Longitudinal Opioid Use in Patients Treated with Buprenorphine: A 'Missing Not at Random' (MNAR) and 'Missing at Random' (MAR) Growth Model Comparison

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BACKGROUND & AIMS

- The missing data mechanism (i.e., "why are the data missing?") is often not reported or evaluated as part of the analytic strategy in substance abuse clinical trials.[1]
- There is a potential problem of not thoroughly evaluating and reporting the mechanism of missing information because treatment efficacy can vary as a function of how the missing information is handled analytically.[2,3]
- Appropriate decision making regarding how the missing data is handled is critical in order to make sound clinical inference based on randomized trials of substance use treatment, but missing not at random (MNAR) methodologies have not been explored in this context with real data.[4-6]
- This investigation compares 3 different modeling strategies for the handling of missing values (i.e., missing at random (MAR) model versus 2 different missing not at random (MNAR) models; Diggle-Kenward and Wu-Carroll selection modeling), and we hypothesized that the treatment effect (i.e., impact of Trial Arm on linear urine analysis (UA) slope) is dependent on the missing data strategy used.

METHODS

- Data for this investigation came from National Drug Abuse Treatment Clinical Trials Network #0003, a clinical trial (N=516) of 2 different buprenorphine tapering schedules (7- versus 28-day).[7]
  - –The primary purpose of this trial was to compare a 7-day versus 28-day taper (i.e., stepwise decrease in the amount of administered buprenorphine/naloxone) on the likelihood of a UA for opioid use at the end of the taper.
- The current investigation used UA data collected at the baseline visit and 4 subsequent weekly visits during the treatment period.
- We utilized latent growth modeling procedures in order to compare 3 different methods of handling the missing information:
  1) Basic latent growth model that uses maximum likelihood to handle the missing data (i.e., missing at random (MAR) model).[4,8,9]
  2) Diggle and Kenward (1994) missing not at random (MNAR) selection model where dropout is a function of previous and concurrent UA submitted (see Figure 1 for a diagram of this model).[10]
  3) Wu and Carroll (1988) MNAR selection model where dropout is a function of the random effects (i.e., intercept and linear slope growth factors (see Figure 2 for a diagram of this model).[11]

RESULTS

- The MAR model showed an effect of the 28-day taper (B= -0.45, p<.05) being predictive of the opioid UA slope (i.e., those in the 28-day taper were less likely to submit positive UAs over time; see Table 1).

The intercept growth factor (i.e., baseline UA) was also predictive of the UA slope (B= -0.14, p<.05).

- The MNAR Diggle & Kenward (1994) model demonstrated an effect of the 28-day taper group (B= -0.64, p<.05) on the slope also. While visit-specific UA did not predict either subsequent or concurrent dropout (see Table 2), the 28-day taper group was predictive of dropout after week 1 (OR= 0.43, p<.05), 2 (OR= 0.41, p<.05), and 3 (OR= 82.01, p<.05).

Again, the intercept was predictive of the UA slope (B= 0.15, p<.05), but in the opposite direction compared to the above-referenced MAR model.

- The MNAR Wu & Carroll (1988) model demonstrated that the 28-day taper showed a significant effect on the UA slope (B= -0.41, p<.05; see Table 3), and the 28-day taper predicted dropout after week 3 (OR= 71.31, p<.05).

The baseline UA was predictive of the UA slope (B= -0.12, p<.05), similar in size and direction as the MAR model.

CONCLUSION

- The trial arm effect on the UA slope (i.e., UA change over time), and other covariate effects, changed in a meaningful way across the MAR and MNAR growth models, indicating that missing data assumptions are critical to understand and explain in clinical trials.
- It is not only important for the research team to consider what the most likely missing data assumption is (i.e., MAR or MNAR), but also consider whether or not the additional assumptions associated with each MNAR and MAR model are reasonable.[1,2,4-6]
- This investigation highlights the potential for these modern approaches to missing data to shed new light on outcomes of interest (e.g., time-specific dropout) other than the primary outcome of UA.
- Given that randomized clinical trials form the foundation of building the most efficacious treatment modalities for substance abusing populations, observing how treatment effects vary across missing data treatments should move future research teams to explore their missing data patterns and assumed mechanism(s) thoroughly.[12]

Table 1. Random Linear Growth Model of UAs Across Baseline and 4 Subsequent Weekly Visits During Treatment: Missing at Random (using Maximum Likelihood)

Covariates	Outcomes	Unstandardized Estimate	(95% CI)
Trial Arm →	UA Intercept	0.944ns	(-0.289 - 2.178)
Age →	UA Intercept	-0.046ns	(-0.127 - 0.035)
Sex →	UA Intercept	-0.234ns	(1.039 - 2.219)
Trial Arm →	UA Slope	-0.454*	(-0.678 - -0.229)
Age →	UA Slope	-0.001ns	(-0.012 - 0.010)
Sex →	UA Slope	0.330*	(0.083 – 0.576)
UA Intercept →	UA Slope	- 0.140*	(-0.214 - -0.066)

UA = opioid urine analysis. The dependent measure was a negative or positive UA at the end of the taper (0 = negative UA; 1 = positive UA). Trial Arm represents the 7- and 28-day taper groups (0 = 7-day; 1 = 28-day). ns = non-significant. *p < .05.

Table 2. Growth Model of UAs Across Baseline and 4 Subsequent Weekly Visits: Missing not at Random, Diggle and Kenward (1994) Selection Model

Covariates	Outcomes	Unstandardized Estimate	(95% CI)
Trial Arm →	UA Intercept	0.677*	(0.167-1.188)
Age →	UA Intercept	-0.022*	(-0.044-0.000)
Sex →	UA Intercept	-0.072ns	(-0.683-0.540)
Trial Arm →	UA Slope	-0.637*	(-0.921- -0.352)
Age →	UA Slope	-0.001ns	(-0.014-0.011)
Sex →	UA Slope	0.339*	(0.018-0.660)
UA Intercept →	UA Slope	0.149*	(0.064-0.235)
Covariates	**Outcomes**	**Odds Ratio**	**(95% CI)**
Trial Arm →	Dropout Week 2	0.432*	(0.231-0.806)
Age →	Dropout Week 2	0.982ns	(0.954-1.012)
Sex →	Dropout Week 2	0.481ns	(0.230-1.005)
Trial Arm →	Dropout Week 3	0.410*	(0.238-0.677)
Age →	Dropout Week 3	1.006ns	(0.985-1.027)
Sex →	Dropout Week 3	0.909ns	(0.538-1.536)
Trial Arm →	Dropout Week 4	82.013*	(39.915-168.510)
Age →	Dropout Week 4	1.015ns	(0.985-1.046)
Sex →	Dropout Week 4	1.015ns	(0.518-1.989)
UA Weeks 1-3 →	Dropout Weeks 2-4	1.367ns	(0.683-2.734)
UA Weeks 2-4 →	Dropout Weeks 2-4	0.850ns	(0.279-2.586)

UA = opioid urine analysis. The dependent measure was a negative or positive UA at the end of the taper (0 = negative UA; 1 = positive UA). Trial Arm represents the 7- and 28-day taper groups (0 = 7-day; 1 = 28-day). ns = non-significant. *p < .05.

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Table 3. Growth Model of UAs Across Baseline and 4 Subsequent Weekly Visits: Missing not at Random, Wu and Carroll (1988) Selection Model

Covariates	Outcomes	Unstandardized Estimate	(95% CI)
Trial Arm →	UA Intercept	0.502ns	(-0.346-1.351)
Age→	UA Intercept	0.981*	(-0.115 - -0.002)
Sex →	UA Intercept	1.518 ns	(-1.208-0.633)
Trial Arm →	UA Slope	-0.413*	(-0.721- -0.105)
Age →	UA Slope	-0.001ns	(-0.011-0.009)
Sex →	UA Slope	0.318*	(0.096-0.540)
UA Intercept →	UA Slope	-0.121*	(-0.210- -0.032)
Covariates	**Outcomes**	**Odds Ratio**	**(95% CI)**
Trial Arm →	Dropout Week 2	0.382ns	(0.118-1.013)
Age →	Dropout Week 2	0.984ns	(0.955-1.013)
Sex →	Dropout Week 2	0.531ns	(0.172-1.645)
Trial Arm →	Dropout Week 3	0.355ns	(0.105-1.198)
Age →	Dropout Week 3	1.006ns	(0.985-1.028)
Sex →	Dropout Week 3	1.006ns	(0.384-2.635)
Trial Arm →	Dropout Week 4	71.307*	(25.374-200.394)
Age →	Dropout Week 4	1.017ns	(0.986-1.048)
Sex →	Dropout Week 4	1.135ns	(0.373-3.452)
UA Intercept →	Dropout Weeks 2-4	1.002ns	(0.734-1.367)
UA Slope →	Dropout Weeks 2-4	0.759ns	(0.055-10.483)

UA = opioid urine analysis. The dependent measure was a negative or positive UA at the end of the taper (0 = negative UA; 1 = positive UA). Trial Arm represents the 7- and 28-day taper groups (0 = 7-day; 1 = 28-day). ns = non-significant. *p < .05.

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Figure 1. Estimated Diggle and Kenward (1994) random linear growth model of time-specific dropout predicting both subsequent and concurrent dropout with additional covariates effects. (1) and (2) indicates regression paths that wee held equal.

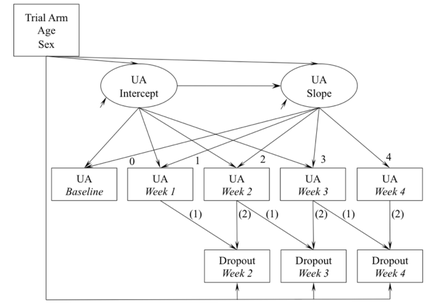
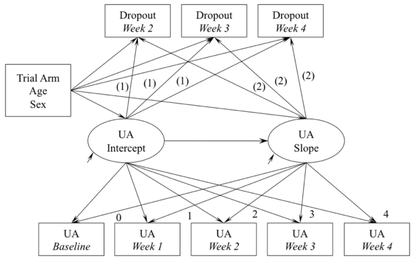


Figure 2. Estimated Wu and Carroll (1988) random linear growth model of intercept and slope growth factors predicting dropout with additional covariates effects. (1) and (2) indicates regression paths that were held equal.



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