

Supplemental Figure 2

Supplemental Figure 2 depicts the association between SSRI dose and SMD improvement in 4 dose categories of SSRIs. The 4 chosen dose categories of SSRIs: <100mg, 100-199mg, 200-250mg and >250mg were based on a meta-analysis that failed to demonstrate a dose-response relationship in antidepressant medications (not exclusively SSRIs) [interaction=0.0008 (95%CI: 0.0002-0.0014; p<0.001)]. Dosages are expressed in imipramine equivalents. 100mg of imipramine = 120mg of sertraline = 100mg of fluvoxamine = 20mg of paroxetine or fluoxetine=33.3 mg of citalopram=16.7 mg of escitalopram. Abbreviations: SMD=Standardized Mean Difference.

Supplemental Figure 3

Supplemental Figure 3A is a scatterplot depicting the association between SSRI dosage in imipramine equivalents and difference in improvement compared to placebo (standardized mean difference). Within the scatterplot, circles represent individual studies with the size of the circle corresponding to its weight in the meta-analysis. The regression line reflects the significant positive relationship between SSRI dosage and difference of improvement compared to placebo ($\beta=0.00029$, 95% CI -0.00010–0.00066, $z = 1.44$, $p = 0.15$). Supplemental Figure 3B depicts the association between SSRI dose and difference of improvement in 4 dose categories of SSRIs ($\chi^2=42.4$, $df=3$, $p<0.001$). The 4 chosen dose categories of SSRIs: <100mg, 100-199mg, 200-250mg and >250mg were based on a meta-analysis that failed to demonstrate a dose-response relationship in antidepressant medications (not exclusively SSRIs). Dosages are expressed in imipramine equivalents. 100mg of imipramine = 120mg of sertraline = 100mg of fluvoxamine = 20mg of paroxetine or fluoxetine=33.3 mg of citalopram=16.7 mg of escitalopram. Abbreviations: SMD=Standardized Mean Difference. Supplemental Figure 3C is a scatterplot depicting the association between SSRI dosage in imipramine equivalents and response in SSRIs compared to placebo (Odds Ratio). The regression line reflects the non-significant positive relationship between SSRI dosage and response compared to placebo ($\beta=0.0015$, 95% CI 0.0003–0.0026, $z = 2.47$, $p = 0.013$). Supplemental Figure 3D depicts the association between SSRI dose and remission in 4 dose categories of SSRIs ($\chi^2=11.4$, $df=3$, $p=0.01$). Abbreviations: SMD=Standardized Mean Difference.

Supplemental Figure 4

Supplemental Figure 4A is a scatterplot depicting the association between SSRI dosage in imipramine equivalents and all-cause dropouts without fluvoxamine. Within the scatterplot, circles represent individual studies with the size of the circle corresponding to its weight in the meta-analysis. The regression line reflects the significant positive relationship between SSRI dosage and all-cause dropout compared to placebo ($\beta=-0.00092$, 95% CI -0.00174– (-0.00010), $z = -2.20$, $p = 0.03$). Supplemental Figure 4B depicts the association between SSRI dose and dropout due to side-effects in 4 dose categories of SSRIs without fluvoxamine ($\beta=0.00249$ 95% CI 0.00073– 0.00425, $z = 2.77$, $p = 0.006$). The 4 chosen dose categories of SSRIs: <100mg, 100-199mg, 200-250mg and >250mg were based on a meta-analysis that failed to demonstrate a dose-response relationship in antidepressant medications (not exclusively SSRIs). Dosages are expressed in imipramine equivalents. 100mg of imipramine = 120mg of sertraline = 100mg of fluvoxamine = 20mg of paroxetine or fluoxetine=33.3 mg of citalopram=16.7 mg of escitalopram. Supplemental Figure 4C depicts the association between SSRI dose and dropout in 4 dose categories of SSRIs without fluvoxamine ($\chi^2=3.7$, $df=3$, $p=0.29$).

Supplemental Figure 1

Actual OR of Treatment Response			Estimated OR based on Effect Size		
<i>Placebo</i>	<i>Subtherapeutic SSRI</i>	<i>Low-dose SSRI</i>	<i>Placebo</i>	<i>Subtherapeutic SSRI</i>	<i>Low-dose SSRI</i>
1.81 (1.48-2.21)			2.41 (2.01-2.90)		
1.94 (1.58-2.37)	1.07 (0.87-1.31)		3.25 (2.78-3.79)	1.35 (1.15-1.57)	
2.72 (2.08-3.54)	1.50 (1.15-1.96)	1.40 (1.07-1.82)	5.07 (4.34-5.91)	2.10 (1.80-2.45)	1.56 (1.34-1.82)
2.64 (2.20-3.18)	1.46 (1.22-1.76)	1.36 (1.13-1.64)	2.99 (2.58-3.46)	1.24 (1.07-1.44)	0.92 (0.79-1.06)
Actual NNT of Treatment Response*			Estimated NNT based on Effect Size*		
<i>Placebo</i>	<i>Subtherapeutic SSRI</i>	<i>Low-dose SSRI</i>	<i>Placebo</i>	<i>Subtherapeutic SSRI</i>	<i>Low-dose SSRI</i>
7 (5-11)			5 (4-6)		
6 (5-9)	64 (16-∞)		3 (3-4)	14 (9-30)	
4 (3-6)	10 (6-30)	12 (7-64)	3 (2-3)	6 (5-7)	9 (7-14)
4 (4-5)	11 (7-21)	14 (8-35)	4 (3-4)	20 (11-64)	No Benefit*
Actual OR of Dropout Due to Side-Effects			Actual OR of All Cause Dropout		
<i>Placebo</i>	<i>Subtherapeutic SSRI</i>	<i>Low-dose SSRI</i>	<i>Placebo</i>	<i>Subtherapeutic SSRI</i>	<i>Low-dose SSRI</i>
1.58 (0.92-2.72)			0.77 (0.59-0.99)		
1.69 (1.13-2.51)	1.07 (0.72-1.59)		1.06 (0.86-1.30)	1.38 (1.12-1.69)	
3.16 (2.32-4.32)	2.00 (1.47-2.73)	1.87 (1.37-2.56)	0.80 (0.68-0.95)	1.03 (0.88-1.23)	0.75 (0.64-0.90)
3.06 (2.25-4.17)	1.94 (1.42-2.64)	1.81 (1.33-2.47)	0.72 (0.62-0.84)	0.94 (0.81-1.09)	0.68 (0.58-0.79)
Actual NNH of Dropout Due to Side-Effects					
<i>Placebo</i>	<i>Subtherapeutic SSRI</i>	<i>Low-dose SSRI</i>			
33 (12-∞)					
28 (13-142)	263 (32-∞)				
10 (7-15)	19 (12-40)	24 (14-57)			
10 (7-16)	21 (12-45)	22 (13-51)			

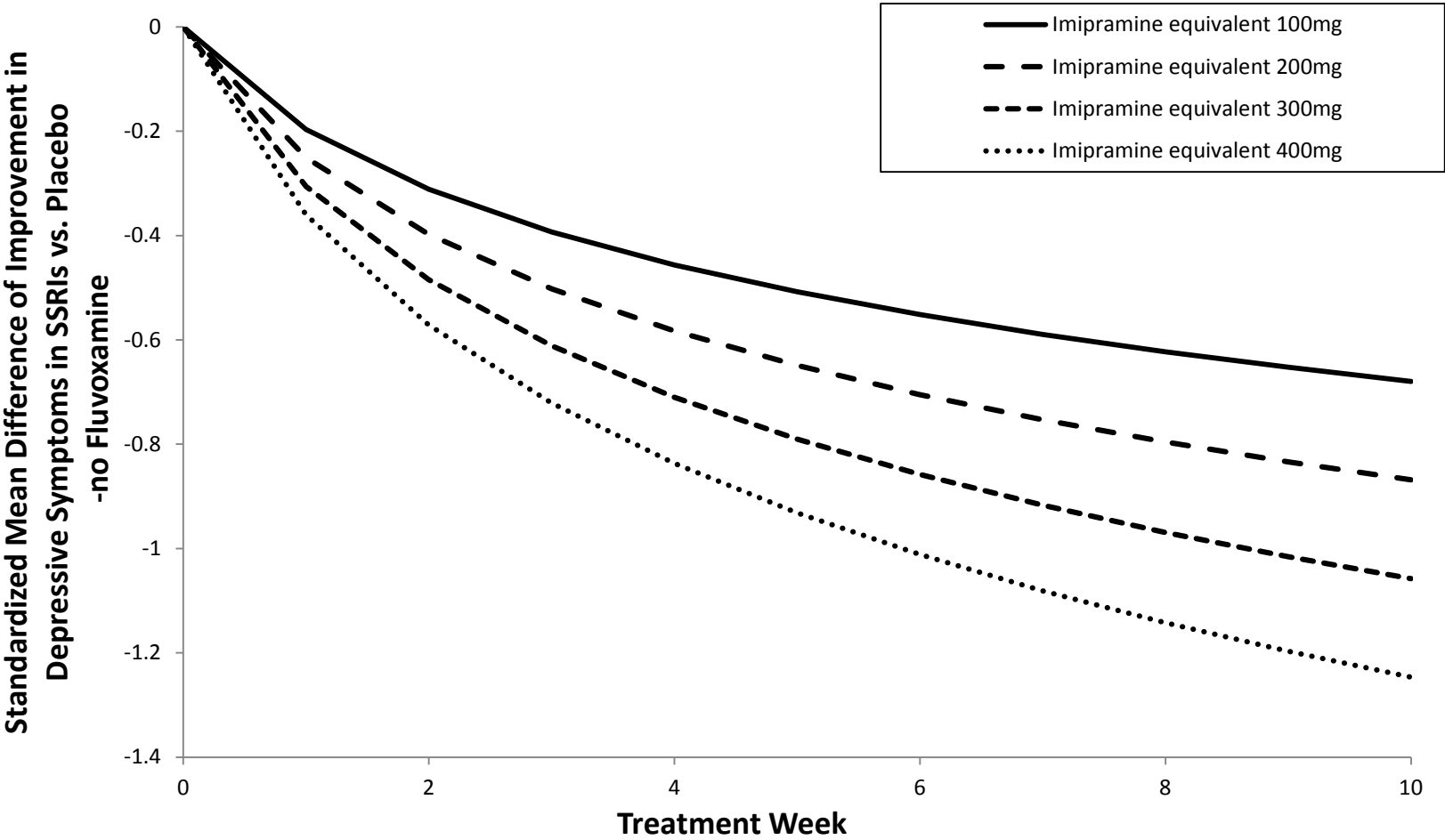
Supplemental Figure 1 depicts the actual and estimated OR, NNT, and NNH for treatment response, effect size, and dropout for all trials. Abbreviations: OR = Odds Ratio, NNT = Number Needed to Treat, NNH = Number Needed to Harm

Supplemental Figure 1

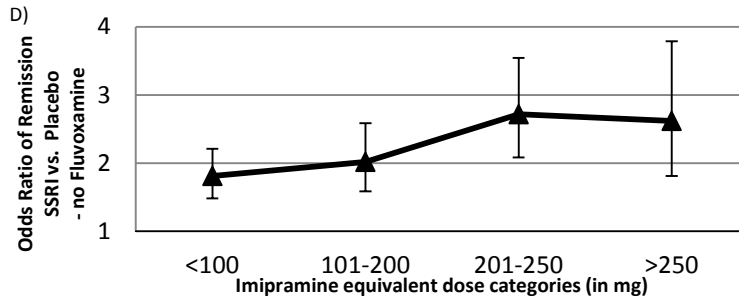
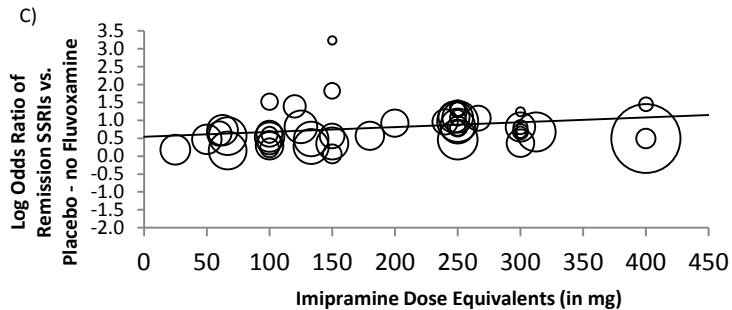
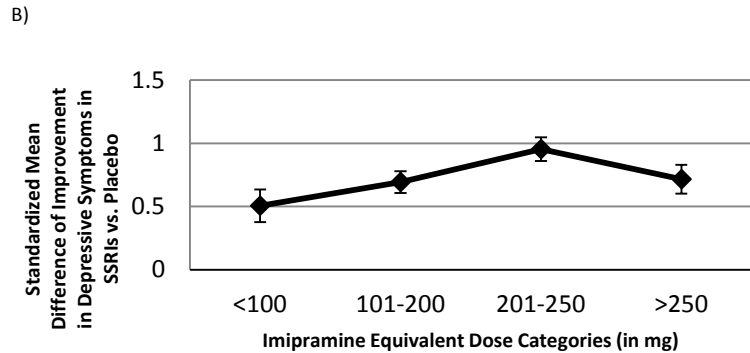
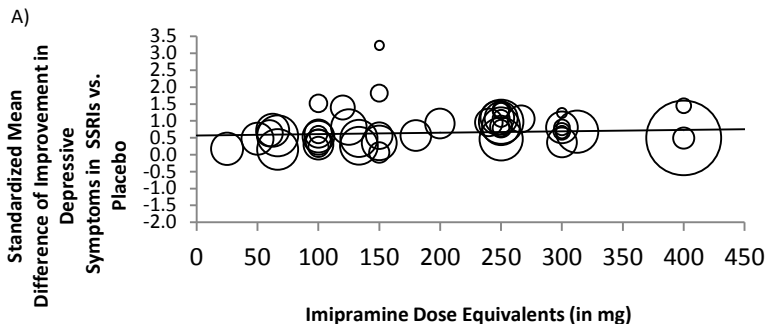
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Actual OR of Dropout Due to Side-Effects			Actual OR of All Cause Dropout		
<i>Placebo</i>	<i>Subtherapeutic SSRI</i>	<i>Low-dose SSRI</i>	<i>Placebo</i>	<i>Subtherapeutic SSRI</i>	<i>Low-dose SSRI</i>
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Supplemental Figure 1 depicts the actual and estimated OR, NNT, and NNH for treatment response, effect size, and dropout for all trials. Abbreviations: OR = Odds Ratio, NNT = Number Needed to Treat, NNH = Number Needed to Harm

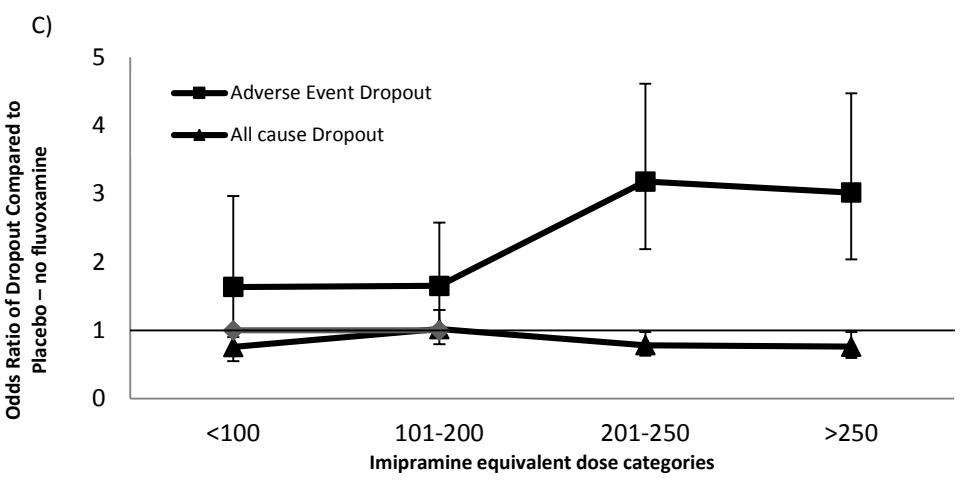
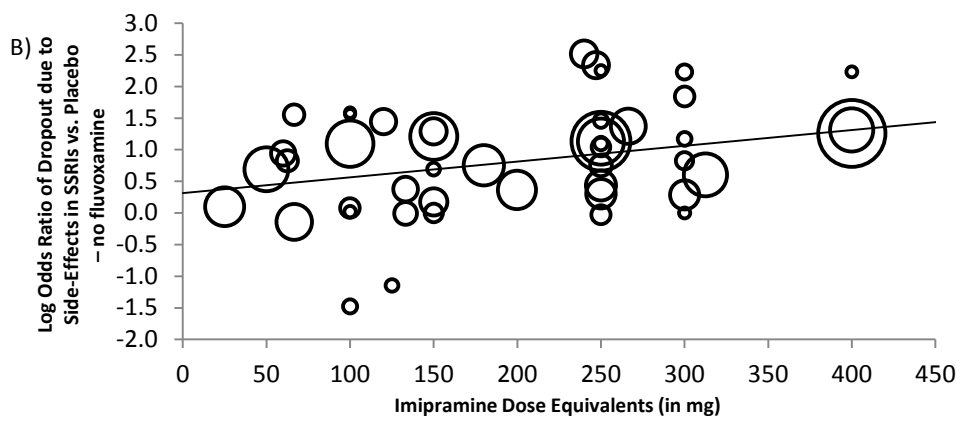
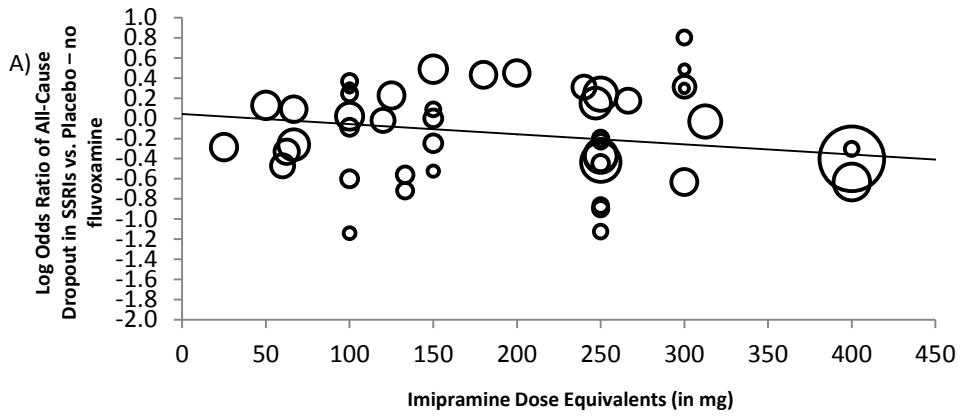
Supplemental Figure 2



Supplemental Figure 3



Supplemental Figure 4



Supplementary Table 1: Characteristics of Included Studies

Author	Year	Number of active treatment arms	SSRI	Dose (mg)	Imipramine Dose Equivalents (mg)	Duration of Trial (weeks)	Depression Scale	N ^a	Completer vs ITT
Byerley	1988	1	Fluoxetine	80	400	6	HAM-D	61	Completer
Claghorn	1996	1	Fluvoxamine	150	150	6	HAM-D21	89	ITT
Claghorn	1992	1	Paroxetine	50	250	6	HAM-D	337	ITT
Cohn	1992	1	Paroxetine	50	250	6	HAM-D	71	ITT
Corrigan	2000	1	Fluoxetine	20	100	8	HAM-D	70	ITT
DeRubeis	2005	1	Paroxetine	50	150	8	HAM-D	180	ITT
Detke	2004	1	Paroxetine	20	100	8	HAM-D17	179	ITT
Dominguez	1985	1	Fluvoxamine	300	300	4	HAMD17	64	Completer
Dunbar	1993	1	Paroxetine	50	250	6	HAM-D	273	ITT
Edwards	1993	1	Paroxetine	30	150	6	HAM-D	41	ITT
Fabre	1996	1	Fluvoxamine	150	150	6	HAM-D21		ITT
Fabre	1992	1	Paroxetine	50	250	6	HAM-D	74	ITT
Fabre	1995	3	Sertraline	50, 100, 200	60, 120, 240	6	HAM-D	369	Completer
Fava	2005	1	Fluoxetine	20	100	6	HAM-D17	90	ITT
Feighner	1993	1	Paroxetine	50	250	6	HAM-D	480	ITT
Feighner	1989	1	Fluoxetine	80	400	6	HAM-D21	99	Completer
Feighner	1999	1	Citalopram	n/a ^b	n/a ^b	6	HAM-D	650	ITT
Feighner	1992	1	Paroxetine	50	250	6	HAM-D	76	ITT
Golden	2002	2	Paroxetine IR, XR	50, 62.5	250, 312.5	12	HAM-D	827	ITT
Heiligenstein	1993	1	Fluoxetine	20	100	8	MADRS	89	ITT

Kiev	1999	1	Paroxetine	50	250	6	HAM-D	66	Completer
Lepola	2003	2	Escitalopram Citalopram	20,40	133.2, 199.8	8	MADRS	623	ITT
Lydiard	1989	1	Fluvoxamine	300	300	6	HAM-D	36	Completer
March	1990	1	Fluvoxamine	300	300	7	HAM-D	25	Completer
Mendels	1999	1	Citalopram	80	266.4	4	HAM-D	180	ITT
Nierenberg	2007	1	Escitalopram	10	66.6	8	HAM-D17	411	ITT
Porro	1988	1	Fluvoxamine	150	150	4	HAM-D	41	Completer
Reimherr	1990	1	Sertraline	n/a ^b	n/a ^b	8	HAM-D	283	ITT
Rickels	1989	1	Paroxetine	50	250	6	HAM-D	111	ITT
Roth	1990	1	Fluvoxamine	300	300	6	HAM-D	56	Completer
Rudolph	1999	1	Fluoxetine	60	300	8	MADRS	200	ITT
Silverstone	1999	1	Fluoxetine	60	300	12	HAM-D	237	ITT
Smith	1992	1	Paroxetine	50	250	6	HAM-D	66	ITT
Sramek	1995	1	Fluoxetine	20	100	9	HAM-D	142	ITT
Stahl	2000	2	Citalopram, Sertraline	50, 150	133.2, 180	24	HAM-D	423	ITT
Tollefson	1994	1	Fluoxetine	80	400	6	HAM-D21	1398	ITT
Trivedi	2004	2	Paroxetine	12.5, 25	62.5, 125	8	HAM-D	447	ITT
Wade	2002	1	Escitalopram	10	66.6	8	MADRS	380	ITT
Walczak	1996	4	Fluvoxamine	25, 50,100, 150	25, 50,100,150	6	HAM-D13	599	ITT
Perahia	2006	1	Paroxetine	20	100	8	HAM-D	196	ITT

Supplementary Table 1: Overview of The Characteristics of Included Studies. Abbreviations: ITT=Intent-to-treat, SSRI=Selective-Serotonin Reuptake Inhibitor, HAM-D=Hamilton Depression Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale