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Imputation Approach for Missing Binary Outcomes in Buprenorphine/Naloxone Treatment for Opioid Dependent

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The opioids is useful to treat the chronic pain. Recently, the opioid mistreatment increased dramatically. The kidney damage may occur due opioid abuse treatment. The creatinine level can be measured to detect the level of kidney damage. The goal of this study is to know the effective drug to control the creatinine among opioid dependent patients. The dependent prior with Bayesian approach is applied to compare the treatment effect. The secondary data on Buprenorphine (BUP) was considered to compare the two drug treatments, viz. (1) BUP+ Standard Medical Management (SMM) and (2) BUP+Extended Medical Mangament (EMM), in opioid dependent patients. In both drug groups the mean creatinine level was found controlled over the duration of the treatment. No rapid changes of creainine level among the patients are observed. At the end of study it is found that the means of creatinine level are higher in BUP+EMM group. The Bayesian dependent prior is found to offer effective tool for drug treatment effect comparison. The drug treatment effect BUP+EMM is found to be more effective to control the creatinine among the patients.

Key words: Missing observation, MAR, MNAR, Jeffreys's prior

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INTRODUCTION

The National Institute on Drug Abuse Clinical Trials Network (NIDACT) has conducted the study to compare the drug treatment effect between BUP+ Standard Medical Management (SMM) with BUP+Extended Medical Management (EMM). The individual drug counselling has been provided with SMM and described as EMM. The study has been carried to obtain the beneficial effect of individual drug counselling on opioid analgesics patients. The methadone or buprenorphine is effective for drug on opioid dependence (Johnson *et al*., 1992; Ling *et al*., 1996; Ball and Ross, 1991). The sublingual buprenorphine is useful to treat the opioid dependent drug user through the primary health care setup. However, the failed performance of buprenorphine is also document. The OBOT with buprenorphine (OBOT-B) treatment is highly associated for risk of illness and death among the high prevalence of addicted patients (Fiellin and O'Connor, 2002; Stein *et al*., 2005; Burt *et al*., 1999). The OBOT-B is highly failed to treat the homeless opioid dependent individual (Thomas *et al*., 1990; Song *et al*., 2000; Blanchon *et al*., 2003). The presence of low social support and insecure living environment is the contributing factor for the high treatment failure of opioid dependent (Galanter *et al*., 2004; Kertesz *et al*., 2003).

The strict, sensitive pharmacological dose regimens are important to monitor the dug effect success. The drug screening collection is useful for drug treatment effect integrity (Barbanel *et al*., 2002; Kapur *et al*., 1999; Kintz *et al*., 1996; Preston *et al*., 1999). It is very much important to monitor the blood sample to compare the drug treatment effect (Katz and Fanciullo, 2002). The creatinine is useful to detect the level of metabolism (Hawks, 1983). It is the leading factor for kidney functioning effect. It is also proportioned with muscle mass and body weight. The repeated observation of blood samples in different visits is usually taken in clinical trial to compare the drug treatment effect. The repeated measurement of the same patients through follow-up period observations opens the chances of occurrence of missing observations in the data set. The existence of missing observations in the data can generate the inconsistent results. The power of the inference goes down due to presence of missing observation. The clinical trials result becomes ignored due the presence missingness. It is required to accommodate the missing information in the data modelling rather than emphasize on complete case analysis (Little, 1993, 1994 and 1995). The work is contributed to explore the drug treatment effect through changes of creatinine level in follow-up visits in the conducted study of (NIDACT). However, to the best of our knowledge no work has been devoted to explore and compare the effect BUP with SMM and EMM among the opoid dependent patients on creatinine level changes.

The goal of this work is to find out whether the extended drug counselling effects with BUP along with SMM among the opiod dependent drug user improve the response. The level of creatinine in the blood sample is considered in this study to point out the treatment effect.

MATERIALS AND METHODS

The secondary data was been collected from the protocol Number CTN-30, available in the link www.ctndatashare.org. The primary data was captured between April, 2006 to November, 2009 into two phase, multi-centric clinical trial to determine whether treatment outcome for subjects dependent on prescription opioid analgesics can be improved by adding individual drug counselling to the prescription of buprenorphine/naloxone with standard medical management or not. The participant after obtaining the 1-day BUP were allocated for one month outpatient treatment with taper. The dose of the treatment was administered by doctor in view of participants well being. The maximum daily dose of BUP was reported with 32 mg. The randomization was conducted for the participant included in the Phase-I to allocate Buprenorphine +Standard Medical Management (BUP+SMM) or Buprenorphine+Extended Medical Management (BUP+EMM). The follow up visits were conducted in Weeks 6 and 8, respectively. Those participant failed to participate in the Phase-I, were considered in the Phase-II. The participant missed three or more days visits of BUP were included in the Phase-II. However, to deal with lost to follow up in less than three visits in both the Phases the MAR was applied to obtain the robust statistical inferences. The blood sample of each participant was collected during every two weeks for eight weeks after study initiation. The duration of the study was finalized with 12 week for Phase-I and 24-week for Phase-II.

The level of creatinine was assessed whether a buprenorphine drug therapy could prevent the progression of creatinine secretions in the blood or not. The normal range of creatinine was considered with 0.5 to 1.0 mg dL^{-1} for women and 0.7 to 1.2 mg dL^{-1} for men (Yamamoto *et al*., 2009). The normal level of creatinine is denoted with 1 otherwise 0.The measurements obtained through follow-up visits through collection of blood sample among the patients were considered as response of interest. The missing observations of the repeated

creatinine measurements were handled with simulated value obtained though MCMC iteration procedure. The prior distribution of the measured mean value of each visit in different treatment group was applied to generate the simulated value.

Data analysis: The statistical analysis was performed using WinBUGS version 1.4.3. The regression coefficient on the creatinine as the effect of BUP control was fitted. The presence of missing observation was handled with MAR assumption. The amount of creatinine in the repeated observation was classified into two group (i.e., normal range =1 and not normal = 0). The level of changes of creatinine was compared with previous visits observation of each patient.

Statistical model: The response variable Y with the covariates of interest X is predicted through the consideration of missing values. The parameter R is considered as the indicator variable to represents the presences missing value. The fully observed and incomplete observed covariates and responses are denoted with:

$$X_{i,obs} = \{X_{i,m+1},...X_{ip}\} \text{ and } X_{i,mis} = \{X_{i1},...X_{im}\} \quad (1)$$

$$Y_{i,obs} = \{Y_{i,m+1},...Y_{ip}\} \text{ and } Y_{i,mis} = \{Y_{i1},...Y_{im}\} \quad (2)$$

The missingness indicator is specified by:

$$R_i = \{R_{i1},...R_{im}\} \quad (3)$$

The joint density of the subject to missingness is denoted by:

$$p(Y,X,R_x \mid \eta,\beta,\theta) = p(R_X,R_Y \mid Y,X,\eta)p(Y \mid X,\beta)p(X \mid \theta) \quad (4)$$

The covariates X is assumed as the subject to missingness by:

$$p(Y,X,R_X \mid \eta,\beta,\theta) = p(R_X \mid Y,X,\eta)p(Y \mid X,\beta)p(X \mid \theta) \quad (5)$$

The one-dimensional conditional distribution for the subject to missingness is specified by Ibrahim *et al.* (2001):

$$p(X_{1i1},...X_{1im} \mid \theta) = p(X_{1im} \mid X_{i(i,m-1)},...X_{1i1m},\theta_{in})...p(X_{1i2} \mid X_{2i1}.\theta_{i2})p(X_{1i1} \mid \theta_{i1}) \quad (6)$$

Further, the joint model:

$$p(R_i \mid Y_i,X_i,\eta) \text{ with } X_i = (X_{i,mis},X_{i,obs})$$

for the possible combination of non-response as categories.

The covariates X_i is segregated into $\{X_{i1},X_{i2}\},X_{i3}$. The terms $\{X_{i1},X_{i2}\}$ are used as present the incomplete observation and X_{i3} with fully observed variable. In case of fully observed Y, the joint density becomes to:

$$p(X_{i2} \mid X_{i1},\theta_2)p(X_{i1} \mid \theta_1) \quad (7)$$

The Eq. 7 is further extended to bivariate normal distribution through:

$$p(X_{i1} \mid X_{i2} \mid \theta_1,\theta_2) \quad (8)$$

The binary regression of X_{i4} is observed through the partially missing $\{X_{i1},X_{i2}\}$ and observed data X_{i3} by:

$$g[\pi_4(X_{i4} \mid X_{i1},X_{i2},X_{i3},\theta_4)] = \theta_{40} + \theta_{41}X_{i1} + \theta_{42}X_{i2} + \theta_{43}X_{i3} \quad (9)$$

The link function g(.) is observed through $\pi_4 = P(X_{i4} = 1)$. In this pattern the regression extension can be formulated through X_{i5} with:

$$g[\pi_5(X_{i5} \mid X_{i1},X_{i2},X_{i3},X_{i4},\theta_5)] = \theta_{50} + \theta_{51}X_{i1} + \theta_{52}X_{i2} + \theta_{53}X_{i3} + \theta_{54}X_{i4} \quad (10)$$

The extension of full model for the missingness of can be generalized through (Ibrahim *et al.*,2001):

$$g(p[R_{i1} = 1]) = \eta_{i1} + \eta_{i2}X_{i1} + \eta_{i3}X_{i2} + \eta_{i4}X_{i3} + \eta_{i5}X_{i4} + \eta_{i6}X_{i5} + \eta_{i7}X_{i6} \quad (11)$$

and so on for pr(R_{i4} = 1) conditional on R_{i1} and R_{i2} and Pr (R_{i5} = 1) conditional on R_{i1}, R_{i2} and R_{i4}.

In this study, the missingness is assumed with MAR through the consideration of η_{12}, η_{13}, η_{14}, η_{15}, η_{16} = 0 for R_{i1}. The MCAR is assumed with η_{12} = 0. When X_{i1} is completes at random.

Multiple imputations: The ignorable and non-ignorable missingness in the data can be handled with multiple imputation approach. The small amount of m of the samples of the missing data X_{mis}, I, j, j = 1,….m, i = 1,…n. can be drawn through the predictive density:

$$p(X_{mis} \mid X_{obs}) = \int p(X_{mis} \mid X_{obs})p(\gamma \mid X_{obs})d\gamma \quad (12)$$

The fully imputed observations can be analyzed through Bayesian approach. The observed covariates of Y on:

$$X = (X_{mis}, X_{obs}) \tag{13}$$

The relation between Y on X is observed through posterior mean of $\beta^{(1)}$, ...$\beta^{(m)}$. However, the $\beta^{(1)}$, ...$\beta^{(m)}$ can be obtained for s parameter by $\{\beta_s^{(1)}, ...\beta_s^{(m)}\}$ with $V_{1s},\ldots V_{ms}$, respectively. The estimated mean of imputed value of β_s is calculated with:

$$\bar{V}_S = \sum_{j=1}^{m} V_{js}/m \tag{14}$$

The estimated variance by:

$$B_S = \sum_{j=1}^{m} (B^{(m)}{}_S - \bar{B}_S)^2/(m-1) \tag{15}$$

The estimated total variance of the B_k is:

$$B_S(1+\frac{1}{m}) + V_S \tag{16}$$

The response variable Y has been assumed to follow the Bernoulli distribution by:

$$Y_{ij} \sim Bern(\pi_{ij}), j = 1,2. \tag{17}$$

$$\log it(\pi_{i1}) = \beta_0 + \beta_1\delta(C_i = 1) + \beta_2\delta(G_i = 1) + \beta_3\delta(C_i = 1, G_i = 1) \tag{18}$$

$$\log it(\pi_{i2}) = \gamma_0 + \gamma_1\delta(C_i = 1) + \gamma_2\delta(G_i = 1) + \gamma_3\delta(C_i = 1, G_i = 1) \tag{19}$$

Here, C_i = 1 for male and 0 for female G_i = 1 for BUP+SMM and 0 for BUP+EMM. where, δ (A), if A is true. The non-irnorables model has been assumed through:

$$p(R_1 \mid X, Y_1) \text{ and } p(r \mid X, Y_1, Y_2) \text{ where, } X=(C,G). \tag{20}$$

The Δ_i is used to show the percentage reduction between two groups (i = 1 for sex and 2 for type of treatment). The dependent prior has been used as supportive tool for compare the treatment effect. The precise hypothesis has been applied to narrow down difference between treatment effects on creatinine level. The dependent prior has been considered and found suitable in this scenario.

Dependent prior: The success and failure rate of both treatment were calculated through frequency by a, c, b, d. The success rate of treatment 1 and treatment 2 were measured by a/n_1 and c/n_1, respectively. The proportion of success in both treatment were estimated through P by $\hat{p} = (\hat{p}_1, \hat{p}_2)$, where:

$$\hat{p}_1 = \frac{a}{n_1} \text{ and } \hat{p}_2 = \frac{a}{n_2}$$

The comparison between p_1 and p_2 was performed through the likelihood by $l(p_1, p_2)$, where:

$$l(p_1, p_2) = p_1^{\,a}(1-p_1)^b p_2^{\,c}(1-p_2)^d \tag{21}$$

The value of a, b, c, d were obtained through sample observation a, b, c and d.

The Hypothesis H_1, was fixed for $p_1 > p_2$ and the correspondence evidence of probability computed with:

$$\frac{\int_{p_1=0}^{1}\int_{p_2=0}^{p_1} l(p_1, p_2)dp_2dp_1}{\int_{p_1=0}^{1}\int_{p_2=0}^{p_1} l(p_1, p_2)dp_2dp_1} \tag{22}$$

The details about the conditional and unconditional discussion are well documented (Berger *et al*., 1997; Little, 1989; Howard, 1998).The statistical inference was obtained through the iteration procedure of the sample value of this clinical trial. The joint density function of p_1 and p_2 was formulated with $f(p_1,p_2)$ by observed the posterior probability ($p_1 > p_2$) by:

$$\frac{\int_{p_1=0}^{1}\int_{p_2}^{p_1} p_1^{a}(1-p_1)^b p_2^{c}(1-p_2)^d f(p_1,p_2)dp_1dp_2}{\int_{p_1=0}^{1}\int_{p_2}^{1} p_1^{a}(1-p_1)^b p_2^{c}(1-p_2)^d f(p_1,p_2)dp_2dp_1} \tag{23}$$

The joint function in Eq. 23 was replaced by considering independent Haldane prior Little 1989. The Eq. 23 becomes to:

$$k\frac{\int_{p_1=0}^{1}\int_{p_2}^{p_1} p_1^{a-1}(1-p_1)^{b-1}p_2^{c-1}(1-p_2)^{d-1}dp_2dp_1}{\int_{p_1=0}^{1}\int_{p_2}^{1} p_1^{a-1}(1-p_1)^{b-1}p_2^{c-1}(1-p_2)^{d-1}dp_2dp_1} = \frac{1}{B(a,b)B(c,d)}\int_{x=0}^{1}\int_{y=0}^{x} x^{a-1}(1-x)^{b-1}y^{c-1}(1-y)^{d-1}dydx \tag{24}$$

For a, b, c, d>0 where B(a, b) is the beta function.

It can be pointed that the dependent prior can solve many purposes in applied statistics. The application of dependent prior was found very limited in the scientific

literature. The performance of posterior likelihood of two independent proportions between Haldane and Jeffreys's prior can be discussed with:

$$f(p_1,p_2)\propto p_1^{-1}(1-p_1)^{-1}p_2^{-1}(1-p_2)^{-1} \quad (25)$$

where, p_1 and p_2 are the two independent proportions. The $f(p_1,p_2)$ was used as the joint density function of p_1 and p_2, respectively.

The log-odds link function was applied to measure the dependence between two proportions by:

$$\theta_1 = \text{In}(\frac{p_1}{1-p_1}) \text{ and } \theta_2 = \text{In}(\frac{p_2}{1-p_2}) \quad (26)$$

The terms were assumed to independent with uniform distribution(-8, 1).

The terms in the Eq. 21 was generalized to the proportion of Eq. 22 by:

$$\exp[-(\frac{1}{2})^{u^2}p_1^{\alpha-1}(1-p_1)^{\beta-1}p_2^{\gamma-1}(1-p_2)^{\delta-1}] \quad (27)$$

Where:

$$u = \frac{1}{\sigma}\text{In}(\frac{p_1(1-p_2)}{p_2(1-p_1)}) \quad (28)$$

The terms $\alpha = \beta = \gamma = \delta = 0$ and $\sigma = 1$ are called as vegue prior (Howard, 1998). The stated model was been applied in the creatinine level of the patients randomized into two treatments. The observations of creatinine of each visit were compared with initial observed level. The total creatinine of each patients were captured in 1st, 2nd, 3rd , 4th and 5th visits, respectively. The comparison of proportion of success of treatment at 2nd , 3rd , 4th and 5th visits were compared with initial observation of creatinine taken at 1st visit, respectively. The between normal range of creatinine was considered as success of treatment.

RESULTS

The probability of success of treatment with respect to sex is given in Table 1. The success of treatment was calculated through normal range of creatinine. The probability of success was computed with dependent prior. The probability of success of treatment 1 with respect to treatment 2 was denoted with $p_i>p_j$. It can be stated that the success in 2nd visit is comparison to 1st is 0.43 and 1 in 5 visit in comparison to 1st visit for BUP+SMM group. In case of BUP+EMM the success in 2nd visit in comparing to 1st has been observed with 0.59 followed by 1 in other visits, respectively.

It can be shown that the percentage changes of Δ are not significant in both the side. The changes of 0.76% was found for 1st to 2nd visit and 0.14% for 1st to 3rd visit respectively. The term Δ was used to estimate the difference of the drug treatment effect. The estimated posterior mean with standard deviation and HPD are given in Table 2. The estimated posterior mean of Δ_1 and Δ_2 were found positive and significant. The levels of value Δ_3 and Δ_4 were found negative and non-significant. It confirmed that, the drug treatment effect BUP +SEM is better to control group. It can be concluded that BUP+SEM group has performed better than BUP+EEM for both sex.

DISCUSSION

The effect of BUP through blood sample monitoring procedure is required to be going through specific assessment (Katz and Fanciullo, 2002). The method to quantify BUP in blood sample is documented (Schottenfeld and Pakes, 1997). The biased inference can only be drawn from the fully observed original data set. The replicated data are not an exact of the original data, but gives power evidence of the real scenario. The assumption about the pattern of missingness can be considered for as robust inference. Extension of this work through concentration of missing observations of the creatinine's repeated observation can contribute for drug treatment effect of Buprenorphine among the opioid dependent patients. The buprenorphine is effective to prevent the primary and secondary level HIV (Amass *et al*., 2000). The BUP can also be prescribed to the pregnant women (O'Connor *et al*., 1998). The level of creatinine is found to be reduced more in BUP+SMM (female) patients to -0.16 from 1st to 2nd visit than BUP+EMM (male) with 0.22. However, in case of male it was increased with 0.76 and reduced by 0.11 in BUP+EMM from 1st visit to 2nd visit. The study shows that the SUP+EMM reduce more creatinine level in any follow-up visits in comparison to earlier one. The

Table 1: Computed and comparable figure of success in repeated measurement of creatinine

						$P_{BUP+SMM}>P_{BUP+EMM}$				
Sex	Treatment	$P_1>P_2$	$P_1>P_3$	$P_1>P_4$	$P_1>P_5$	1st	2nd	3rd	4th	5th
Male	BUP+SMM	0.43	0.99	0.99	1	0.17	0.27	0.14	0.68	0.55
	BUP+EMM	0.59	1	1	1					
Female	BUP+SMM	0.43	1	0.99	1	1	0.68	0.19	0.99	0.58
	BUP+EMM	0.65	1	1	1					

Table 2: The repeated imputation inference by treatment and experimental group through posterior estimates

Visit	Experiment	Mean	SD	2.5%	97.5%
1st vs 2nd	Δ_1:BUP+EMM (Male)	0.76	0.47	0.73	0.80
	Δ_2: BUP+SMM(Female)	0.22	0.41	-0.08	0.08
	Δ_3: BUP+EMM(Male)	-0.11	0.39	-0.08	0.06
	Δ_4: BUP+SMM(Female)	-0.16	0.42	-0.10	0.06
1st vs 3rd	Δ_1:BUP+EMM(Male)	0.14	0.25	0.11	0.16
	Δ_2: BUP+SMM(Female)	0.10	0.10	0.09	0.11
	Δ_3: BUP+EMM(Male)	0.92	0.24	0.06	0.11
	Δ_4: BUP+SMM(Female)	-0.78	0.66	-0.14	-0.01
1st vs 4th	Δ_1:BUP+EMM(Male)	0.11	0.25	0.07	0.15
	Δ_2: BUP+SMM(Female)	0.74	0.12	-0.23	0.16
	Δ_3: BUP+EMM(Male)	0.45	0.06	-0.13	0.08
	Δ_4: BUP+SMM(Female)	-0.18	0.20	-0.53	0.06
1st vs 5th	Δ_1:BUP+EMM(Male)	0.42	0.61	-0.16	0.07
	Δ_2: BUP+SMM(Female)	0.36	0.42	-0.04	0.11
	Δ_3: BUP+EMM(Male)	-0.08	0.39	-0.07	0.08
	Δ_4: BUP+SMM(Female)	-0.14	0.49	-0.09	0.10

work can be extended to deal with missing imputation approach observed in any other longitudinal data analysis.

CONCLUSION

The data were affected with missing observation due to lost to follow-up. The question about validity of the study becomes important in this scenario. The study may be neglected due of missing observation. The close comparison between periods-to period performance is also important in drug treatment effect. The imputation approach is applied to control the missing observation. The dependent prior is explored to obtain the period-to period performance compliance among the patients. The work with creatinine is required to be explored as drug treatment effect comparison. The present work can be put for more light with drug treatment effect comparison. The urine sample need to monitor and level of creatinine is also need to be captured as drug treatment effect.

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