Dose-effect meta-analysis for psychopharmacologic interventions using randomized data

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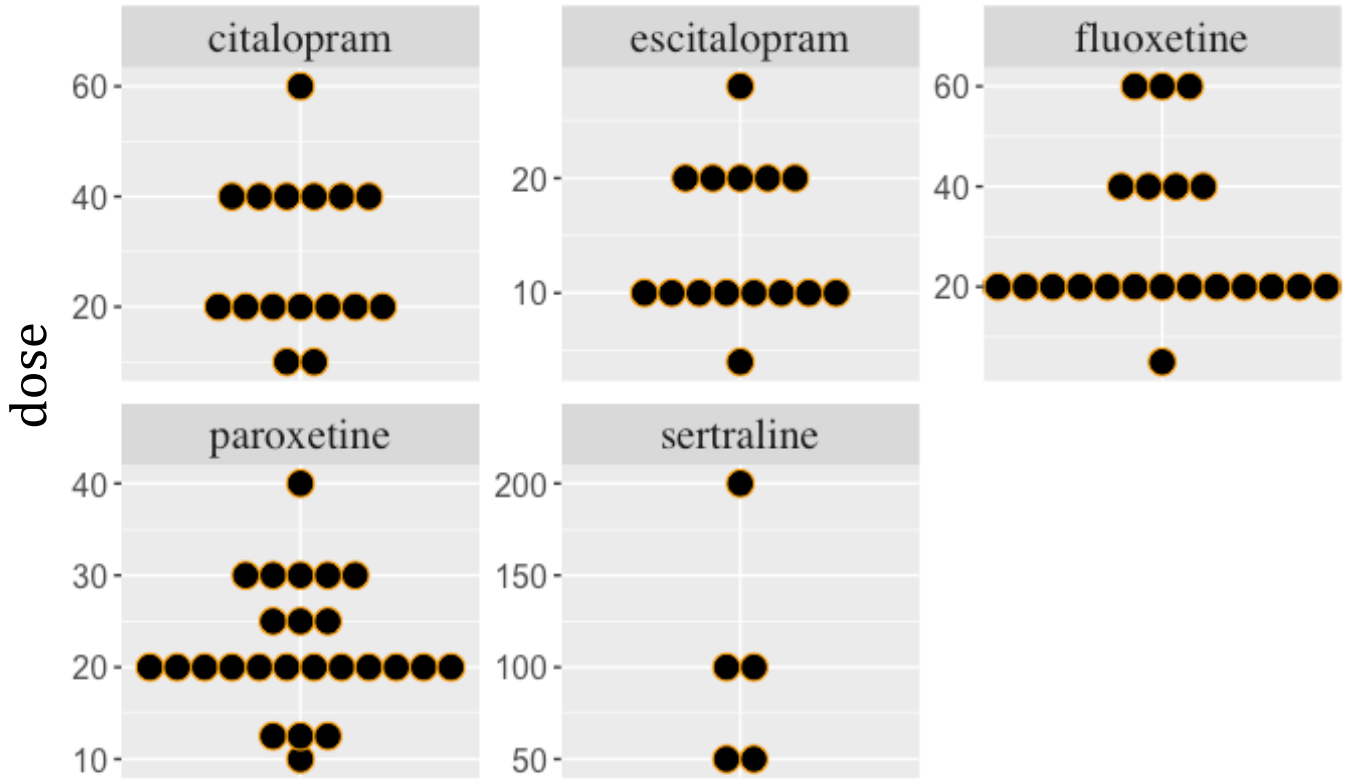
Additional Figures and Tables

Appendix Figure 1 The dose distribution of the SSRI antidepressants (fluoxetine-equivalent dose).



Appendix Figure 2 The dose distribution of the SSRI antidepressants (original doses).

Drug	Number of events	Number of patients	Number of studies	Number of doses
citalopram	1002	1928	9	16
escitalopram	1089	2405	11	15
fluoxetine	901	2265	18	25
paroxetine	1389	2669	19	25
placebo	2183	5556	59	59
sertraline	134	351	3	5
citalopram	1002	1928	9	16

Appendix Table 1 Summary of the data of each drug

R code

Dose-effect meta-analysis

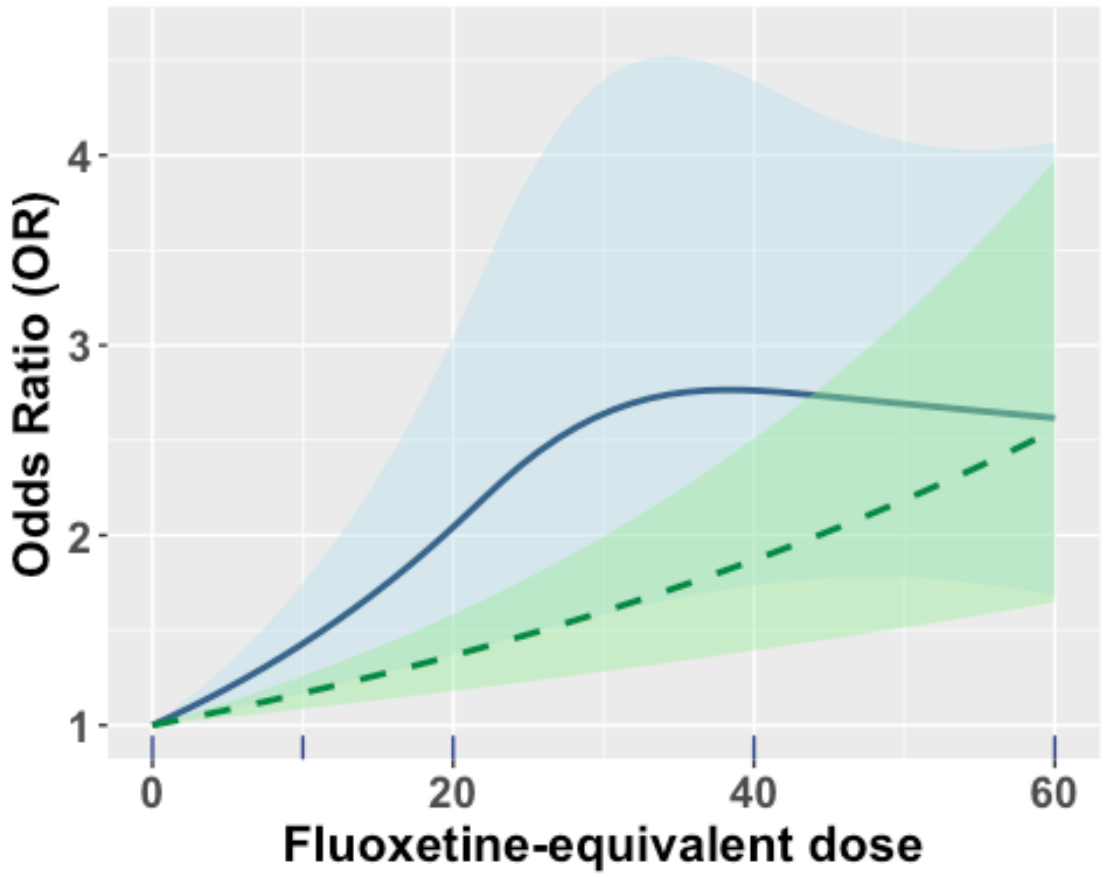
```
# Run dose-effect meta-analysis:
# 1. one-study analysis (with linear and RCS)
# 2. multi-studies analysis: 1stage and 2stage (with RCS)

library(rms) # rcs()
library(dosresmeta) # dosresmeta()
library(meta) # metaprop()
library(dplyr)
source('fun to analyze EBMH.R') # include createORreference.fun()

# ---------- load data and prepare ----------

# load and exclude single arm studies
mydata <-  read.csv('DOSEmainanalysis.csv')
antidep=mydata[mydata$exc==F,]

# add OR
antidep <- antidep%>%arrange(Study_No,hayasaka_ddd) # arrange doses per study
antidep$studyid <- as.numeric(as.factor(antidep$Study_No))
antidep$nonResponders <- antidep$No_randomised- antidep$Responders
logORmat <- sapply(unique(antidep$studyid),function(i)
createORreference.fun(antidep$Responders[antidep$studyid==i],antidep$No_rando
mised[antidep$studyid==i]),simplify = FALSE)
logORmat <- do.call(rbind,logORmat)
antidep$logOR <- c(logORmat[,1])
antidep$selogOR <- c(logORmat[,2])

# knots
knots=
quantile(antidep$hayasaka_ddd[antidep$hayasaka_ddd!=0],c(0.10,0.50,0.90))

# ---------- 1.one-study analysis ----------
study_87 <- antidep[antidep$Study_No=='87',]

# linear
lin_1study <- dosresmeta(formula=logOR~hayasaka_ddd,
                         id=Study_No,
                         type=type,
                         cases=Responders,
                         n=No_randomised,
                         se=selogOR,
                         data=study_87,
                         method = 'reml')

# RCS
```

```r
rcs_1study <- dosresmeta(formula=logOR~rcs(hayasaka_ddd,knots),
                         id=Study_No,
                         type=type,
                         cases=Responders,
                         n=No_randomised,
                         se=selogOR,
                         data=study_87,
                         method = 'reml')

# ---------- 1.multi-study analysis ----------
# 1-stage
rcs_pooled1 <- dosresmeta(formula=logOR~rcs(hayasaka_ddd,knots),
                          proc="1stage",
                          id=Study_No,
                          type=type,
                          cases=Responders,
                          n=No_randomised,
                          se=selogOR,
                          data=antidep,
                          method = 'reml')
print(waldtest(b=coef(rcs_pooled1)[2],
         Sigma=vcov(rcs_pooled1)[2,2],
         Terms=1)) # wald test for spline coefficient

## Wald test:
## ----------
##
## Chi-squared test:
## X2 = 39.9, df = 1, P(> X2) = 2.7e-10

# 2-stage
# include studies with at least 3 arms
studies_2arm <- unique(antidep$Study_No)[table(antidep$Study_No)<3]
antidep_2stage <- antidep[!antidep$Study_No%in%studies_2arm,]

rcs_pooled2 <- dosresmeta(formula=logOR~rcs(hayasaka_ddd,knots),
                          proc="2stage",
                          id=Study_No,
                          type=type,
                          cases=Responders,
                          n=No_randomised,
                          se=selogOR,
                          data=antidep_2stage,
                          method = 'reml')

# placebo effect - meta-analysis
antidep_p <- antidep[antidep$Drug=='placebo',]
antidep_p <-
antidep_p[!(is.na(antidep_p$Responders)|is.na(antidep_p$No_randomised)),] #
discard arms with NA
```

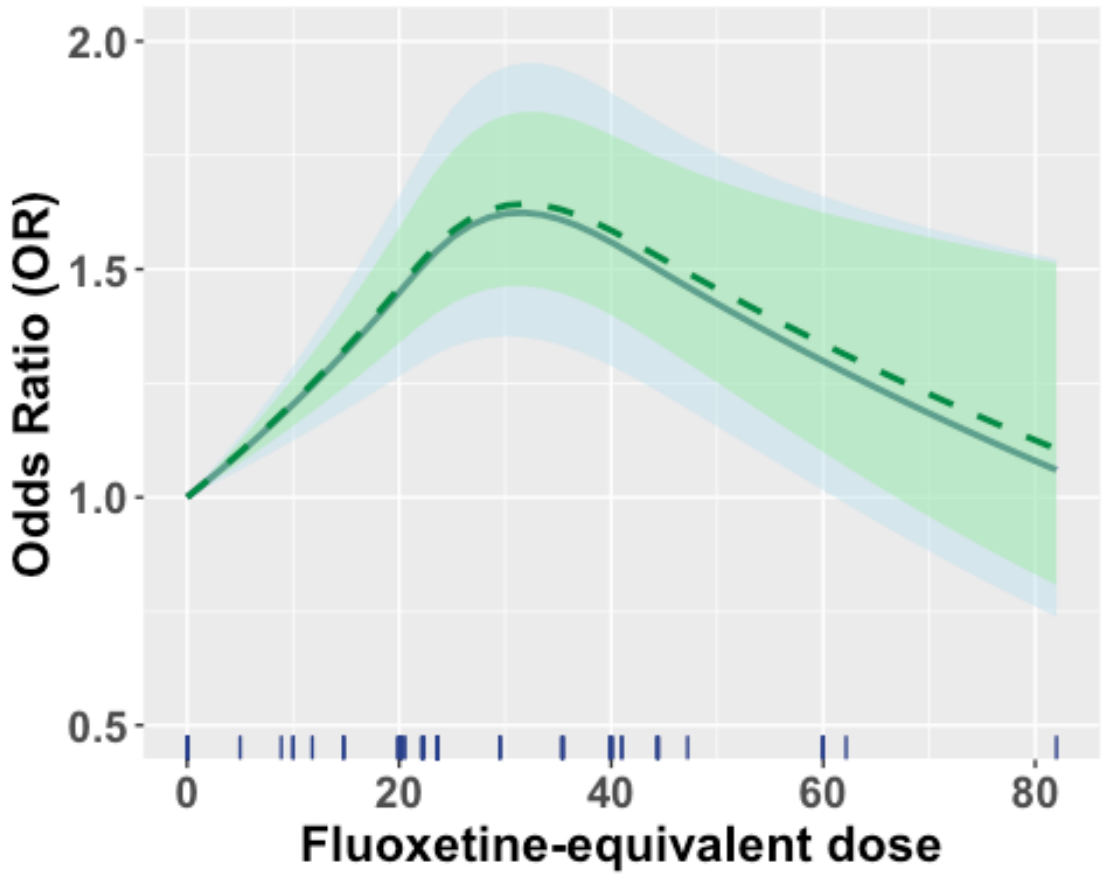
```
meta_pl<-metaprop(event=Responders,
                        n=No_randomised,
                        data=antidep_p,
                        studlab=Study_No,
                        comb.fixed = FALSE)
# back transformation: logit = log (p/(1-p)) -> probability p
pl_eff <- exp(meta_pl$TE.random)/(1+exp(meta_pl$TE.random))
```

Figures and tables

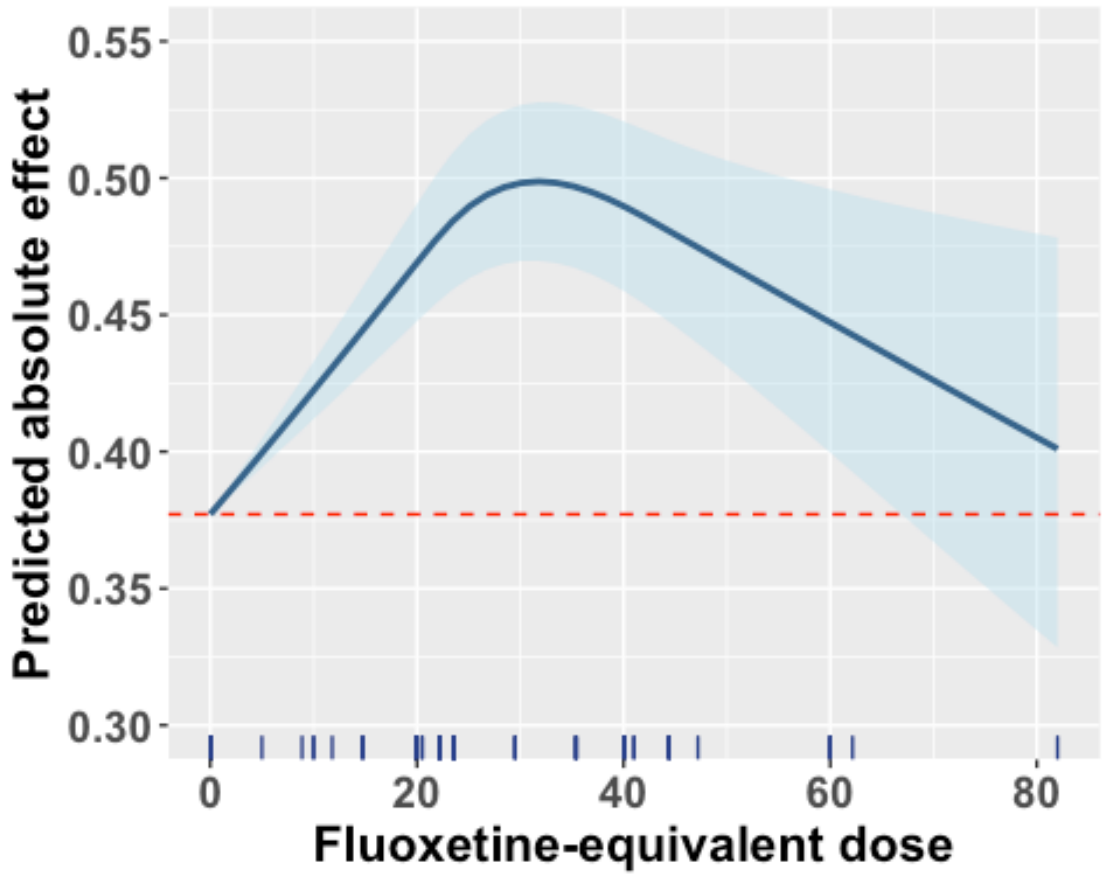
```
source('analyze EBMH.R')

## Wald test:
## ----------
##
## Chi-squared test:
## X2 = 4.6, df = 1, P(> X2) = 0.033

source('fun to plot EBMH.R')

# Table 1 - data of Feighner et al study
tab1()

##   level dose response total   OR   lb   ub logOR selogOR
## 1     0    0       42   129 1.00   NA   NA  0.00      NA
## 2     1   10       61   131 1.81 1.09 2.99  0.59    0.26
## 3     2   20       61   130 1.83 1.11 3.03  0.61    0.26
## 4     3   40       80   131 3.25 1.95 5.41  1.18    0.26
## 5     4   60       73   129 2.70 1.63 4.48  0.99    0.26

# Figure 1 - OR vs flux.dose - RCS and Linear (Feighner et al study)
plotdata1s = plotdata.fun(drma = rcs_1study,
                          data = study_87,
                          knots=knots) # RCS
plotdata2s = plotdata.fun(drma = lin_1study,
                           data = study_87,
                           knots=knots) # Linear

doseres.plot(plotdata = plotdata1s,
             data=study_87,
             ymax = 4.6,
             ymin=1,
             y='OR',
             ub='ubo',
             lb='lbo',
             add2=plotdata2s) # Linear and RCS
```




```r
# Figure 2: OR vs flux.dose - RCS: 2stage & 1stage
plotdata1 = plotdata.fun(drma = rcs_pooled2,
                         data = antidep,
                         knots=knots)

plotdata2 = plotdata.fun(drma = rcs_pooled1,
                         data = antidep,
                         knots=knots,
                         p.eff=pl_eff)


doseres.plot(plotdata =plotdata1,
             data=antidep,
             ymax = 2,
             ymin=0.5,
             y='OR',
             ub='ubo',
             lb='lbo',
             add2=plotdata2,
             add3=NULL) # RCS 1stage and 2stage
```



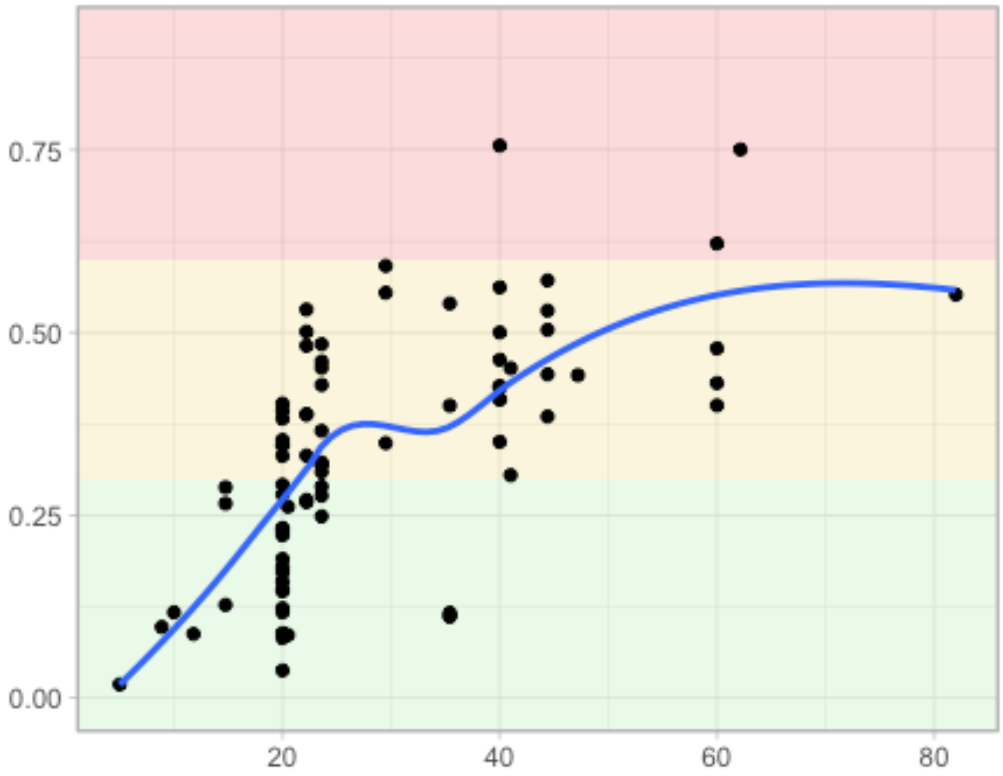

```
# Figure 3: prob vs flux.dose - RCS 1stage
doseres.plot(plotdata =plotdata2,
             data=antidep,
             ymax = 0.55,
             ymin=0.3,
             y='prob',
             ub='ubp',
             lb='lbp',
             labs = c('Predicted absolute effect','Fluoxetine-equivalent
dose')) # RCS 1stage
```




```
# Figure 4: VPC vs dose

# VPC
df <- antidep[!is.na(antidep$selogOR),]
df$vpc <- vpc(rcs_pooled1)
min(df$vpc[df$hayasaka_ddd==20])

## [1] 0.03776123

max(df$vpc[df$hayasaka_ddd==20])

## [1] 0.4027483

max(df$vpc)

## [1] 0.7556904

ggplot(df, aes(hayasaka_ddd,vpc)) +
  annotate("rect", xmin = -Inf, xmax = Inf, ymin = -Inf, ymax = 0.3, fill=
"darkseagreen2", alpha=0.3)  +
  theme_light()+
  annotate("rect", xmin = -Inf, xmax = Inf, ymin = 0.3, ymax = 0.6 , fill=
"lightgoldenrod2", alpha=0.3) +
  theme_light()+
```

```
  annotate("rect", xmin = -Inf, xmax = Inf, ymin = 0.6, ymax = Inf, fill=
"lightcoral", alpha=0.3) +
  theme_light()+
  geom_point() +
  geom_smooth(method = "loess",se=FALSE)+
  coord_cartesian(clip="off", ylim=c(0,0.9))+
  theme(axis.title=element_blank(),
        plot.margin = unit(c(5,10,10,5), "mm"))
```

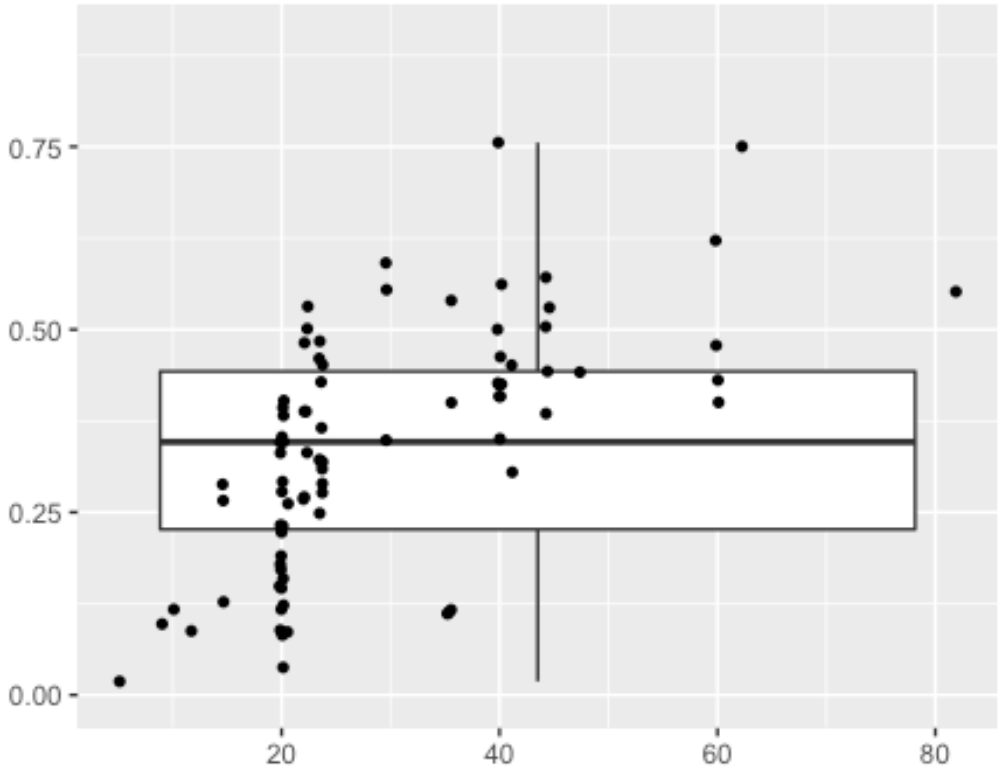
```
## `geom_smooth()` using formula 'y ~ x'
```




```
ggplot(df, aes(hayasaka_ddd,vpc)) +
  coord_flip()+
  geom_boxplot() +
 geom_jitter(shape=16, position=position_jitter(0.2))+
  coord_cartesian(clip="off", ylim=c(0,0.9))+
  theme(axis.title=element_blank(),
        plot.margin = unit(c(5,10,10,5), "mm"))
```

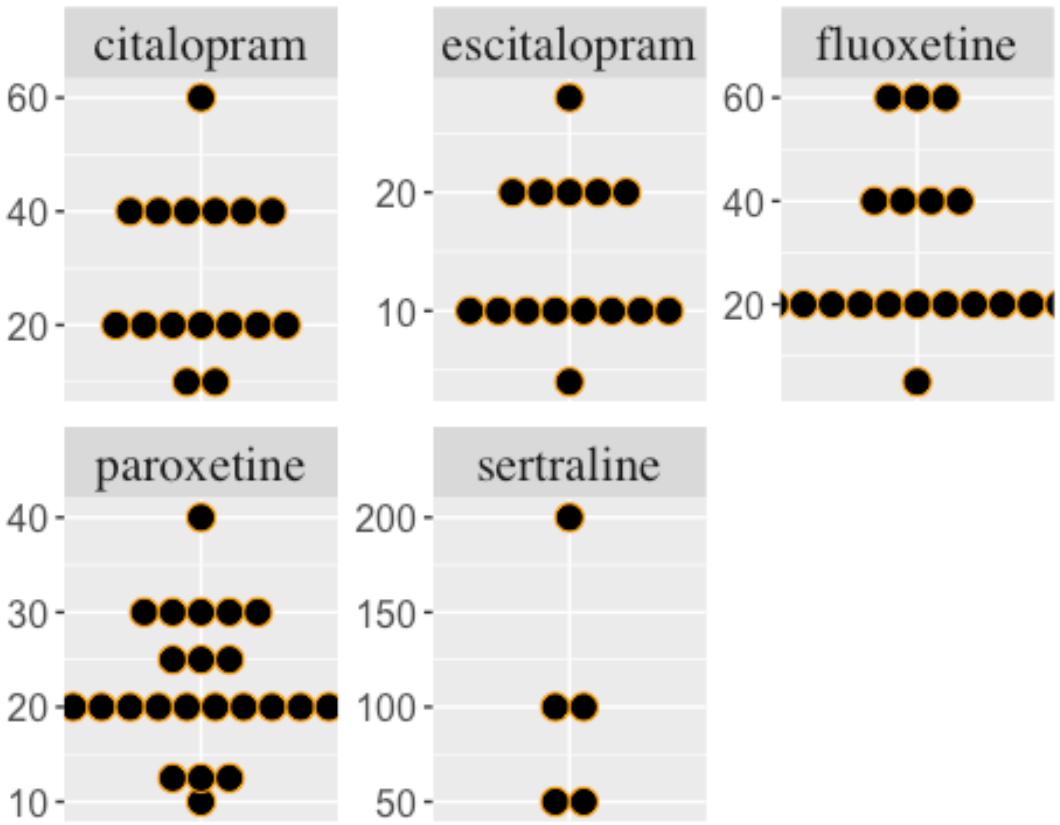
```
## Coordinate system already present. Adding new coordinate system, which
will replace the existing one.
```

```
## Warning: Continuous x aesthetic -- did you forget aes(group=...)?
```




```
# Appendix figure 1
dose_dist1()

## `stat_bindot()` using `bins = 30`. Pick better value with `binwidth`.
```


```
# Appendix figure 2
dose_dist2()

## `stat_bindot()` using `bins = 30`. Pick better value with `binwidth`.
```




```
# Appendix table
app.tab()
```

```
## # A tibble: 6 x 4
##   `Number of events` `Number of patient… `Number of studi… `Number of non-
zero …
## *              <int>               <int>             <int>
<int>
## 1               1002                1928                 9
16
## 2               1089                2405                11
15
## 3                901                2265                18
25
## 4               1389                2669                19
25
## 5               2183                5556                59
59
## 6                134                 351                 3
5
```