

# Antidepressants and suicidal behaviour?

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## Intro

In 1990 Teicher et al. (1990) reported unexpected suicidal ideation in depressed patients treated with fluoxetine. Since then, several studies investigated suicide risk. A recent study by Hengartner et al. (2018) performed a re-analysis of the FDA database and evaluated newer-generation antidepressants and suicide risk in Randomized Controlled Trials.

They refer to Khan et al 2018 who report decreased suicidality in newer generation antidepressants and no decreased suicidality as compared to placebo.

Khan et al. calculate person person exposure year (PEY).

Hengartner et al. argue that suicides occur in the beginning of treatment so PEY is not the appropriate analysis.

We critically review the literature and reanalyze the re-analysis.

This is the data from Hengartner et al. (2018) Of note, there is considerable variance between the studies.

study	ADsuicides	ADparticipants	PLCsuicides	PLCparticipants
Sertraline (1991)	2	2053	0	786
Paroxetine (1992)	5	2963	2	554
Venlafaxine (1993)	3	2181	1	451
Nefazodone (1994)	9	3496	0	875
Mirtazapine (1996)	8	2425	0	494
Venlafaxine ER (1997)	1	705	0	285
Citalopram (1998)	8	4168	1	691
Escitalopram (2002)	0	715	0	592
Duloxetine (2002)	0	2314	0	723
Desvenlafaxine (2008)	1	2667	0	803
Trazodone ER (2010)	0	202	0	204
Vilazodone (2011)	0	2177	0	997
Levomilnacipran (2013)	0	2655	0	1004
Vortioxetine (2013)	0	3060	0	1621

The analysis is run on the sum of the above mentioned data:

	Placebo	Antidepressant
no suicide	10076	31744
suicide	4	37

## Reproducing Hengartner et al. results

```
## $tab
##           Placebo           p0 Antidepressant           p1 oddsratio
## no suicide  10076 0.9996031746          31744 0.998835782    1.00000
## suicide      4 0.0003968254              37 0.001164218    2.83487
##           lower    upper    p.value
## no suicide    NA      NA      NA
## suicide    1.133143 9.671619 0.02354558
##
```

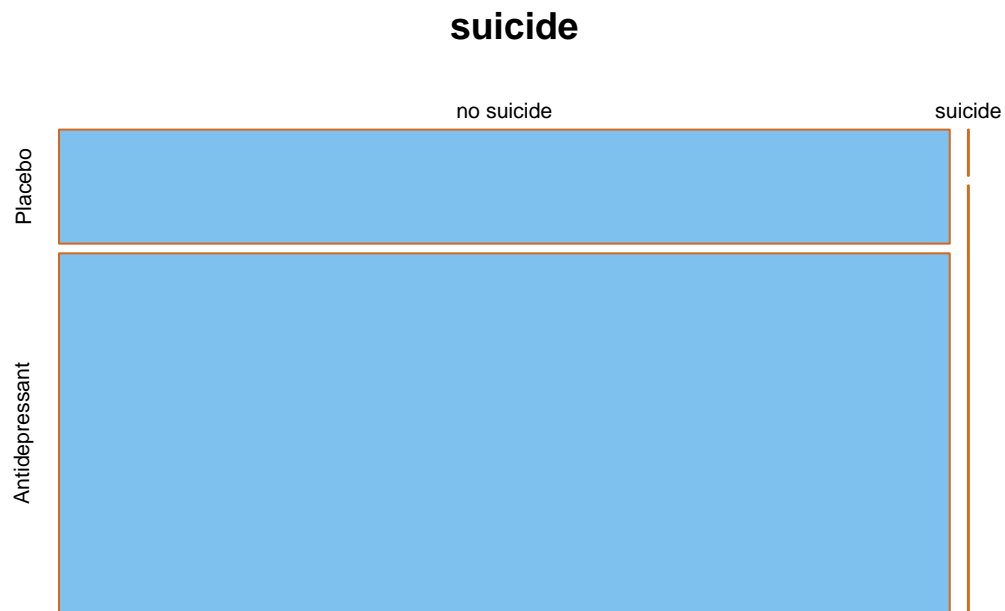
```

## $measure
## [1] "midp"
##
## $conf.level
## [1] 0.95
##
## $pvalue
## [1] "midp.exact"
##
## $x
##           Placebo Antidepressant
## no suicide  10076          31744
## suicide      4           37
##
## $data
##           Placebo Antidepressant Total
## no suicide  10076          31744 41820
## suicide      4           37   41
## Total      10080          31781 41861
##
## $p.exposed
##           Placebo Antidepressant      Total
## no suicide 0.9996031746    0.998835782 0.9990205681
## suicide    0.0003968254    0.001164218 0.0009794319
## Total      1.0000000000    1.000000000 1.0000000000
##
## $p.outcome
##           Placebo Antidepressant Total
## no suicide 0.24093735      0.7590626   1
## suicide    0.09756098      0.9024390   1
## Total      0.24079692      0.7592031   1
##
## $p.value
##           NA
## two-sided  midp.exact fisher.exact chi.square
## no suicide      NA           NA           NA
## suicide    0.02354558    0.02855102 0.04960071
##
## $correction
## [1] TRUE

```

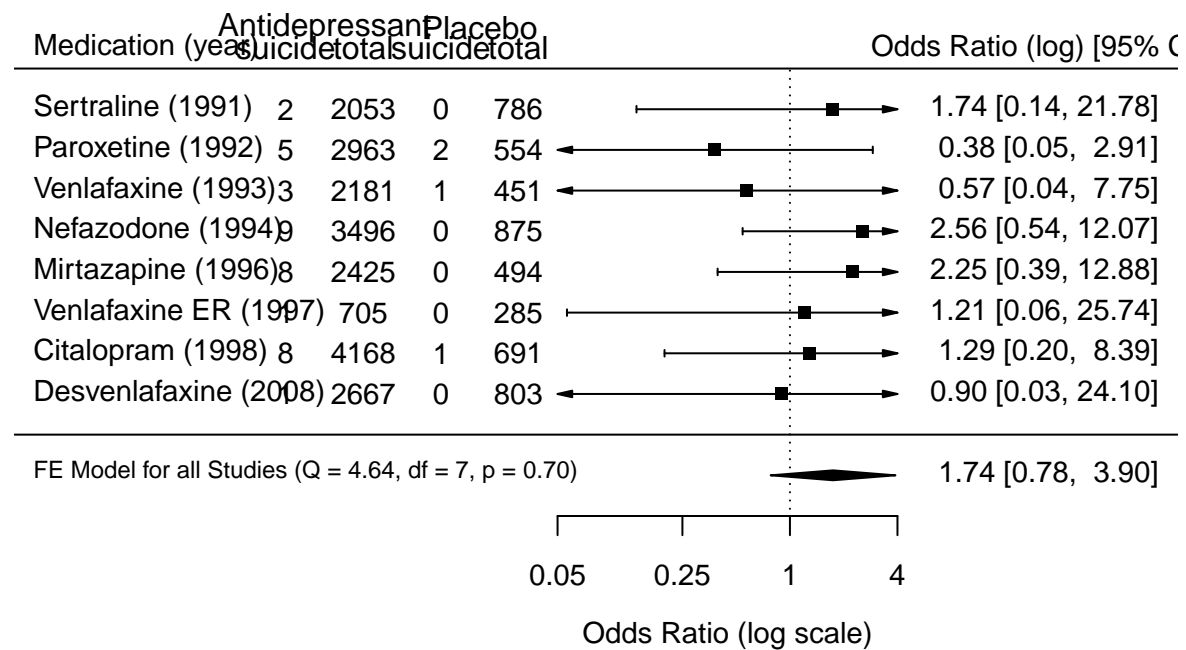
First one has to visualize the data.

## Mosaic plot

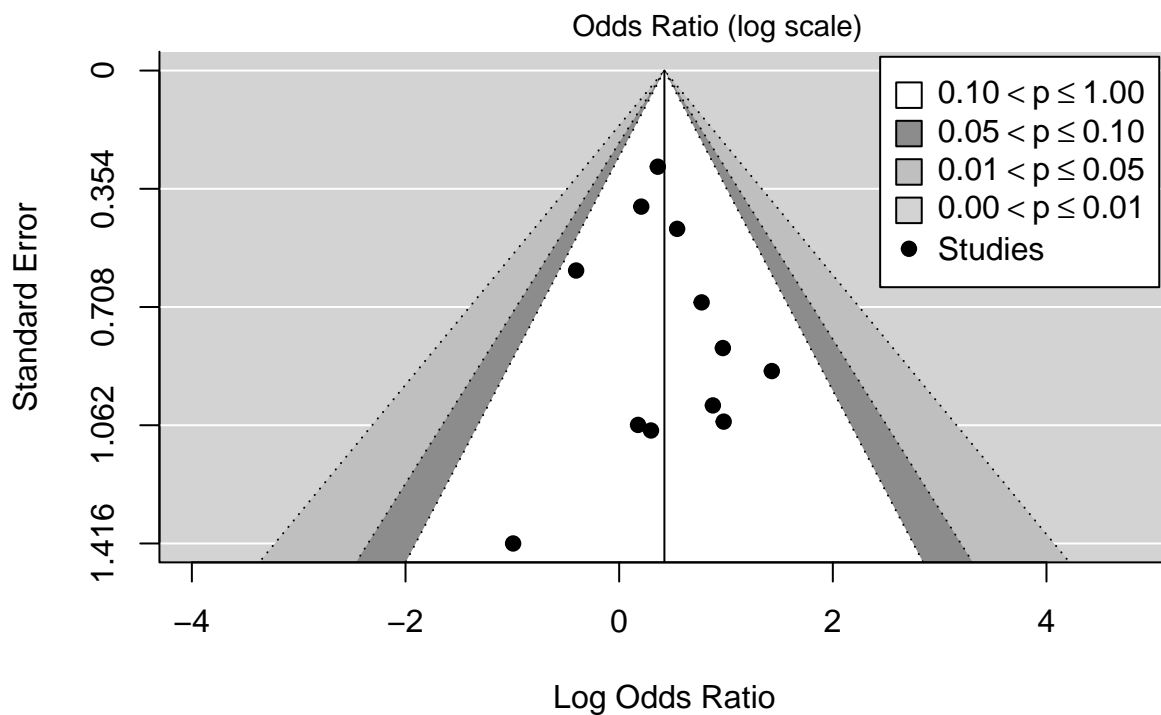
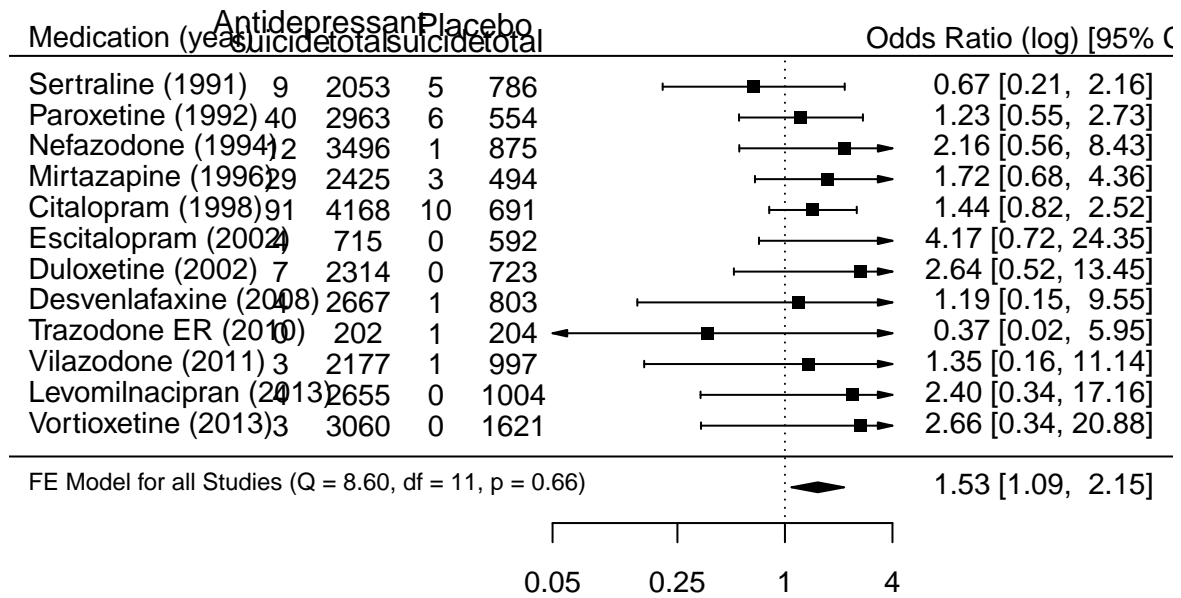


Then we reanalyzed the data using meta analytical approach taking the variance between studies into account  
 peto method <http://www.metafor-project.org/doku.php/analyses:yusuf1985>

## suicide

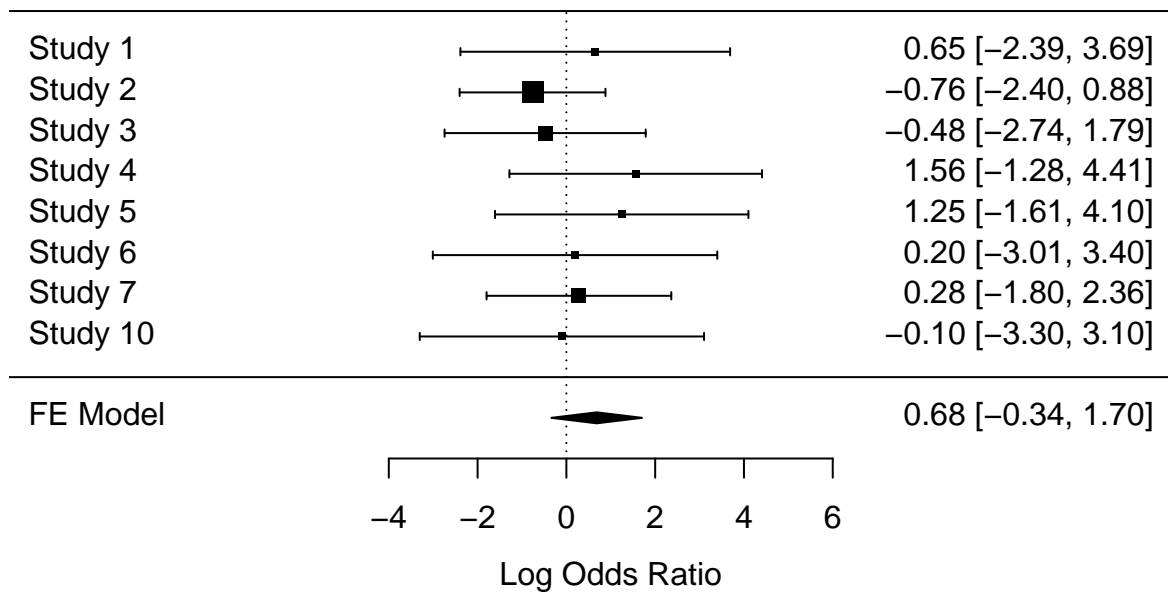


## suicide attempts



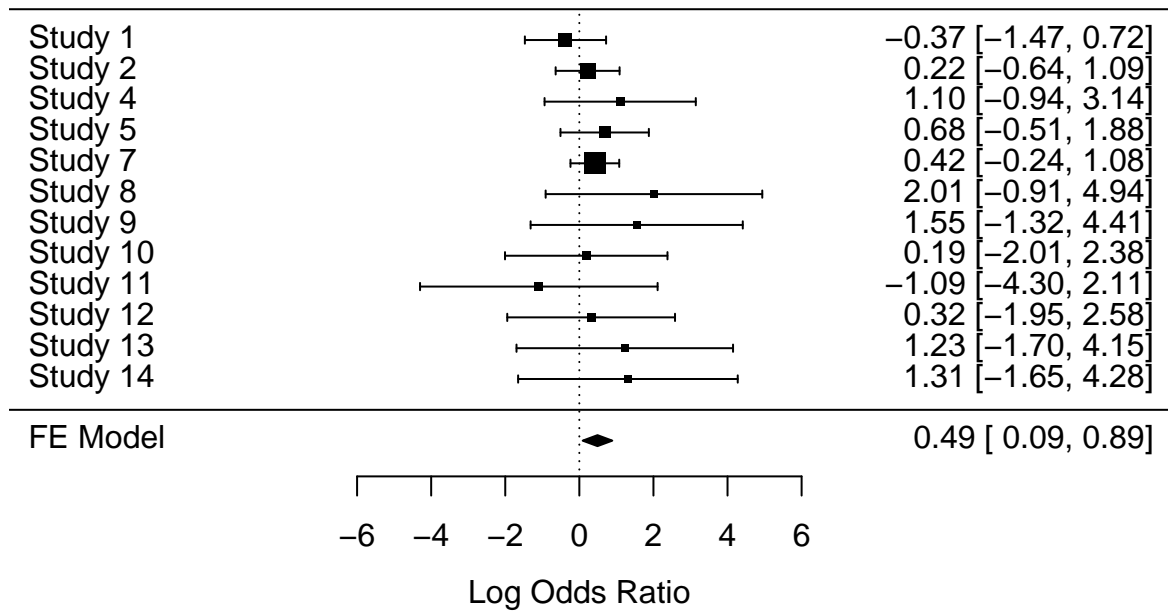
## suicide

Mantel-Haenszel (MH) Methode. Recommended for rare events, and unequal group sizes: Ref: <https://ebmh.bmj.com/content/21/2/72>

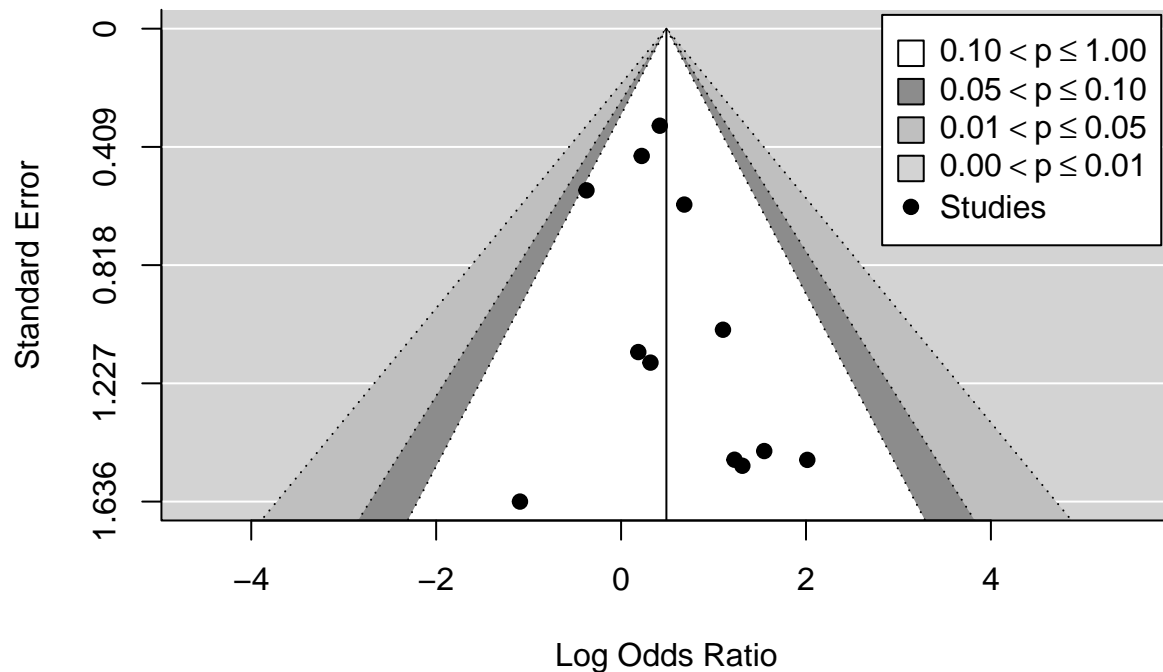


```
##
## Fixed-Effects Model (k = 14)
##
## Test for Heterogeneity:
## Q(df = 7) = 4.9623, p-val = 0.6646
##
## Model Results (log scale):
##
## estimate      se    zval    pval    ci.lb    ci.ub
##  0.6828  0.5211  1.3103  0.1901  -0.3386  1.7042
##
## Model Results (OR scale):
##
## estimate    ci.lb    ci.ub
##  1.9794    0.7128    5.4968
##
## Cochran-Mantel-Haenszel Test:    CMH = 1.8312, df = 1, p-val = 0.1760
## Tarone's Test for Heterogeneity: X^2 = 7.5084, df = 7, p-val = 0.3779
```

# suicide attempts



```
##
## Fixed-Effects Model (k = 12)
##
## Test for Heterogeneity:
## Q(df = 11) = 6.3883, p-val = 0.8462
##
## Model Results (log scale):
##
## estimate      se      zval      pval      ci.lb      ci.ub
##    0.4901    0.2038    2.4053    0.0162    0.0907    0.8895
##
## Model Results (OR scale):
##
## estimate      ci.lb      ci.ub
##    1.6325    1.0950    2.4340
##
## Cochran-Mantel-Haenszel Test:      CMH = 5.9428, df = 1, p-val = 0.0148
## Tarone's Test for Heterogeneity: X^2 = 10.4092, df = 11, p-val = 0.4940
```



calculating NNH with <https://ebm-tools.knowledgetranslation.net/calculator/converter/>

patient expected event rate of 3.7% according to

<https://www.cdc.gov/mmwr/preview/mmwrhtml/ss6013a1.htm>

NNH=45

Or from risk difference according to [https://handbook-5-1.cochrane.org/chapter\\_12/12\\_5\\_4\\_1\\_computing\\_nnt\\_from\\_a\\_risk\\_difference\\_rd.htm](https://handbook-5-1.cochrane.org/chapter_12/12_5_4_1_computing_nnt_from_a_risk_difference_rd.htm)

```
res <-rma.mh(df$suica_ad, df$part_ad-df$suica_ad,
  df$suica_plc, df$part_plc-df$suica_plc,
  df$part_ad, df$part_plc,
  to="only0", drop00=FALSE, add=1/2,
  level=95, verbose=FALSE, measure="RD", correct = FALSE)
res
```

```
##
## Fixed-Effects Model (k = 12)
##
## Test for Heterogeneity:
## Q(df = 11) = 12.4491, p-val = 0.3309
##
## Model Results:
##
## estimate      se      zval      pval      ci.lb      ci.ub
## 0.0021 0.0007 2.7588 0.0058 0.0006 0.0035
```

NNH

1/0.0021

```
## [1] 476.1905
```

## age effect

In the original of the FDA data Stone et al. describe a strong age effect.

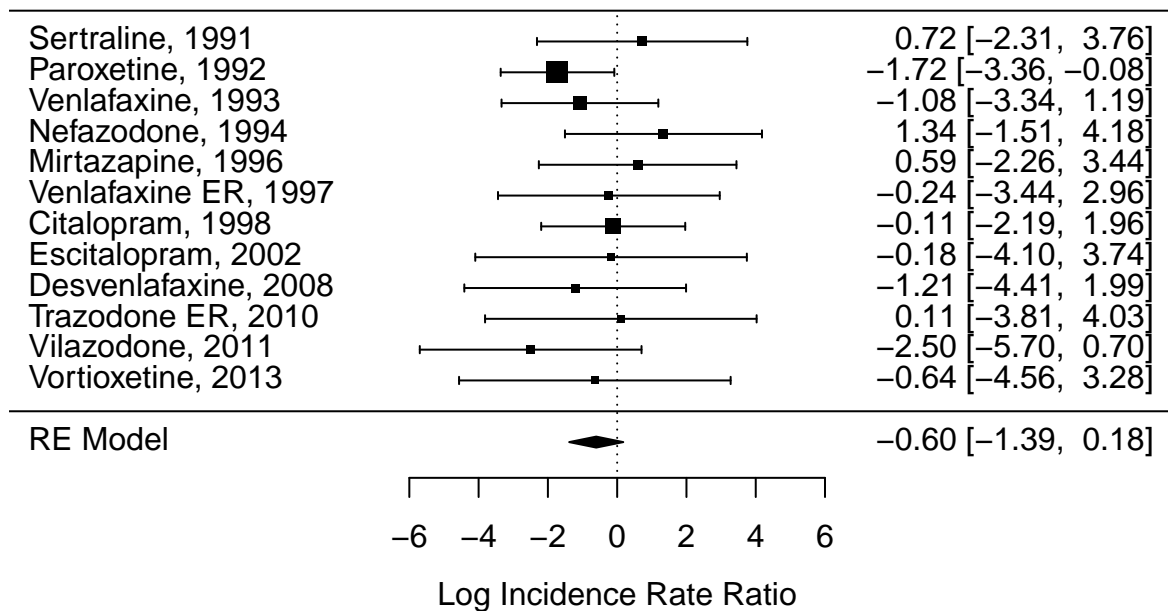
## reanalyzing Khan et al. with patient exposure year (PEY)

year	medication	NAD	PEYAD	NPLC	PEYPLC	ADSuicide	PlaceboSuicide	ADSuicideattempt	Pla
1991	Sertraline	2053	507.9	786	209.0	2	0	9	
1992	Paroxetine	2963	1008.0	554	72.0	5	2	40	
1993	Venlafaxine	2181	879.0	451	100.0	3	1	NA	
1994	Nefazodone	3496	1018.0	875	204.0	9	0	12	
1996	Mirtazapine	2425	671.7	494	71.4	8	0	29	
1997	Venlafaxine ER	705	161.6	285	42.4	1	0	NA	
1998	Citalopram	4168	1347.7	691	150.3	8	1	91	
2002	Escitalopram	715	99.0	592	83.0	0	0	4	
2002	Duloxetine	2314	754.0	723	NA	0	0	7	
2008	Desvenlafaxine	2667	1137.2	803	112.8	1	0	4	
2010	Trazodone ER	202	25.9	204	28.8	0	0	0	
2011	Vilazodone	2177	551.5	997	136.1	0	1	3	
2013	Levomilnacipran	2655	899.5	NA	NA	0	0	4	
2013	Vortioxetine	3060	406.3	1621	213.4	0	0	3	

## suicide

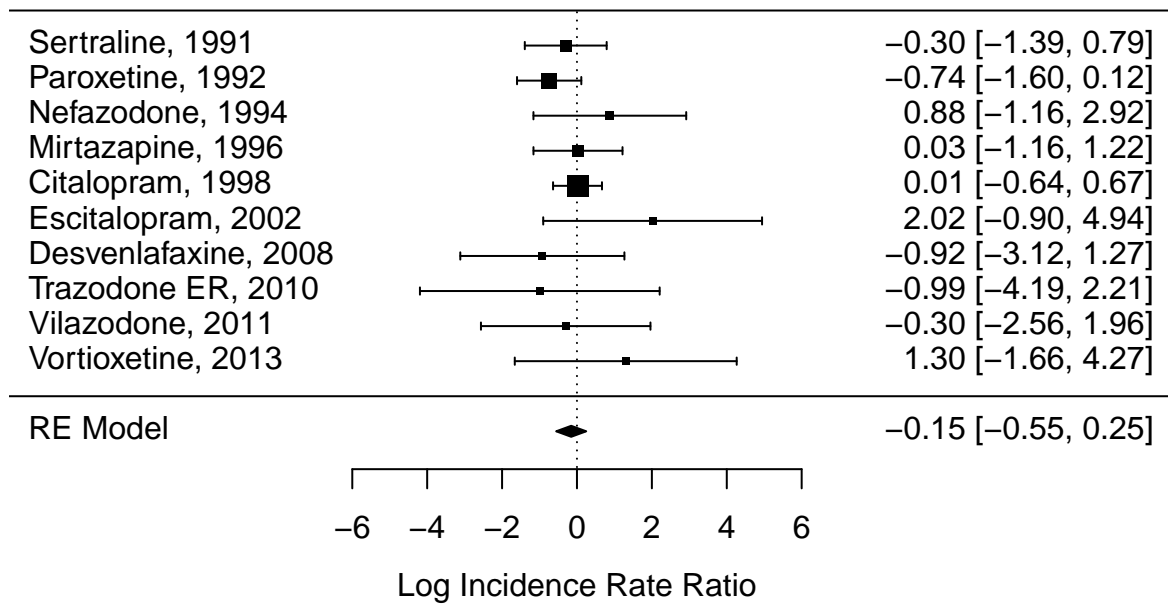
```
##
## Random-Effects Model (k = 12; tau^2 estimator: REML)
##
## tau^2 (estimated amount of total heterogeneity): 0 (SE = 0.7326)
## tau (square root of estimated tau^2 value):      0
## I^2 (total heterogeneity / total variability):    0.00%
## H^2 (total variability / sampling variability):    1.00
##
## Test for Heterogeneity:
## Q(df = 11) = 7.0702, p-val = 0.7934
##
## Model Results:
##
## estimate      se      zval      pval      ci.lb      ci.ub
## -0.6047  0.3982  -1.5184  0.1289  -1.3851  0.1758
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```





#### suicide attempts

```
##
## Random-Effects Model (k = 10; tau^2 estimator: REML)
##
## tau^2 (estimated amount of total heterogeneity): 0 (SE = 0.1581)
## tau (square root of estimated tau^2 value):      0
## I^2 (total heterogeneity / total variability):    0.00%
## H^2 (total variability / sampling variability):    1.00
##
## Test for Heterogeneity:
## Q(df = 9) = 7.0107, p-val = 0.6360
##
## Model Results:
##
## estimate      se      zval      pval      ci.lb      ci.ub
## -0.1539  0.2046  -0.7522   0.4519  -0.5548   0.2471
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```



Kahn et al. specifically report a reduction of suicide and suicide attempts in newer studies. Probably confounded by more rigid exclusion criteria of suicidal patients in newer studies.

Problem with PEY: if suicide attempts occur causally after treatment initiation than PEY will water down effect.