A Comparative Example of Missing Data Strategies in Substance Abuse Clinical Trials Using Generalized Estimating Equations (GEE)

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BACKGROUND AND AIMS

- Substance abuse treatment research is often characterized by having a non-trivial amount of missing data, especially in longitudinal, randomized clinical trials.[1,2]
- A review of substance abuse clinical trials indicates that listwise deletion and single imputation (i.e., imputing missing values with a positive urine analysis) are the most commonly used procedures to deal with missing information.[3,4]
- Due to the prevalence and complex nature of missing data in substance abuse research, the best missing data procedures need be employed and tailored to each unique missing data situation so as to maximize the likelihood of arriving at the most accurate conclusions.[3,5,6]
- Our aim is to compare the outcomes from two common missing data handling procedures with the outcomes from the multiple imputation (MI) procedure in the context of generalized estimating equations (GEE) in order to demonstrate that interpretations of treatment effectiveness and other baseline covariate effects can change as a function of how the missing information is handled.

METHODS

- Listwise deletion, single imputation (i.e., positive UA imputation) and MI missing data procedures were used to comparatively examine the effect of two different buprenorphine/naloxone tapering schedules (7- or 28-days) for opioid addiction on the likelihood of a positive urine analysis (UA+; Clinical Trial Network 0003) across 4 weeks of post-randomization urine submissions during treatment.
- 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 results showed that those enrolled in the 7-day taper had significantly less chance of testing positive for opioid use compared to the 28-day taper.[7]
- This study used positive UA imputation to treat the missing information. Our purpose was to demonstrate how to use the MI procedure in conjunction with auxiliary variables to provide an alternative way to treat missing data in substance abuse research.
- Robust GEE procedures were the analytic approach used to evaluate opioid use over time across the three different methods of missing data treatment.

RESULTS

- The listwise deletion model (the most commonly reported method of handling missing information when utilizing GEE) demonstrated that those in the 28-day taper group were significantly less likely to submit an UA+ for opioids during the 4 weeks after being randomized (OR=0.55, CI: 0.37-0.80).
  - Younger patients were significantly less likely (OR=0.98, CI: 0.97-0.99) to submit a UA+ over time, and females were also more likely (OR=1.53, CI: 1.05-2.24) to submit a UA+ over time.
  - Lastly, time was positively related to UA+ (OR=1.20, CI: 1.04-1.40), and baseline UA+ was predictive of UA+ over time (OR=8.89, CI: 5.91-13.36).
- The positive UA imputation model evidenced that those in the 28-day taper group were significantly less likely to submit an UA+ during the 4 weeks after being randomized (OR=0.43, CI: 0.34-0.55).
  - While there was no effect of age or sex, time was positively related to UA+ (OR=1.26, CI: 1.16-1.39).
  - Baseline opioid UA+ was predictive of opioid UA+ over time (OR=5.56, CI: 4.02-7.69), and baseline cocaine UA+ was predictive of opioid UA+ over time (OR=1.36, CI: 1.05-7.42).
- The multiple imputation model also demonstrated that those in the 28-day taper group were significantly less likely to submit UA+ during the 4 weeks after being randomized (OR=0.57, CI: 0.42-0.77).
  - Similar to the listwise deletion model, younger patients were significantly less likely (OR=0.98, CI: 0.97-0.99) to submit a UA+ over time, and females were also more likely (OR=1.52, CI: 1.09-2.13) to submit a UA+ over time.
  - Again, time was positively related to UA+ (OR=1.18, CI: 1.01-1.38), and baseline UA+ was predictive of UA+ over time (OR=9.89, CI: 7.19-13.61).

Table 1. Likelihood of a Positive Urine Analysis for a 7-Day and 28-Day Buprenorphine Taper across the 4-Week Treatment Period Using Generalized Estimation Equations: Impact of Missing Data Treatment Choice on Outcomes

	Listwise Deletion (n = 394)		Positive UA Imputation (n = 516)		Multiple Imputation (n = 516)	
Covariates	**Odds Ratio**	**(95% CI)**	**Odds Ratio**	**(95% CI)**	**Odds Ratio**	**(95% CI)**
Trial Arm	0.546*	(0.371-0.802)	0.432*	(0.341-0.549)	0.572*	(0.424-0.775)
Age	0.981*	(0.965-0.997)	0.991ns	(0.981-1.00)	0.984*	(0.971-0.997)
Sex	1.518*	(1.039-2.219)	1.187ns	(0.932-1.511)	1.524*	(1.089-2.133)
Race	0.931ns	(0.806-1.075)	0.920ns	(0.841-1.005)	0.964ns	(0.850-1.093)
Time	1.202*	(1.035-1.398)	1.268*	(1.160-1.387)	1.183*	(1.184-1.383)
Baseline Opioid UA	8.886*	(5.912-13.356)	5.562*	(4.020-7.694)	9.873*	(7.194-13.617)
Baseline Cocaine UA	1.460ns	(0.975-2.185)	1.358*	(1.053-1.751)	1.191ns	(0.867-1.639)

UA = 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.

Figure 1. Estimated percent of participants with a positive UA result using all available data across the 4 weeks of treatment by Trial Arm.

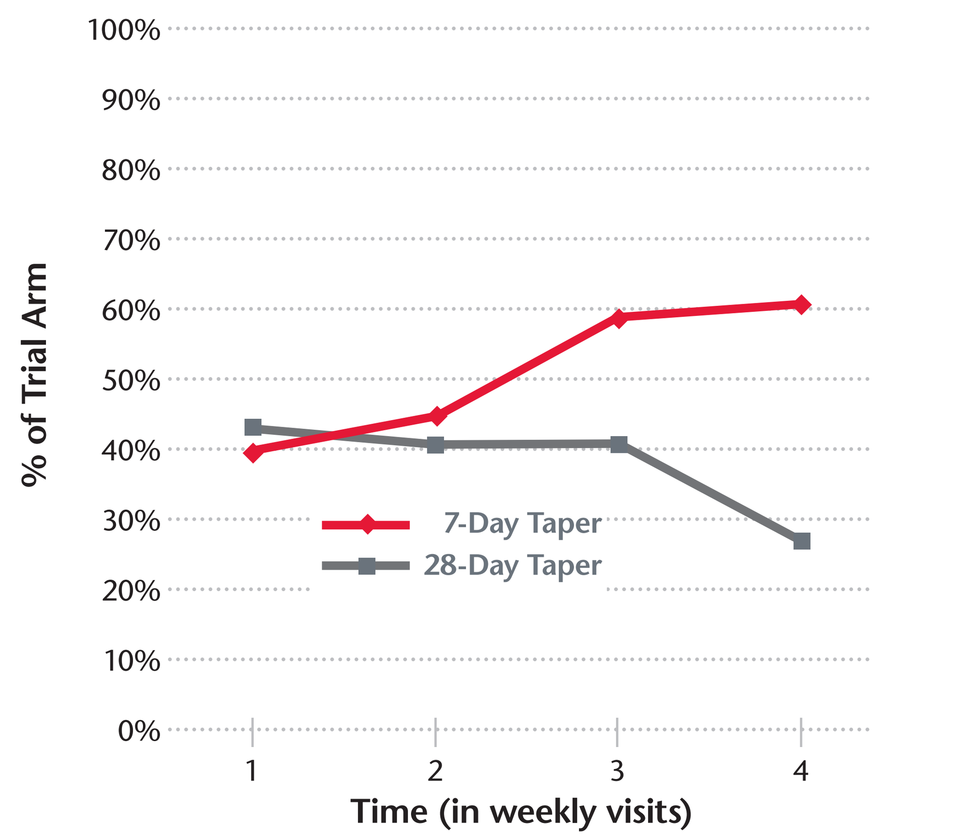
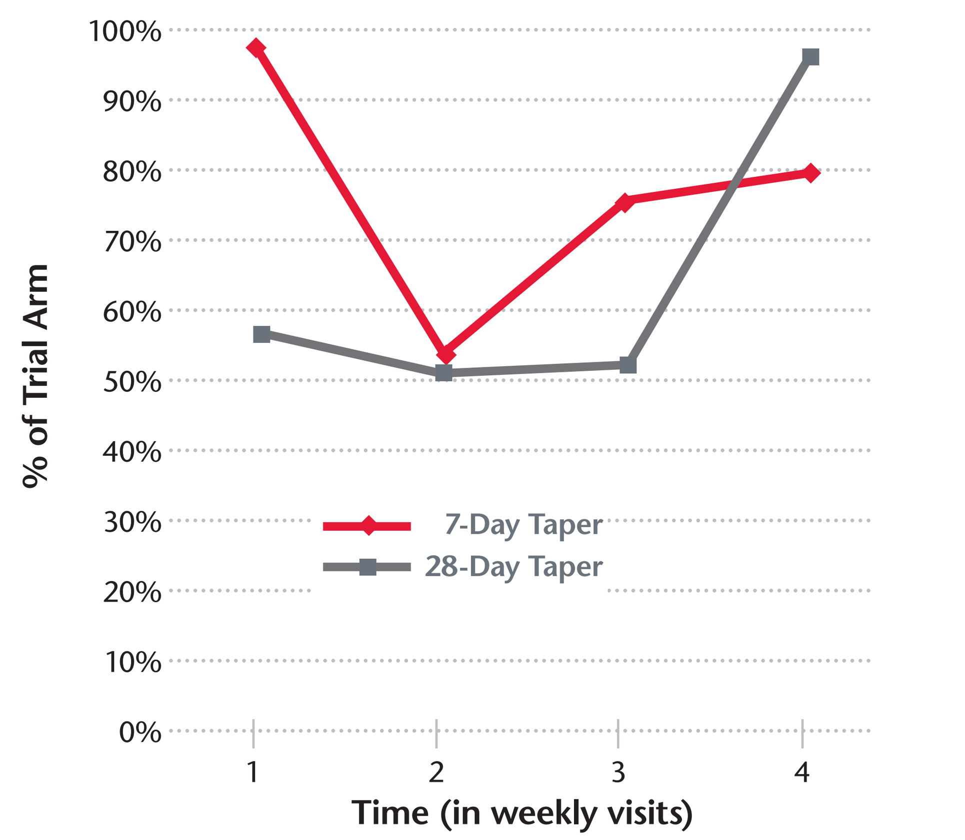


Figure 2. Estimated percent of participants with a positive UA result (imputing all missing values as positive) across the 4 weeks of treatment by Trial Arm.



CONCLUSIONS

- This investigation demonstrates how treatment efficacy can vary as a function of how the missing information is treated when there is a significant amount (e.g., > 23% in this analysis) of missing information.
- While this analysis demonstrated that the listwise deletion model was consistent with the multiple imputation model, this is not always the case as is evidenced with other missing data handling comparison investigations.[8]
- Missing data theory suggests that listwise deletion and single imputation models should not be used to account for missing information, and that MI has advantages with respect to internal and external validity when the assumption of missing at random can be reasonably supported.[5,9]
- Future researchers may find utilization of the MI procedure in conjunction with the common method of GEE analysis as a helpful analytic approach compared to commonly used procedures (i.e., listwise deletion or positive UA imputation) when the missing at random assumption is justifiable.

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