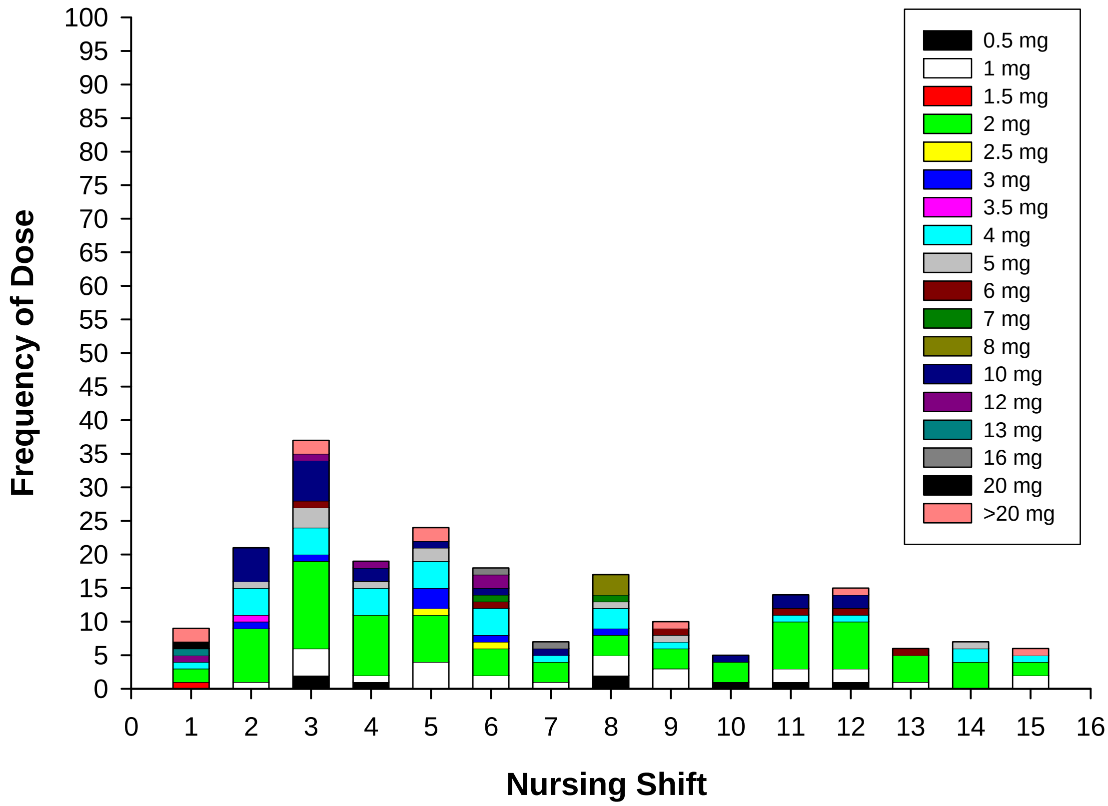
Frequency of Midazolam Dosage by Nursing Shift



Web Appendix: Software Code from SAS and WinBUGS for Models in Article

1. Frequentist ZIP Model in SAS (assumes vertical dataset where each row is a person-observation)

```
*zero inflated poisson, ;
title 'NLMIXED of ZIP Model for Midazolam';
proc nlmixed data=temC.Midaz3Vert;
       parameters  b1=0 b2=0 b3=0 b4=0 b5=0 b6=0 b7=0 b8=0 b9=0 b10=0 b11=0
               a1=0 a2=0 a3=0 a4=0 a5=0 a6=0 a7=0 a8=0 a9=0 a10=0 a11=0 s2u=1
;

   /* linear predictor for the inflation probability      */
   linpinfl = a1 + a2*shift + a3*night + a4*nonwhite + a5*male + a6*iqcodeA +
      a7*intubated + a8*APS
                         + a9*icudeath + a10*age + a11*LOSlt5d ;
                        ;
   /* infprob = inflation probability for zeros           */
   /*         = logistic transform of the linear predictor*/
   infprob  = 1/(1+exp(-linpinfl));
   /* Poisson mean */
   lambda   = exp(b1 + b1R + b2*shift + b3*night + b4*nonwhite + b5*male +
b6*iqcodeA +      b7*intubated + b8*APS
                         + b9*icudeath5 + b10*age + b11*LOSlt5d );
   /* Build the ZIP log likelihood */
   if MidazDose=0 then
        ll = log(infprob + (1-infprob)*exp(-lambda));
   else ll = log((1-infprob)) - lambda  + MidazDose*log(lambda) -
lgamma(MidazDose + 1);
   model MidazDose ~ general(ll);
   random b1R  ~ normal(0,s2u) subject=studyid;

run;
```

2. Bayesian ZIP Model in WinBUGS (assumes horizontal dataset with single row per person)

```
model
{

#################################################################
## we nest the 15 shifts within each studyid among the cohort of ICU survivors
##who were in ICU >= 3 days and received Midazolam during that time
## the Midazolam doses have been rounded to nearest unit for use with Poisson
## this is the classic mixture form of the ZIP model where occurrences of zeroes
## are modeled with a logistic regression and the positive integers with a Poisson
## and final likelihood is a mix of the two distributions


                for(studyid in 1 : N) {
                        for(shift in 1 : NumShifts[studyid]) {  # a column called NumShifts is person specific

                # logistic likelihood for extra zeroes
                # coefficients centered around the sample mean of study population to facilitate convergence
```

```
        logExtraZ[studyid,shift] <-     beta[1]
                                        + beta[2]*(shift - 8) +
                                        + beta[3]*(night[shift] - 0.33)
                                        + beta[4]*(nonwhite[studyid]  - 0.17)
                                        + beta[5]*(male[studyid]  - 0.55)
                                        + beta[6]*(iqcodea[studyid]  - 0.3)
                                        + beta[7]*(intubated[studyid]  - 0.75)
                                        + beta[8]*(aps[studyid]   - 24.3)
                                        + beta[9]*(icudeath[studyid] - 0.17)
                                        + beta[10]*(age[studyid]  - 73.4)
                                        + beta[11]*(losLT5d[studyid]  - 0.29)
                                        + Rint[studyid, 1]   # this is the random intercept for each person in logistic model


        probZ[studyid,shift] <- 1/(1 + exp(-logExtraZ[studyid,shift]))  # probZ = probability of a zero dose


                                # Poisson likelihood for positive integers

        log(lambda[studyid,shift]) <-   alpha[1]
                                        + alpha[2]*(shift - 8)
                                        + alpha[3]*(night[shift] - 0.33)
                                        + alpha[4]*(nonwhite[studyid]  - 0.17)
                                        + alpha[5]*(male[studyid]  - 0.55)
                                        + alpha[6]*(iqcodea[studyid]  - 0.3)
                                        + alpha[7]*(intubated[studyid]  - 0.75)
                                        + alpha[8]*(aps[studyid]   - 24.3)
                                        + alpha[9]*(icudeath[studyid] - 0.17)
                                        + alpha[10]*(age[studyid]  - 73.4)
                                        + alpha[11]*(losLT5d[studyid]  - 0.29)
                                        + Rint[studyid, 2]  # this is the random intercept for each person in Poisson model


        probGTZ[studyid,shift] <- probZ[studyid,shift]*(1 - exp(-lambda[studyid,shift])) # prob of MidazDose  > 0

        d[studyid,shift] <- step(MidazDose[studyid,shift] - 1)


# Log Likelihood is a Mixture of logistic and Poisson

LogLLH[studyid,shift] <-        (1 -  d[studyid,shift])*log(1 - probGTZ[studyid,shift])          # for all zero doses
                                + d[studyid,shift]*(log(probGTZ[studyid,shift]) + MidazDose[studyid,shift]*log(lambda[studyid,shift])
                                - lambda[studyid,shift] - loggam(MidazDose[studyid,shift] + 1) - log(1 - exp(- lambda[studyid,shift])))

                                # following lines employ the zeroes trick, i.e., WinBUGS' equivalent of general() in SAS
                                K <- 10000  # constant required for "zeros trick"
                                zeros[studyid,shift] <- 0
                                zeros[studyid,shift] ~ dpois(phi[studyid,shift])
                                phi[studyid,shift] <- -LogLLH[studyid,shift] + K


                        }  # close shift loop
                        }  # close studyid loop
#################################################################

################################################


                        # prior distributions for fixed  model terms

                                for (i in 1:11)
                                        {
                                        alpha[i] ~ dnorm(0,0.1)
                                        }

                                        for (i in 1:11)
                                        {
                                        beta[i] ~ dnorm(0,0.1)
                                        }
```

```
##################################################################
                    # prior distributions for random terms

            # first for normal locations
            for (i in 1:113)
                    {
                    Rint[i,1] ~ dnorm(0,tau1)
                    m[i] <- psi*Rint[i,1]
                    Rint[i,2] ~ dnorm(m[i], tau2)
                    }

                    psi~dnorm(0, 0.001)
                    tau1 ~ dgamma(0.1,0.1)
                    tau2 ~ dgamma(0.1,0.1)

            # second for variances

                    sigma1 <- 1/sqrt(tau1)          # SD of Rint[,1]
                    denom1 <- pow(psi,2)/tau1 + 1/tau2
                    sigma2 <- sqrt(denom1)          # SD of Rint[,2]
                    denom2 <- sqrt(denom1/tau1)
                    num <- psi/tau1
                    rho <- num/denom2               # corr(Rint[,1],Rint[,2])

####################################################################
                    }
##################################################################
```

3. Bayesian Random Effects Poisson Model in WinBUGS (assumes horizontal dataset with single row per person)

```
model
{

###############################################################
## we nest the 15 shifts within each studyid among the cohort of ICU survivors
##who were in ICU >= 3 days and received Midazolam during that time


            for(studyid in 1 : N) {
            for(shift in 1 : NumShifts[studyid]) { # a column called NumShifts is person specific

            # Poisson likelihood for observed doses
            MidazDose[studyid,shift] ~ dpois(mu[studyid,shift])
            log(mu[studyid,shift]) <-       alpha[1]
                                            + alpha[2]*(shift - 8)
                                            + alpha[3]*(iqcodea[studyid]  - 0.3)
                                            + alpha[4]*(nonwhite[studyid]  - 0.17)
                                            + alpha[5]*(male[studyid]  - 0.55)
                                            + alpha[6]*(night[shift] - 0.33)
                                            + alpha[7]*(intubated[studyid]  - 0.75)
                                            + alpha[8]*(aps[studyid]   - 24.3)
                                            + alpha[9]*(icudeath[studyid] - 0.17)
                                            + alpha[10]*(age[studyid]  - 73.4)
                                            + alpha[11]*(losLT5d[studyid]  - 0.29)
                                            + theta[studyid] + perShift[studyid,shift] # random effects person-shift
```

```
                                                            }
                                                            }
##################################################################

        # Prior distribution for the person-shift intercepts
                for(studyid in 1 : N) {
                        for(shift in 1 : 15) {
                                        perShift[studyid,shift] ~dnorm(0,tau.perShift)
                                        }
                                        }


        # Prior distribution for the random intercepts
                        for (studyid in 1:N)
                                {
                                theta[studyid]~dnorm(0,tau.theta)
                                }

##################################################


                # prior distributions for the model coefficients

                        alpha[1:11]~dmnorm(alphamu[],Sigma[,])


#####################################################################
                #Hyperprior distributions on inverse variance parameter of random effects

                                 tau.theta  ~ dgamma(1,1)
                                tau.perShift ~  dgamma(1,1)

                                }
#######################################################################

#####################################################################
```