

# Effectiveness of Switching from Antipsychotic Polypharmacy to Monotherapy

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# ABSTRACT

**Background** – Absent data, clinical guidelines discourage antipsychotic polypharmacy either by omission or recommending it only after evidence-based approaches have failed (1). We provide data from a randomized controlled trial addressing the relative risks and benefits of staying on two antipsychotic medications versus switching to monotherapy. **Methods** - 15 study sites in the NIMH Schizophrenia Trials Network and 5 sites in the public mental health system in Connecticut recruited adults (18 and older) with a SCID diagnosis of schizophrenia or schizoaffective disorder who were currently taking two prescribed antipsychotics, defined by a plasma level greater than zero. 127 Participants were randomly assigned to stay on both antipsychotic medications or to discontinue one. The choice of which to discontinue was made by the participant and physician. Treatment was open label with assessment by blinded raters. Paralleling CATIE Phase 1 (2) and post-hoc stay or switch analyses of CATIE (3), we used Kaplan-Meier and Cox regression to examine the impact of Staying on polypharmacy compared to Switching to monotherapy on time to all-cause treatment discontinuation. Similarly, we applied mixed models to examine the effect of Stay or Switch on changes in total PANSS score, weight, and prolactin through the first 6 study months. We examined intent-to-treat and two as-treated models, one where treatment crossovers were excluded entirely and one where data from treatment crossovers were excluded only following crossover. **Results** - Individuals assigned to Switch from antipsychotic polypharmacy to monotherapy had significantly shorter times to all-cause discontinuation than those who were assigned to Stay on polypharmacy ( $p < .05$ ). In both intent-to-treat and as-treated models, Groups did not differ through time for total PANSS, though there were significant effects for both Time ( $p < .05$ ) and Time2 ( $p < .05$ ). Those assigned to Switch to monotherapy lost weight compared to those assigned to Stay on polypharmacy who gained weight, a difference that was significant when crossovers were excluded entirely and marginally significant in other models. There were no significant Group-by-Time or Time effects for prolactin. **Conclusions** – While discontinuing one of two antipsychotics was followed by an additional medication change more often than if both antipsychotics had been continued, individuals switched to monotherapy had equivalent symptom control and weight loss compared to those who continued on polypharmacy. More prospective studies of adding a second antipsychotic are needed.

## ADDITIONAL METHODS

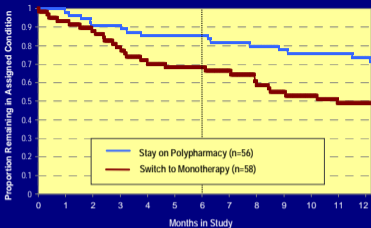
We extended the analyses of data through 12 study months. We adopted Schooler and Kane's (4) research criteria for Tardive Dyskinesia (presence of at least "moderate" movements in one or more body areas or at least "mild" movements in two or more body areas as rated on the Abnormal Involuntary Movement Scale). We defined possible EPS as an average of  $>0.3$  across items on the Simpson-Angus scale.

**DISCLOSURES:** Drs. Essock and Covell – none. Dr. McEvoy – Honoraria from Eli Lilly & Co., Janssen Pharmaceutica, and Pfizer. Consultant for Eli Lilly & Co., Organon, and Solvay. Dr. Schooler -Honorarium from Organon, OrthMcNeil Janssen, Schering Plough; Grants from Astra Zeneca, Bristol Meyers Squibb, Eli Lilly & Co, OrthMcNeil Janssen. Dr. Stroup - Consultant for Eli Lilly & Co., Janssen Pharmaceutica. Honoraria from Lundbeck.  
**SOURCE OF FUNDING:** NIMH grant MH59312 (S. Essock, PI)

# RESULTS

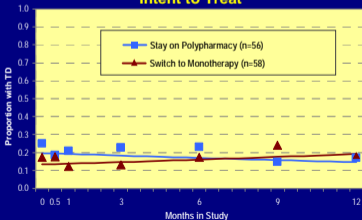
- The most common baseline polypharmacy combinations were quetiapine+risperidone (n=25), quetiapine+FGA (n=25), risperidone+FGA (n=23), olanzapine+FGA (n=22), ziprasidone+FGA (n=12), aripiprazole+quetiapine (n=11), olanzapine+risperidone (n=10), and other combinations totaling 10 or fewer individuals each (n=39).
- Time to treatment discontinuation was shorter for patients assigned to Switch from polypharmacy to monotherapy than for those assigned to Stay on polypharmacy, and switching from polypharmacy to monotherapy was associated with treatment discontinuation significantly more often than continuation of polypharmacy.
- Switching from polypharmacy to monotherapy had no impact on total PANSS, positive PANSS scores, or movement side effects.
- Those assigned to Switch to monotherapy lost weight compared to those assigned to Stay on polypharmacy, who gained weight.
- Most individuals who were assigned to monotherapy but who did not continue on monotherapy went back to their previous polypharmacy combination.

## Time to All Cause Discontinuation



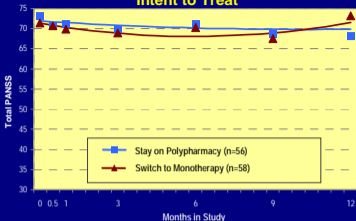
Significant Group difference in time to all cause discontinuation  
(Kaplan-Meier Mantel-Cox  $\chi^2(1) = 6.365$   $p < .05$ ).

## Tardive Dyskinesia Through Time Intent to Treat



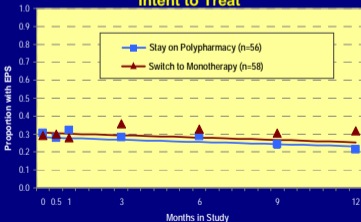
Significant Group by Time interaction (mixed regression  $z = 2.27$ ,  $p < .05$ ). Linear model.  
Results for As-treated analyses yielded a similar pattern.

## Total PANSS Score Through Time Intent to Treat



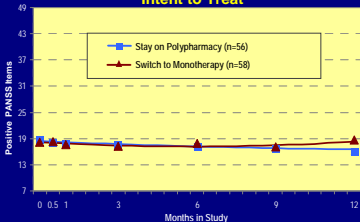
Marginal Group by Time<sup>2</sup> interaction (mixed regression  $z = 1.69$ ,  $p = .09$ ).  
Quadratic Model. Results for As-treated analyses yielded a similar pattern.

## EPS Through Time Intent to Treat



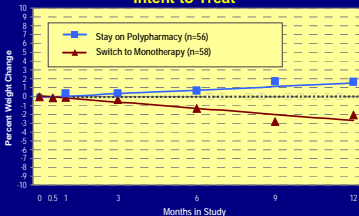
No significant Group by Time interaction;  
Time alone was marginally significant (mixed regression  $z = -1.81$ ,  $p = .07$  for Time).  
Linear model. Results for As-treated analyses yielded a similar pattern.

## Positive PANSS Score Through Time Intent to Treat



No significant Group by Time interaction;  
Time alone was significant (mixed regression  $z = -2.29$ ,  $p < .05$  for Time). Quadratic model.  
Results for As-treated analyses yielded a similar pattern.

## Percent Weight Change Through Time Intent to Treat



Significant Group by Time interaction (mixed regression  $z = -2.39$ ,  $p < .05$ ). Linear model.  
Results for As-treated analyses yielded a similar pattern.

# CONCLUSIONS

This study suggests that individuals with schizophrenia who are receiving two antipsychotics, and their prescribers, may want to give strong consideration to a trial of antipsychotic monotherapy. Such a switch to monotherapy was associated with significant weight loss and equivalent symptom control. This switch did not fit everyone: Individuals who were randomly assigned to switch to monotherapy were more likely to discontinue that regimen (typically by going back to the previous polypharmacy regimen) than were those who continued on their baseline polypharmacy regimen. Nevertheless, at 12 months, roughly half of the individuals randomly assigned to switch to monotherapy were still on that same monotherapy and had lost an average of 3% of their body weight, suggesting that this switch was well tolerated and beneficial to a large proportion of individuals. This weight loss is in sharp contrast to the average weight gain of 2% of their body weight at 12 months for those who stayed on polypharmacy. Because this was an open label study with blinded raters, it may be that the patients (and their prescribers) in the "Switch" condition were more inclined to attribute changes in feelings/symptoms/side effects to the medication than were those in the "Stay" condition, who may have experienced these same changes as part of normal variations in experience. Time to all cause discontinuation may be a more appropriate measure for double blind trials where prescriber and patient expectation effects are controlled.

The results of this study suggest that system administrators and others contemplating prescribing guidelines should encourage trials of antipsychotic monotherapy for individuals receiving antipsychotic polypharmacy, with the caveat that individuals should be free to return to the polypharmacy combination if an adequate trial on antipsychotic monotherapy does not prove to be satisfactory.

While this study demonstrates that individuals on polypharmacy may benefit from discontinuing the polypharmacy, it says nothing about whether the move to polypharmacy is good idea in the first place. Clearly, more prospective studies are needed on the effectiveness of adding a second antipsychotic.

# PARTICIPATING SITES

Participating Schizophrenia Trial Network Sites included: **L. Adler**, Clinical Insights, Glen Burnie, Md.; **M. Byerly**, University of Texas Southwestern Medical Center at Dallas, Dallas; **S. Caroff**, Behavioral Health Service, Philadelphia; **J. Csernansky**, Washington University School of Medicine, St. Louis; **C. D'Souza**, Connecticut Mental Health Center, New Haven; **C. Jackson**, James J. Peters VA Medical Center, Bronx; **T. Manschreck**, Corrigan Mental Health Center, Fall River, Mass.; **J. McEvoy**, Duke University Medical Center, Durham, N.C.; **A. Miller**, University of Texas Health Science Center at San Antonio, San Antonio; **H. Nasrallah**, University of Cincinnati Medical Center, Cincinnati; **S. Olson**, University of Minnesota Medical School, Minneapolis; **J. Patel**, University of Massachusetts Health Care, Worcester; **B. Saltz**, Mental Health Advocates, Boca Raton, Fla.; **R.M. Steinbook**, University of Miami School of Medicine, Miami; and **A. Tapp**, Veterans Affairs Puget Sound Health Care System, Tacoma, Wash, and 5 sites in the public mental health system in CT (**K. Marcus**, Medical Director).

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