Longitudinal dosage records as an indicator of clozapine response

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Introduction

- Although clozapine is the only antipsychotic effective in treating patients with treatment-resistant schizophrenia (TRS)[1], still many of these patients will not respond to clozapine[2].
- Studies on predictors of clozapine often produce conflicting results because of low power. Thus, no predictors have been translated clinically.
- Large case registers could solve the issues of low powered studies, but no clinical indicator of clozapine response exists in case registers.
- Patients' longitudinal dosage records may serve as a reliable clinical indicator of patient response in large medical databases of clinical case notes.

Hypothesis

On average, non-responding patients will display a positive nonzero longitudinal dosage slope; responding patients will display a stable, zero dosage slope.

Methods

Participants

- n=316 TRS patients with their clozapine dosages recorded in the Clinical Records Interactive Search (CRIS) on their first clozapine trial, aged 18-65, with an ICD-10 diagnosis of F20-F29.

Measures

- Binary response measured as a retrospectively double-rated Clinical Global Impressions (CGI-I) score of 1 or 2; CGI-I > 2, non-response. CGI-I scores at 1, 2, 3, 6, 9, and 12m (months).
- CGI-I inter-rater agreement of 95.7%
- Clozapine dosages extracted manually from CRIS clinical case notes in biweekly format and averaged at 3, 6, 9, and 12m.
- Patients discontinuing clozapine before 1m and those never reaching 100mg not included in analyses.

Analysis

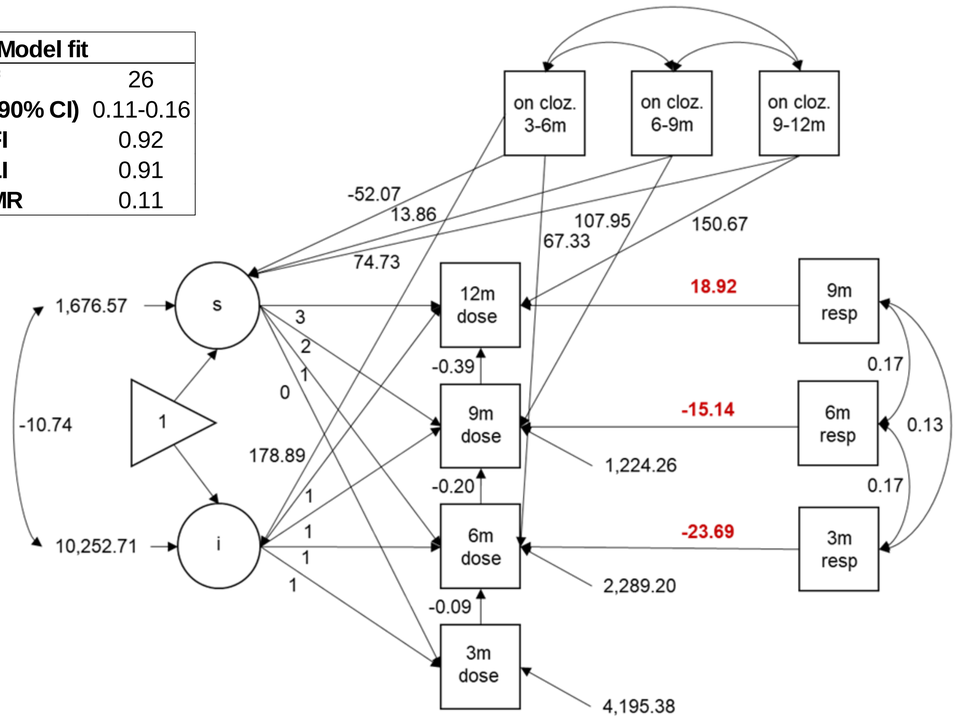
- Latent Growth Curve Model (LGM) to identify if a temporal relationship between clinical response and clozapine dosage exists, controlling for covariates.
- Quadratic two-group LGM to compare average dosage slopes between responders and non-responders.

Results

The final sample contained n=251 patients who were 22.4% African, 69.29% male, with an average age of clozapine initiation of 36.64 (sd=10.59), 75.52% of whom responded in their first year.

Linear Latent Growth Curve Model with Time-Variant Covariates (n=251)

Model fit	
df	26
RMSEA (90% CI)	0.11-0.16
CFI	0.92
TLI	0.91
SRMR	0.11



Two-Group LGM by Response Status (n=243, n=182 Responders [75%])

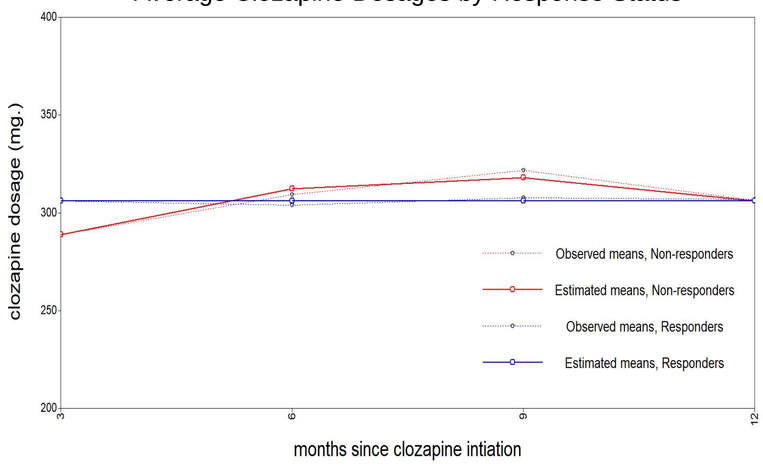
- Excellent model fit (χ^2 p-value=0.21; RMSEA=0.06 [90% CI, 0.00-0.13] CFI/TLI=0.99/0.99)

Latent Factor Parameter Estimates			
Group	Variable	Est. Mean (SE)	P-value
Non-Responders			
	Intercept	288.85 (18.45)	<0.000
	Linear slope	**32.23 (19.5)**	**0.098**
	Quadratic slope	-8.83 (5.6)	0.115
Responders			
	Intercept	306.19 (8.16)	<0.000
	Linear slope	**-0.01 (2.56)**	**0.99**

- Wald test for difference between linear slopes (red values above)

Wald test	
Estimate	2.69
df	1
p-value	0.1

Average Clozapine Dosages by Response Status



Conclusion

Main Findings

- TRS patients' responding to clozapine at 3 and 6m have a lower clozapine dosage at 6 and 9m, respectively; patients responding at 9m have a higher clozapine dosage at 12m.
- Responding patients display 0 linear slope, but no difference from non-responders.

Implications

- Dosage records may be tentatively used for identifying patients not responding to clozapine, but a replication with larger sample is encouraged.

Limitations

- Relatively low power; unbalanced marginal distributions of response status. Monte Carlo simulation (10,000 replications) using empirical parameter estimates indicates only 31.8% power to detect linear slope difference.
- Because low power, parameter estimates should be taken with caution.
- No empirical definition of response/non-response as measured by the CGI-I.

Future Directions

- Future studies should use include more non-responders to ensure accuracy of estimates.
- Test of prediction accuracy is planned.
- Creative and novel strategies will be required to translate these empirical findings to be used as a sampling tool in CRIS or databases alike.

Acknowledgements

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References

1: Chakos et al. (2001). *The American Journal of Psychiatry, 158*(1), 518-526.

2: Fabrazzo et al. (2002). *Neuropsychopharmacology, 27*(1), 1050-1055.