in prolactin levels in patients who switched compared to those assigned to stay on a first-generation injectable (Table 2), with mean prolactin levels for those assigned to risperidone microspheres rising above the threshold considered normal (> 20 ng/mL), after 1 month of treatment (Figure 3). Additionally, men had significantly lower prolactin levels than women (Table 2; Supplementary eTable 1). Each of the secondary (as-treated) models was consistent with findings from primary intent-to-treat analyses.

Of the 24 individuals randomized to switch to risperidone microspheres who began their assigned treatment, 17 (71%) began with 25 mg, 6 (25%) with 37.5 mg, and 1 (4%) with 50 mg of risperidone microspheres. Fourteen individuals (12 on 25 mg, 1 on 37.5 mg, and 1 on 50 mg risperidone microspheres) remained at their starting dosage for the duration of their risperidone microspheres trial. Of the remaining 10, 8 (80%) experienced a dosage increase (3 from 25 mg to 50 mg risperidone microspheres, 3 from 37.5 mg to 50 mg risperidone microspheres, and 2 from 25 mg to 37.5 mg risperidone microspheres), 1 (10%) experienced a dosage decrease (from 37.5 mg to 25 mg risperidone microspheres), and 1 (10%) experienced both an increase and decrease (from 37.5 mg to 50 mg to 37.5 mg risperidone microspheres).

## DISCUSSION

As in previous studies, changing antipsychotics was more likely to result in treatment discontinuation than staying on

**Table 2. Intent-to-Treat Random Regression Analysis of Secondary Outcome Measures of Stay and Switch Groups Through Time[a]**

| Predictor | Regression Coefficient | SE | *z* | *P* Value | 95% CI |
|---|---|---|---|---|---|
| PANSS total score, 6 mo | | | | | |
| Intercept | 65.10 | 4.42 | 14.73 | .00 | 56.44 to 73.76 |
| Switch group | −1.22 | 3.67 | −0.33 | .74 | −8.41 to 5.97 |
| Time | −1.44 | 0.35 | −4.13 | .00 | −2.13 to −0.75 |
| Group by time | 0.52 | 0.51 | 1.03 | .30 | −0.48 to 1.52 |
| Male gender | 0.03 | 3.99 | 0.01 | .99 | −7.79 to 7.85 |
| Haloperidol decanoate baseline | 3.44 | 3.78 | 0.91 | .36 | −3.97 to 10.85 |
| PANSS total score, 12 mo | | | | | |
| Intercept | 64.18 | 4.36 | 14.72 | .00 | 55.63 to 72.73 |
| Switch group | −0.56 | 3.62 | −0.15 | .88 | −7.66 to 6.54 |
| Time | −0.44 | 0.20 | −2.14 | .03 | −0.83 to −0.05 |
| Group by time | 0.04 | 0.31 | 0.11 | .91 | −0.57 to 0.65 |
| Male gender | −0.24 | 3.93 | −0.06 | .95 | −7.94 to 7.46 |
| Haloperidol decanoate baseline | 2.62 | 3.72 | 0.70 | .48 | −4.67 to 9.91 |
| Arizona Sexual Experiences Scale, 6 mo | | | | | |
| Intercept | 16.46 | 1.51 | 10.87 | .00 | 13.50 to 19.42 |
| Switch group | 0.82 | 1.26 | 0.65 | .52 | −1.65 to 3.29 |
| Time | −0.06 | 0.14 | −0.46 | .65 | −0.33 to 0.21 |
| Group by time | 0.05 | 0.20 | 0.25 | .80 | −0.34 to 0.44 |
| Male gender | −2.10 | 1.37 | −1.53 | .13 | −4.79 to 0.59 |
| Haloperidol decanoate baseline | 0.75 | 1.33 | 0.57 | .57 | −1.86 to 3.36 |
| Arizona Sexual Experiences Scale, 12 mo | | | | | |
| Intercept | 16.16 | 1.52 | 10.61 | .00 | 13.18 to 19.14 |
| Switch group | 0.94 | 1.26 | 0.75 | .45 | −1.53 to 3.41 |
| Time | 0.08 | 0.07 | 1.05 | .29 | −0.06 to 0.22 |
| Group by time | −0.07 | 0.12 | −0.64 | .53 | −0.31 to 0.17 |
| Male gender | −2.07 | 1.38 | −1.50 | .13 | −4.77 to 0.63 |
| Haloperidol decanoate baseline | 0.82 | 1.34 | 0.61 | .54 | −1.81 to 3.45 |
| Body mass index—change from baseline, 6 mo | | | | | |
| Intercept | 0.14 | 0.18 | 0.75 | .45 | −0.21 to 0.49 |
| Switch group | −0.08 | 0.15 | −0.54 | .59 | −0.37 to 0.21 |
| Time | 0.05 | 0.06 | 0.85 | .40 | −0.07 to 0.17 |
| Group by time | 0.23 | 0.09 | 2.67 | .01 | −0.05 to 0.41 |
| Male gender | −0.22 | 0.16 | −1.36 | .17 | −0.53 to 0.09 |
| Haloperidol decanoate baseline | 0.24 | 0.15 | 1.54 | .12 | −0.05 to 0.53 |
| Body mass index—change from baseline, 12 mo | | | | | |
| Intercept | 0.15 | 0.21 | 0.68 | .50 | −0.26 to 0.56 |
| Switch group | −0.08 | 0.18 | −0.46 | .65 | −0.43 to 0.27 |
| Time | 0.08 | 0.05 | 1.41 | .16 | −0.02 to 0.18 |
| Time$^2$ | −0.01 | 0.00 | −2.16 | .03 | −0.01 to −0.01 |
| Group by time | 0.25 | 0.08 | 3.13 | .00 | 0.09 to 0.41 |
| Group by time$^2$ | −0.01 | 0.01 | −1.80 | .07 | −0.03 to 0.01 |
| Male gender | −0.28 | 0.19 | −1.47 | .14 | −0.65 to 0.09 |
| Haloperidol decanoate baseline | 0.30 | 0.18 | 1.69 | .09 | −0.05 to 0.65 |
| Prolactin, ng/mL, 6 mo | | | | | |
| Intercept | 22.85 | 3.40 | 6.71 | .00 | 16.19 to 29.51 |
| Switch group | 0.30 | 2.91 | 0.10 | .92 | −5.40 to 6.00 |
| Time | −0.37 | 0.37 | −1.01 | .31 | −1.10 to 0.36 |
| Group by time | 1.32 | 0.53 | 2.48 | .01 | 0.28 to 2.36 |
| Male gender | −9.74 | 2.99 | −3.25 | .00 | −15.6 to −3.88 |
| Haloperidol decanoate baseline | 1.81 | 2.79 | 0.65 | .52 | −3.66 to 7.28 |
| Prolactin, ng/mL, 12 mo | | | | | |
| Intercept | 20.36 | 3.10 | 6.56 | .00 | 14.28 to 26.44 |
| Switch group | 0.15 | 3.12 | 0.05 | .96 | −5.97 to 6.27 |
| Time | −0.38 | 0.45 | −0.85 | .40 | −1.26 to 0.50 |
| Time$^2$ | 0.02 | 0.03 | 0.62 | .54 | −0.04 to 0.08 |
| Group by time | 1.81 | 0.71 | 2.57 | .01 | 0.42 to 3.20 |
| Group by time$^2$ | −0.12 | 0.05 | −2.31 | .02 | −0.22 to −0.02 |
| Male gender | −6.40 | 2.38 | −2.69 | .01 | −11.1 to −1.74 |
| Haloperidol decanoate baseline | 1.64 | 2.20 | 0.74 | .46 | −2.67 to 5.95 |

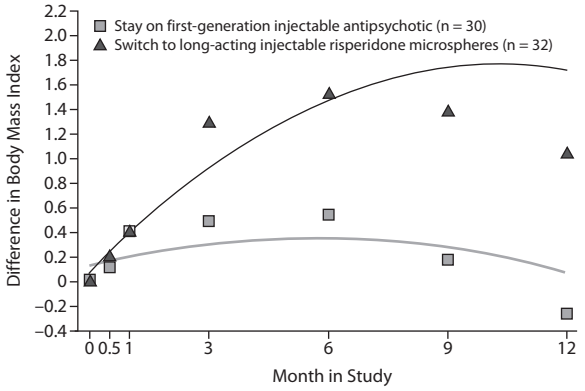
[a]A significant group-by-time interaction indicates that stay and switch groups differed significantly through time. Intercept represents the estimate of the baseline score for the stay group. The switch group (0 = stay, 1 = switch) estimate indicates whether groups differed at baseline. The time estimate indicates whether there was any significant change through time. Male gender (0 = female, 1 = male) and haloperidol decanoate baseline (0 = fluphenazine decanoate, 1 = haloperidol decanoate) estimates indicate whether gender or baseline medications, respectively, significantly impact the outcome.
Abbreviation: PANSS = Positive and Negative Syndrome Scale.

the original antipsychotic regimen.[17,19] Individuals randomly assigned to switch to long-acting injectable risperidone microspheres were more likely to discontinue treatment within 1 year than were those who continued on their baseline first-generation injectable antipsychotic medication. The extent to which this increased rate of discontinuation for switchers was due to risperidone microspheres being less well tolerated than a first-generation injectable antipsychotic medication versus the bias associated with staying on a medication already known to be tolerated is unclear. Answering that question would require comparing outcomes for individuals switched to a first-generation injectable antipsychotic medication with individuals switched to risperidone microspheres. A recently published retrospective study compared 726 individuals initiated on risperidone microspheres to 1,484 who were initiated on a first-generation injectable while hospitalized.[20] The authors reported that those initiated on risperidone microspheres were less likely to be discharged on that same medication and offered, as 1 possible explanation, that risperidone microspheres, in the dosages commonly used, may not be as efficacious as first-generation injectable medications.[20]

Similar to earlier studies,[8] we found that individuals in this small trial could switch from conventional depot antipsychotics to risperidone microspheres without compromising clinical stability. Adverse effects often are limiting factors in a medication's use and acceptability. We did not find significant differences between the medications studied with respect to new-onset EPS, tardive dyskinesia, or sexual side effects. While individuals with some side effects were eligible to participate in the study, those with side effects so bothersome that a change in medication was indicated were not eligible to participate. Hence, it may be that the study excluded those most vulnerable to developing EPS or tardive dyskinesia. We did find significant differences in BMI and prolactin that favored fluphenazine decanoate and haloperidol decanoate over risperidone microspheres.

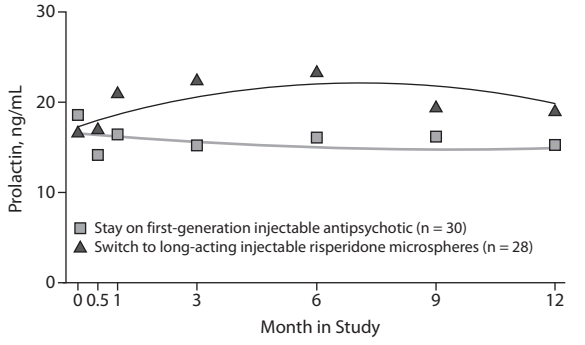
Because this was an open-label study, patients (and their prescribers) in the switch condition may have been more inclined to attribute changes in feelings/symptoms/side effects to the medication than were those in the stay condition, who may have experienced similar changes as part of normal variations in their illness. Because the study excluded individuals who could not tolerate remaining on their baseline treatment, those assigned to stay may have been advantaged with respect to measures of discontinuation. Treatment discontinuation may also be subject to expectation bias in an open-label study. Hence, time to all-cause discontinuation may be a more appropriate measure for double-blind trials in which prescriber and patient expectation effects are controlled. In contrast, ratings of EPS and tardive

**Figure 2. Difference in Body Mass Index Through Time[a,b]**




[a]Gray and black solid lines represent the trend estimated by the random regression models for the stay and switch groups, respectively. Squares and triangles represent actual mean values for the stay and switch groups, respectively.
[b]Significant group-by-time interaction ($z = 2.67$, $P = .01$, at 6 months; $z = 3.13$, $P = .00$, at 12 months).

**Figure 3. Prolactin Through Time[a,b]**




[a]Gray and black solid lines represent the trend estimated by the random regression models for the stay and switch groups, respectively. Squares and triangles represent actual mean values for the stay and switch groups, respectively.
[b]Significant group-by-time interaction (at 6 months, $z = 2.48$, $P = .01$; at 12 months, $z = 2.57$, $P = .01$; for group by time, $z = -2.31$, $P = .02$ for group by time[2]).

dyskinesia were conducted by blinded raters, and measures of weight and prolactin levels were based on objective measures and unlikely to be influenced by knowledge of the treatment assignment.

A limitation of the study is its modest sample size and limited statistical power. Additionally, our study was both too small and too short to allow evaluation of the long-term cost implications of the switch from first-generation injectables to risperidone microspheres. Nevertheless, we were able to detect a significant difference in the primary outcome measure at 12 months and in important secondary measures. For other important secondary measures, including psychiatric symptoms, hospitalizations, new-onset EPS, and new-onset tardive dyskinesia, we found no trends that would suggest a large difference between treatment groups. A larger and longer study, however, might reveal differences that are clinically and statistically significant. Additionally, the small sample size precluded subgroup analyses that may have identified groups that did better on one of the treatments.

Given the aim of this study—to determine the relative risks and benefits of changing from haloperidol decanoate or fluphenazine decanoate to risperidone microspheres—generalizability of the findings is necessarily limited to people who are already receiving long-acting injectable antipsychotics. Those who are prescribed long-acting injectable medications likely differ from individuals who are prescribed oral therapy. Hence, these findings do not inform the relative risks and benefits of switching from oral antipsychotics to risperidone microspheres.

Despite these limitations, this study adds to the literature suggesting that, for individuals who have responded somewhat to their current antipsychotic but who still have residual symptoms, switching to a different antipsychotic is unlikely to improve symptom control, and new side effects are likely. Given this finding, physicians should review with patients the side effects associated with various antipsychotics as an important component of shared decision making.

***Drug names:*** haloperidol (Haldol and others), olanzapine (Zyprexa), paliperidone (Invega), quetiapine (Seroquel), risperidone (Risperdal and others).

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***Potential conflicts of interest:*** **Dr McEvoy** has received grant/research support from Merck, GlaxoSmithKline, and Hoffman Laroche and has served on speakers or advisory boards of Eli Lilly, Merck, and Sunovion. **Dr Schooler** has been a consultant to H. Lundbeck; has received grant/research support from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Ortho-McNeil Janssen, and Pfizer; and has served on speakers or advisory boards of Merck, Janssen-Cilag, and Johnson & Johnson. **Drs Covell**, **Stroup**, **Jackson**, and **Essock** and **Ms Rojas** report no competing interests.

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***Supplementary material:*** Available at PSYCHIATRIST.COM.

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THE JOURNAL OF CLINICAL PSYCHIATRY

# Supplementary Material

**Article Title:** Effectiveness of Switching From Long-Acting Injectable Fluphenazine or Haloperidol Decanoate to Long-Acting Injectable Risperidone Microspheres: A Randomized Controlled Trial

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## List of Supplementary Material for the article

1. eFigure 1 — Recruitment Flow for Effectiveness of Switching: Injectable to Injectable
2. eTable 1 — Intent to Treat Means of Secondary Outcome Measures Through Time for People with Schizophrenia-Spectrum Disorders in a Randomized Controlled Study of Staying on a First Generation Antipsychotic Injectable versus Switching to Long-Acting Injectable Risperidone Microspheres

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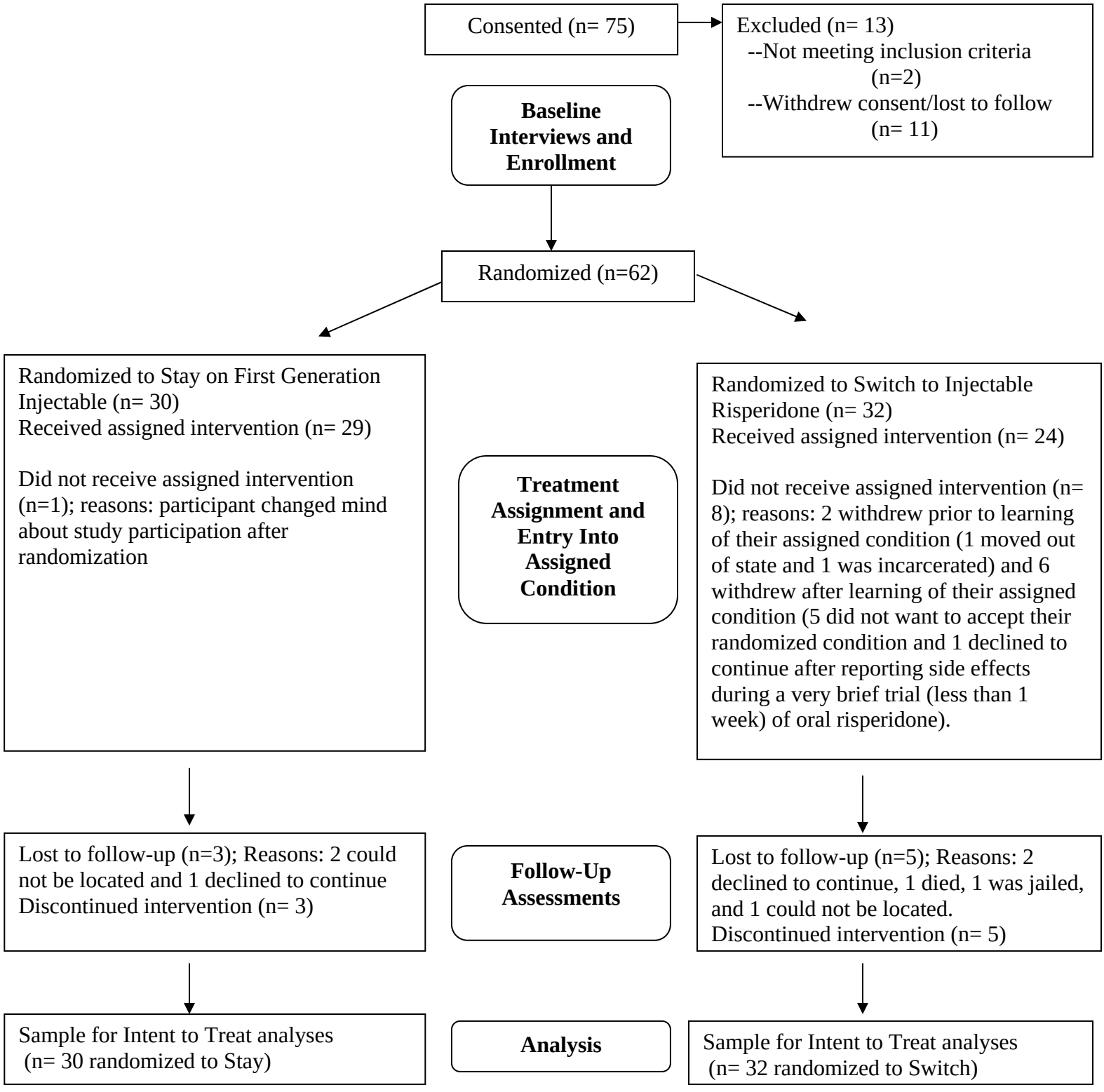
Supplementary eFigure 1. Recruitment Flow for Effectiveness of Switching: Injectable to Injectable



**Supplementary eTable 1. Intent to Treat Means of Secondary Outcome Measures Through Time for People with Schizophrenia-Spectrum Disorders in a Randomized Controlled Study of Staying on a First Generation Antipsychotic Injectable versus Switching to Long-Acting Injectable Risperidone Microspheres**

| | **Randomly Assigned to Stay on First Generation Injectable** (N=30) | | | **Randomly Assigned to Stay on Fluphenazine Decanoate** (N=11) | | | **Randomly Assigned to Stay on Haloperidol Decanoate** (N=19) | | | **Randomly Assigned to Switch to Long-Acting Injectable Risperidone Microspheres** (N=32) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PANSS Total Score | | | | | | | | | | | | |
| | **N** | **Mean** | **SD** | **N** | **Mean** | **SD** | **N** | **Mean** | **SD** | **N** | **Mean** | **SD** |
| Baseline | 30 | 69.9 | 17.9 | 11 | 65.8 | 18.2 | 19 | 72.2 | 17.8 | 32 | 65.4 | 14.0 |
| 2 Weeks | 26 | 65.8 | 17.9 | 10 | 68.2 | 20.1 | 16 | 64.3 | 16.9 | 21 | 67.7 | 14.5 |
| 1 Month | 27 | 64.4 | 17.5 | 9 | 67.0 | 19.6 | 18 | 63.2 | 16.8 | 24 | 66.8 | 13.2 |
| 3 Months | 26 | 62.4 | 17.8 | 9 | 60.0 | 17.8 | 17 | 63.8 | 18.3 | 23 | 63.1 | 13.6 |
| 6 Months | 24 | 61.0 | 19.3 | 9 | 58.6 | 19.3 | 15 | 62.5 | 19.8 | 22 | 60.9 | 10.7 |
| 9 Months | 26 | 64.2 | 16.3 | 9 | 64.6 | 18.7 | 17 | 64.1 | 15.5 | 17 | 57.9 | 10.5 |
| 12 Months | 25 | 62.2 | 20.0 | 9 | 67.6 | 24.2 | 16 | 59.3 | 17.2 | 18 | 64.0 | 19.2 |
| Proportion of those without evidence of Tardive Diskinesia at baseline | | | | | | | | | | | | |

| who had evidence of Tardive Dyskinesia at follow-up | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | **N** | **Mean** | **SD** | **N** | **Mean** | **SD** | **N** | **Mean** | **SD** | **N** | **Mean** | **SD** |
| Baseline | 21 | 0 | 0 | 8 | 0 | 0 | 13 | 0 | 0 | 19 | 0 | 0 |
| 2 Weeks | 19 | .11 | 0.3 | 8 | .13 | 0.4 | 11 | .09 | 0.3 | 11 | .18 | 0.4 |
| 1 Month | 19 | .00 | 0.0 | 7 | .00 | 0.0 | 12 | .00 | 0.0 | 14 | .14 | 0.4 |
| 3 Months | 19 | .00 | 0.0 | 7 | .00 | 0.0 | 12 | .00 | 0.0 | 12 | .17 | 0.4 |
| 6 Months | 18 | .17 | 0.4 | 7 | .29 | 0.5 | 11 | .09 | 0.3 | 12 | .25 | 0.5 |
| 9 Months | 19 | .16 | 0.4 | 7 | .14 | 0.4 | 12 | .17 | 0.4 | 9 | .11 | 0.3 |
| 12 Months | 18 | .06 | 0.2 | 7 | .00 | 0.0 | 11 | .09 | 0.3 | 10 | .50 | 0.5 |

| Proportion of those without evidence of EPS at baseline who had evidence of EPS at follow-up | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | **N** | **Mean** | **SD** | **N** | **Mean** | **SD** | **N** | **Mean** | **SD** | **N** | **Mean** | **SD** |
| Baseline | 22 | 0 | 0 | 9 | 0 | 0 | 13 | 0 | 0 | 18 | 0 | 0 |
| 2 Weeks | 19 | .05 | 0.2 | 8 | .13 | 0.4 | 11 | .00 | 0.0 | 10 | .10 | 0.3 |
| 1 Month | 19 | .05 | 0.2 | 7 | .00 | 0.0 | 12 | .08 | 0.3 | 12 | .00 | 0.0 |
| 3 Months | 19 | .05 | 0.2 | 7 | .00 | 0.0 | 12 | .08 | 0.3 | 11 | .09 | 0.3 |
| 6 Months | 18 | .06 | 0.2 | 7 | .00 | 0.0 | 11 | .09 | 0.3 | 11 | .09 | 0.3 |
| 9 Months | 19 | .16 | 0.4 | 7 | .14 | 0.4 | 12 | .17 | 0.4 | 8 | .13 | 0.4 |
| 12 Months | 18 | .17 | 0.4 | 7 | .14 | 0.4 | 11 | .18 | 0.4 | 9 | .11 | 0.3 |

| Change in Body Mass Index | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **N** | **Mean** | **SD** | **N** | **Mean** | **SD** | **N** | **Mean** | **SD** | **N** | **Mean** | **SD** |
| Baseline | 30 | 0 | 0 | 11 | 0 | 0 | 19 | 0 | 0 | 32 | 0 | 0 |
| 2 Weeks | 26 | .10 | 1.0 | 10 | -.12 | 1.2 | 16 | .24 | 0.8 | 21 | .20 | 1.1 |
| 1 Month | 27 | .39 | 1.0 | 9 | .20 | 1.0 | 18 | .49 | 0.9 | 23 | .40 | 1.2 |
| 3 Months | 26 | .48 | 1.4 | 9 | .00 | 1.0 | 17 | .73 | 1.6 | 23 | 1.29 | 1.9 |
| 6 Months | 24 | .53 | 1.3 | 9 | .48 | 1.0 | 15 | .56 | 1.4 | 22 | 1.53 | 2.2 |
| 9 Months | 25 | .16 | 1.3 | 9 | .36 | 0.9 | 16 | .05 | 1.5 | 17 | 1.38 | 2.4 |
| 12 Months | 24 | -.28 | 1.7 | 9 | .09 | 1.3 | 15 | -.50 | 1.9 | 17 | 1.04 | 2.0 |

| Arizona Sexual Experiences Scale Total | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **N** | **Mean** | **SD** | **N** | **Mean** | **SD** | **N** | **Mean** | **SD** | **N** | **Mean** | **SD** |
| Baseline | 27 | 15.2 | 5.0 | 10 | 17.0 | 5.1 | 17 | 14.2 | 4.7 | 29 | 15.9 | 5.6 |
| 2 Weeks | 23 | 15.9 | 5.7 | 8 | 16.5 | 4.3 | 15 | 15.5 | 6.4 | 19 | 16.6 | 5.7 |
| 1 Month | 23 | 15.7 | 6.2 | 7 | 16.6 | 6.6 | 16 | 15.4 | 6.2 | 21 | 17.7 | 4.1 |
| 3 Months | 24 | 14.9 | 5.1 | 7 | 15.7 | 5.4 | 17 | 14.5 | 5.1 | 20 | 16.6 | 4.9 |
| 6 Months | 23 | 15.4 | 5.2 | 8 | 16.4 | 5.4 | 15 | 14.9 | 5.2 | 18 | 16.7 | 6.3 |
| 9 Months | 23 | 15.4 | 6.6 | 8 | 16.0 | 7.3 | 15 | 15.1 | 6.4 | 15 | 16.7 | 5.3 |
| 12 Months | 24 | 17.0 | 7.1 | 8 | 17.6 | 6.9 | 16 | 16.7 | 7.5 | 16 | 16.9 | 5.7 |

| Prolactin (ng/ml) – All Study Participants | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **N** | **Mean** | **SD** | **N** | **Mean** | **SD** | **N** | **Mean** | **SD** | **N** | **Mean** | **SD** |
| Baseline | 23 | 18.5 | 13.8 | 7 | 19.3 | 12.4 | 16 | 18.2 | 14.7 | 26 | 16.7 | 9.8 |
| 2 Weeks | 20 | 14.1 | 6.6 | 7 | 12.9 | 3.5 | 13 | 14.7 | 7.9 | 17 | 17.1 | 18.1 |
| 1 Month | 22 | 16.4 | 10.1 | 8 | 14.9 | 5.2 | 14 | 17.2 | 12.2 | 21 | 21.1 | 19.6 |



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| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 3 Months | 22 | 15.1 | 7.6 | 8 | 13.1 | 5.8 | 14 | 16.2 | 8.5 | 19 | 22.5 | 19.1 |
| 6 Months | 21 | 16.0 | 7.5 | 9 | 16.7 | 8.9 | 12 | 15.5 | 6.6 | 18 | 23.4 | 13.8 |
| 9 Months | 18 | 16.2 | 8.0 | 7 | 12.6 | 2.8 | 11 | 18.5 | 9.4 | 15 | 19.5 | 12.1 |
| 12 Months | 18 | 15.2 | 5.1 | 7 | 16.1 | 6.3 | 11 | 14.7 | 4.4 | 14 | 19.0 | 10.6 |
| Prolactin (ng/ml) – Women only | | | | | | | | | | | | |
| | **N** | **Mean** | **SD** | **N** | **Mean** | **SD** | **N** | **Mean** | **SD** | **N** | **Mean** | **SD** |
| Baseline | 5 | 26.9 | 22.7 | 2 | 29.1 | 22.2 | 3 | 25.4 | 28.0 | 8 | 23.6 | 11.3 |
| 2 Weeks | 4 | 18.0 | 11.5 | 1 | 16.5 | -- | 3 | 18.5 | 14.1 | 5 | 34.6 | 25.9 |
| 1 Month | 5 | 21.3 | 16.1 | 2 | 15.7 | 4.0 | 3 | 25.0 | 21.4 | 5 | 34.8 | 32.5 |
| 3 Months | 6 | 14.6 | 6.9 | 2 | 13.0 | 6.1 | 4 | 15.4 | 8.0 | 5 | 36.7 | 29.3 |
| 6 Months | 7 | 15.4 | 10.5 | 3 | 21.2 | 14.7 | 4 | 11.1 | 4.6 | 4 | 38.9 | 19.1 |
| 9 Months | 6 | 12.4 | 5.6 | 2 | 11.7 | 4.3 | 4 | 12.8 | 6.8 | 2 | 33.1 | 5.5 |
| 12 Months | 6 | 16.5 | 6.9 | 3 | 19.0 | 7.3 | 3 | 14.0 | 7.0 | 3 | 23.1 | 14.5 |
| Prolactin (ng/ml) – Men only | | | | | | | | | | | | |
| | **N** | **Mean** | **SD** | **N** | **Mean** | **SD** | **N** | **Mean** | **SD** | **N** | **Mean** | **SD** |
| Baseline | 18 | 16.2 | 9.9 | 5 | 15.3 | 6.4 | 13 | 16.5 | 11.2 | 18 | 13.6 | 7.6 |
| 2 Weeks | 16 | 13.1 | 4.9 | 6 | 12.3 | 3.4 | 10 | 13.6 | 5.8 | 13 | 10.3 | 5.9 |
| 1 Month | 17 | 14.9 | 7.7 | 6 | 14.6 | 5.8 | 11 | 15.1 | 8.8 | 16 | 16.8 | 12.2 |
| 3 Months | 16 | 15.2 | 8.1 | 6 | 13.1 | 6.3 | 10 | 16.5 | 9.1 | 14 | 17.5 | 11.6 |
| 6 Months | 14 | 16.3 | 5.9 | 6 | 14.5 | 4.8 | 8 | 17.7 | 6.6 | 14 | 19.0 | 8.3 |
| 9 Months | 12 | 18.1 | 8.5 | 5 | 12.9 | 2.6 | 7 | 21.8 | 9.5 | 13 | 17.4 | 11.5 |
| 12 Months | 12 | 14.6 | 4.2 | 4 | 14.0 | 5.6 | 8 | 14.9 | 3.7 | 11 | 17.9 | 9.9 |