Falling with Failing Medications: A Bayesian Analysis of the St. Louis OASIS Study

by Michael Floyd

Abstract

The purpose of this paper is to reassess the St. Louis OASIS study through Bayesian analysis. The St. Louis OASIS study was conducted to observe the association between different medications and falling in the elderly population. The results and findings of the OASIS study were published in 1991. While these results showed significant association between the medication population and multiple falls, they also showed insignificant association for almost all individual medications (31 out of 34) [1]. I used a hierarchical normal distribution model with known observation variance and population mean, also termed a one-way normal random-effects model with known data variance. I then processed 2000 iterations using the Gibbs sampling method to draw conditional posteriors for each parameter [g].

The results I obtained when analyzing the same 34 medications are 19 out of the 34 medications show significant association with the odds of falling multiple times [c]. This result seems reasonable, since the medication population has been determined to have significant association with falling through the OASIS study and multiple previous studies [1-2, 4-5]. These medications should be researched and reexamined; further research should also be warranted to examine the individual medications and falling associations in other populations.

Introduction

People in the elderly population tend to be at more risk for falling. These falls can have serious consequences. Previous studies have been conducted to determine the reasons for the falls, to see whether preventative measures can be taken. The results have been similar in the previous studies. All studies have reported that the risk of falling increases with age in the elderly [1-5]. Two different studies have found significant differences in the prevalence of male and female fallers, but the studies produced opposite results [2, 4]. The studies do agree, though, that the prevalence differences subside with increasing age. More than three in every ten elderly people above 65 years old experience one or more falls in a year [2-4]. These falls have been correlated with many factors such as physical activity, cognitive impairment, mobility problems, more frequent history of health problems, and medications [2-5].

Different studies have produced different results about the association of different medications with the risk of falling in the elderly. A study conducted in 1981 found significant associations between diuretics and tranquilizers [2]. A study conducted in 1988 found no significant association between the use of diuretics or tranquilizers, but a significant association between falls and the use of hypnotics and antidepressants was found [4]. A study conducted in 1989 found significant association between the total number of drugs and psychotropic drugs [5]. These different results may signify a difference between different sub-populations, or the need for further investigation.

The St. Louis OASIS study was conducted to determine the correlation between commonly taken medications in the elderly population and the amount of falls from the elderly population. The study was conducted in St. Louis, MO. A stratified sample of people were taken from the 15,000 members of an educational organization or functionally independent, community-dwelling elderly people. A retrospective cohort study was conducted on 1,358 independent elderly people. The study focused on specific medications and sub-groups of medications that were commonly taken among the population [1].

The results of the study focused on the elderly falling two or more times, since clinicians are more concerned with the person who falls frequently. The results of the study showed significance in the correlation between the number of medications taken and the amount of falls. The greater the number of medications, the greater the risk of multiple falls. 85% of the patients took at least one medication, and 48% took three or more. The odds of multiple falls when taking three or more medications was 2.4 when compared to those on no medications [1].

Unadjusted odds ratios were also taken for individual medications taken by more than 40 subjects. Adjusted odds ratios were taken for the medications that had significant unadjusted odds ratios. The adjustments were made based on measures of health and other potential confounders [a]. A multiple logistic regression model was put into place with these confounders and 3 medications of interest showed signs of significance after adjustment of odds ratios. These medications are diazepam, diuretics, and laxatives [1].

These 3 medications do not account for all of the falls, nor do they show the reason for significance when taking multiple medications. The model I created tries to find significance in the odds ratios of other medications that did not show signs of significance. It also gives the expected odds ratio and a simulated confidence interval for a new medication.

Model

I use a Bayesian model, setting the prior distribution for all medications. Since the St. Louis OASIS study and previous studies have shown significance in the association of taking medications and multiple falls, my prior distribution for the odds ratios of the total medication population will be set higher than 1 [2,4-5]. I chose to make the prior population distribution normal. I also set parameters around the mean and variances of the prior population distribution. The mean of my prior population, Mu, distribution is normalized around a natural log odds ratio of 2, with a variance of 0.2. The variance of my prior population, Tao, distribution will be a Uniform distribution from 0 to 1.

The likelihood function, the natural log odds ratio of the medication given by the individuals in the study, will have a normal distribution. I will use the unadjusted odds ratios for the medications in the study. I will calculate the odds ratios for each medication. The mean of the likelihood function will be the natural log odds ratio of each medication, given by the individuals in the study. The variance of my likelihood function, Sigma ^{2}, will be obtained by getting the sum of the inverses of each number contributing to the odds ratios [b].

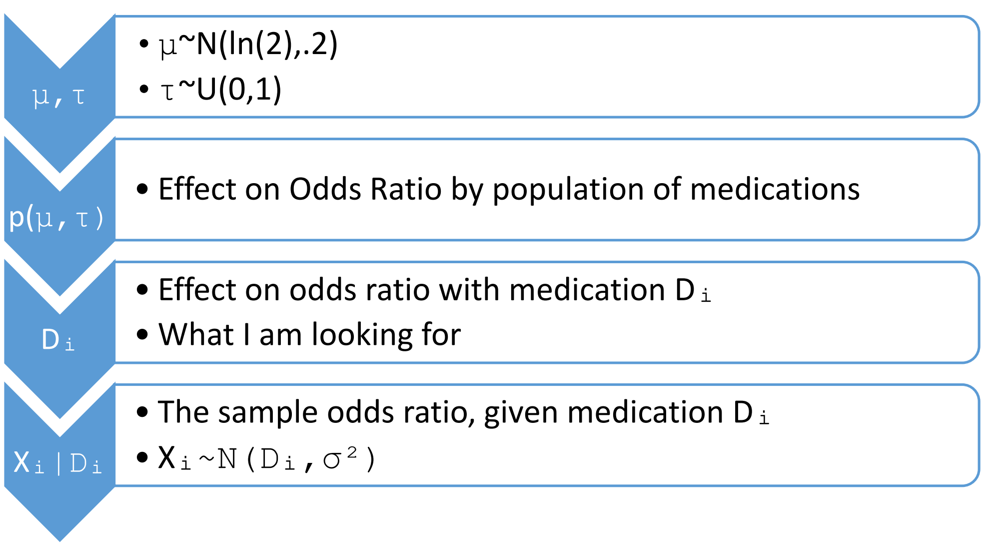


Figure 1: This phase diagram illustrates the hierarchical model used for the Bayesian analysis.

This model will allow me to find a distribution for the effect of each medication on the odds ratio for falling multiple times, given a prior distribution for all medications. One issue documented by the OASIS study is that the number of subjects who reported taking antipsychotics or 'other sedatives' was too small for further analysis. I am able to bypass that issue through Bayesian modeling. I did not include the medications Barbiturates and Verapamil; their odds ratios were zero, making the natural log of the odds ratio and the variance undefined.

I will use R to produce a Gibbs simulation of 2000 iterations based on the model to get computer-based estimates for my parameters.

<u>Results</u>

All odds ratios are calculated as the odds of having multiple fall to 0-1 falls, given medication. There were 34 total medications inputted into the model. After 2000 iterations, my conditional estimate for my population mean, Mu, of the natural log odds ratio is .483 with a 95% confidence interval of (0.34, 0.63). This gives a population odds ratio mean of 1.62 with a 95% confidence interval of (1.40, 1.88). The variance of my population, Tau, averaged to 0.213.

The results for the medications in my Bayesian analysis are different than the results from the study. There are 19 different medications that had significant confidence intervals [c]. The distributions for all the medications were normal.

I also obtained a posterior prediction for a new medication, given the conditional population distributions. The estimates obtained for Tau and Mu are .234 and .481, respectively. The generated value for the natural log odds ratio mean for the new medication is .657. After 400 simulations, the confidence interval obtained for the natural log of the odds ratio is (.632, .681), which approximates the odds ratio confidence interval (1.88, 1.98).

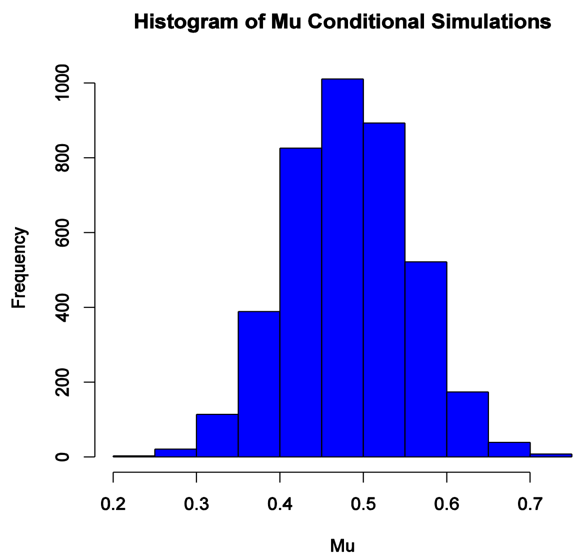
Medication	Posterior OR	2.50%	97.50%
Analgesics and anti-inflammatories	1.584	1.185	2.096
Antacids	1.477	0.887	2.16
Antidepressants	1.699	1.162	2.638
Tricyclics	1.699	1.139	2.718
Amitriptyline	1.584	0.961	2.535
Antihistamines	1.419	0.827	2.075
Antihypertensives	1.31	0.844	1.804
Captopril	1.553	0.951	2.363
Methyldopa	1.699	1.174	2.586
Prazosin	1.537	0.932	2.411
Antipsychotics	1.665	1.041	2.773
Beta blockers	1.323	0.795	1.859
Atenolol	1.448	0.811	2.226
Propranolol	1.553	0.99	2.316
Benzodiazepines	1.584	1.062	2.248
Long-acting	1.751	1.221	2.746
Chlordiazepoxide	1.537	0.878	2.46
Diazepam	2.096	1.405	3.935
Short-acting	1.448	0.861	2.181
Alprazolam	1.522	0.869	2.435
Calcium blockers	1.553	1.03	2.226
Diltiazem	1.822	1.284	2.974
Nifedipine	1.537	0.951	2.316
Digoxin	1.522	1.051	2.138
Diuretics	1.878	1.405	2.612
Oestrogens	1.649	1.083	2.509
Hypoglycaemics(oral)	1.522	0.961	2.293
Laxatives	1.954	1.35	3.158
Sedatives(other)	1.665	1.051	2.773
Thyroid agents	1.492	0.98	2.075
Vasodilators	1.682	1.209	2.363
Dipyridamole	1.616	1.083	2.387
Isosorbide	1.699	1.15	2.638
Nitroglycerin	1.84	1.284	2.974

Figure 2: This chart shows the posterior OR for the medications in the study.

Discussion

In the St. Louis OASIS study, most of the medications produced odds ratios that were above 1, but insignificant [1]. I believe the model that was used did not incorporate enough information. This can be seen by observing the broad confidence intervals of the medications in their model [f]. A Bayesian approach fits in this study because prior information is known. Previous studies have indicated that there will be a produced increase in odds of falling more than once when taking medication [2, 4-5]. Including this information into the model creates an increase in certainty and a decrease in the width of the confidence intervals. 17 drugs in their model had odds ratios above 1.45. Only 7 of them were found to be significant, due to broad confidence intervals. After adjusting for potential confounders, only 3 were found to be significant. The study found significance in the amount of medications taken, yet only 3 out of the 34 commonly taken medications were found significant [1]. The hierarchical Bayesian model I used set a prior population distribution for all medications. Due to this increase in information, 19 medications were found to have significance [c]. My result also appears more likely, given there is a significant increase in the odds ratio when taking medications for 2 or more falls.

Although the population mean odds ratio was initially chose to be normalized at the natural log of 2 or approximately 0.69, successive iterations have measured the conditional population mean and median to be close to 0.48. When viewing the histogram of the iterations, the population is also normalized around the mean. The conditional population variance, Tau, has a mean and median of 0.21. The conditional variance of the population has a distribution shaped similar to a Scaled Inverse Chi-Squared distribution. The numbers for the conditional population mean and variance agree with the initial intuition that there is a significance in taking medications and an increase in the odds of falling more than once.



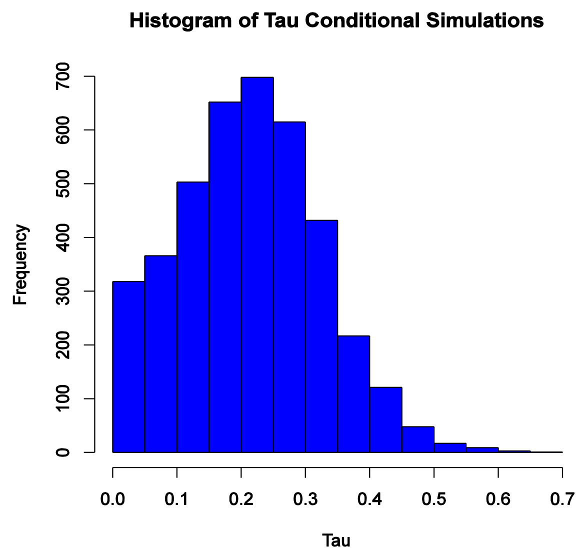


Figure3a and 3b: These two graphs show the conditional distribution of Mu and Tau, respectively.

There were 6 medications that produced insignificant confidence levels, but the confidence levels were close to significance (their 95% confidence intervals for their odds ratios ended above 0.95) [d]. Further research is needed for these medications. Further research can also be done on medications that produced significant confidence intervals, but the intervals were close to insignificance [e]. Further investigation should be done for the significant medications individually to confirm results and to question if the treatment warrants the extra risk [c]. Further research can be used to potentially see if there is significance in medication interaction. Further research is warranted to see if the effects of the medications taken by individuals on the number of falls is similar to its effect on individuals in other populations.

I could not procure the information detailing precisely which individual was taking which medication. This is most likely due to privacy concerns after initial analysis. Additional research can be done to determine if the same medications show significance after adjusting for potential confounders [a].

The results show that an additional medication is most likely to be significant in increasing the odds ratio of falling multiple times. Future common medications prescribed to the elderly should have preliminary studies conducted to determine whether the particular medication will increase the odds of falling.

References

1. Cumming RG, Miller JP. Medications and Multiple Falls in Elderly People: The St. Louis OASIS Study. Age Ageing 1991; 20:455-61.
2. Prudham D, Grimley Evans J. Factors associated with falls in the elderly: a community study. Age Ageing 1981; 10:141-6.
3. Campbell AJ, Reinken J, Allan BC, Martinez GS. Falls in old age: a study of frequency and related clinical factors. Age Ageing 1981; 10:264-70.
4. Blake AJ, Morgan K, Bendall MJ, Dallosso H, et al. Falls by elderly people at home: prevalence and associated factors. Age Ageing 1988; 17:365-72.
5. Campbell AJ, Borne MJ, Spears GF. Risk factors for falls in a community-based prospective study of people 70 years and older. J Geron- tol 1989; 44:M 112-17.

Appendix

a. The confounders adjusted for in the St. Louis OASIS study are measures of health, age, sex, age-sex interaction, number of treated illnesses in the past year, cognitive impairment, diagnosis of depression (ever), multiple very upsetting stressful life events in the previous year, history of drinking alcohol in the past month, and antipsychotic use.
b. $\sigma^2 = \frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}$, where the odds ratio equals $OR = \frac{a*d}{b*c}$.
c. The 19 different medications that have significant odds ratios for falling multiple times are Analgesics and anti-inflammatories, Antidepressants, Tricyclics, Methyldopa, Antipsychotics, Benzodiazepines, Long-acting Benzodiazepines, Diazepam, Calcium blockers, Diltiazem, Digoxin, Diuretics, Oestrogens, Laxatives, Sedatives(other), Vasodilators, Dipyridamole, Isosorbide, and Nitroglycerin.
d. The 6 medications that have insignificant, but close to significant confidence intervals are Amitriptyline, Captopril, Propranolol, Nifedipine, Hypoglycaemics(oral), and Thyroid agents.
e. The medications that have significant, but close to insignificant confidence intervals are Antipsychotics, Calcium blockers, Digoxin, and Sedatives(other).
f. **Figure 4** below is the initial table of unadjusted odds ratios, without Bayesian analysis [1].
g. The parameters of interest in the model are the 34 individual medications and the medication population mean and variance.

Medication	No. of subjects ≥ 2 Falls (n = 108)	0–1 Falls (n = 1250)	Odds ratio	95% Confidence interval
Analgesics and anti-inflammatories	60	556	1.56	1.05–2.31
Antacids	4	52	0.89	0.31–2.45
Antidepressants	8	48	2.00	0.94–4.29
Tricyclics	7	42	1.99	0.87–4.48
Amitriptyline	3	25	1.40	0.42–4.69
Antihistamines	5	74	0.77	0.31–1.95
Antihypertensives	21	253	0.95	0.58–1.56
Captopril	4	38	1.23	0.43–3.50
Methyldopa	9	57	1.90	0.92–3.96
Prazosin	1	22	0.52	0.07–3.78
Antipsychotics	2	10	2.34	0.53–10.35
Barbiturates	0	13	—	—
Beta blockers	10	147	0.77	0.39–1.50
Atenolol	2	47	0.48	0.12–1.96
Propranolol	6	54	1.30	0.55–3.10
Benzodiazepines	13	106	1.48	0.80–2.71
Long-acting	9	50	2.18	1.06–4.49
Chlordiazepoxide	1	20	0.58	0.08–4.22
Diazepam	8	17	5.80	2.44–13.78
Short-acting	4	58	0.79	0.28–2.22
Alprazolam	1	24	0.48	0.07–3.41
Calcium blockers	13	110	1.42	0.77–2.61
Diltiazem	9	41	2.68	1.30–5.52
Nifedipine	4	42	1.11	0.39–3.15
Verapamil	0	27	—	—
Digoxin	16	141	1.37	0.78–2.39
Diuretics	56	413	2.18	1.48–3.22
Oestrogens	6	40	1.78	0.75–4.25
Hypoglycaemics (oral)	6	58	1.21	0.51–2.87
Laxatives	11	43	3.18	1.65–6.16
Sedatives (other)	2	10	2.34	0.53–10.35
Thyroid agents	13	124	1.24	0.68–2.28
Vasodilators:	22	156	1.73	1.06–2.83
Dipyridamole	9	68	1.47	0.72–3.01
Isosorbide	7	41	1.90	0.85–4.27
Nitroglycerin	10	46	2.22	1.11–4.41

Figure 4: The initial unadjusted OR in the St. Louis OASIS study for each individual medication [1].

Code Used in R:

Stan File:

```
data {
	int<lower=0> J;
	real y[J];
	real<lower=0> sigma[J];
}
parameters {
	real mu;
	real<lower=0> tau;
	vector[J] eta;
}
transformed parameters {
	vector[J] theta;
	theta <- mu + tau*eta;
}
model {
```

```
        eta ~ normal(0,1);
        y ~ normal(theta, sigma);
        mu ~ normal(log(2),.2);
        tau ~ uniform(0,1);
}
```

Rcode:

```
report = read.csv("C:\\Users\\Michael\\Desktop\\BiostatFall2014\\Bayesian Theory\\BayesDataReport.csv",
header= TRUE)

J <- nrow(report)
y <- report$logOR
sigma <- sqrt(report$VarOR)

report_fit <- stan (file="C:\\Users\\Michael\\Desktop\\BiostatFall2014\\Bayesian Theory\\report.stan.txt",
data=c("J","y","sigma"), iter=2000, chains=4)
plot(report_fit)
print(report_fit)
report_sim <- extract(report_fit, permuted=TRUE)
hist(report_sim$tau, col='blue', main='Histogram of Tau Conditional Simulations', xlab='Tau')
hist(report_sim$mu, col='blue', main='Histogram of Mu Conditional Simulations', xlab='Mu')
hist(report_sim$theta[,32])
hist(report_sim$theta[,26])
hist(report_sim$theta[,20])
hist(report_sim$theta[,15])
hist(report_sim$theta[,10])
mean(report_sim$mu)
mean(report_sim$tau)
median(report_sim$tau)
median(report_sim$mu)

den = 0
num = 0
stau = sample(report_sim$tau,1)
for (j in 1:34){
        top = report[j,1]/(report[j,2]+stau^2)
        bot = 1/(report[j,2]+stau^2)
num = num + top
den = den + bot
}
smu = num/den
smuvar = 1/den
genmu = rnorm(1,mean=smu,sd=sqrt(smuvar))
gentheta = rnorm(1,mean=genmu,sd=stau)
geny = rnorm(400,mean=gentheta,sd=(stau/20))
hist(geny, breaks=100, xlab="LogOR")
q2.5 = quantile(geny,.025)
q97.5 = quantile(geny, .975)
q2.5
q97.5
```