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# Comparative Risk for Harms of Second-Generation Antidepressants

## A Systematic Review and Meta-Analysis

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## Supplementary Material

This supplementary material contains the table referred to in the full version of this article, which can be found at <http://drugsafety.adisonline.com>. Note the reference citations and reference list are independent from the published article and reference numbering will differ.

**Table S3: Study characteristics, main findings, and quality ratings of double-blinded head-to-head RCTs**

Study	N	Duration	Comparison and Dose (mg/d)	Overall Adverse Events Rates (%)			Quality Rating
				SSRIs vs. other SSRIs	General Adverse Events (%)	Serious Adverse Events (%)	
Burke et al., 2002 <sup>[92]</sup>	491	8 weeks	Citalopram 40 Escitalopram 20	86 vs. 86	Higher rate of nausea with citalopram (22 vs. 14)	Higher rate of sexual dysfunction with escitalopram (4 vs. 12)	Fair
Colonna et al., 2005 <sup>[93]</sup>	357	24 weeks	Citalopram 20 Escitalopram 10	72 vs. 63	Higher rate of weight gain with citalopram (7 vs. 1) Higher rate of nausea with escitalopram (10 vs. 16)	No differences	Fair
Lepola et al., 2003 <sup>[94]</sup>	471	8 weeks	Citalopram 20-40 Escitalopram 10-20	60 vs. 70	No differences	Higher rate of sexual dysfunction with escitalopram (0 vs. 5) Higher rate of suicidality with escitalopram (8 vs. 2)	Fair
Moore et al., 2005 <sup>[95]</sup>	280	8 weeks	Citalopram 40 Escitalopram 20	16 vs. 15	No differences	No differences	Fair
Unpublished Study SCT MD-02 <sup>[96]</sup>	375	8 weeks	Citalopram 20-40 vs. Escitalopram 10-20	NR	Higher rate of diarrhea (15 vs. 10) with citalopram	No differences	Fair
Patris et al., 1996 <sup>[97]</sup>	357	8 weeks	Citalopram 20 Fluoxetine 20	50 vs. 52	No differences	No differences	Fair
Haffmans et al., 1996 <sup>[11]</sup>	217	6 weeks	Citalopram 20-40 Fluvoxamine 100-200	NR	Significantly higher rates of diarrhea (14 vs. NR) and nausea (16 vs NR) with fluvoxamine	No differences	Fair
Ekselius et al., 1997 <sup>[67, 68]</sup>	400	24 weeks	Citalopram 20-60 Sertraline 50-150	86 vs. 90	Higher rate of weight loss with citalopram (10 vs. 5)	Higher rate of sexual dysfunction with citalopram (20 vs. 14)	Good
Kasper et al., 2005 <sup>[98]</sup>	518	8 weeks	Escitalopram 10 Fluoxetine 20	10 vs. 12	No differences	No differences	Fair
Boulenger et al., 2006 <sup>[99]</sup>	459	24 weeks	Escitalopram 20 Paroxetine 40	NR	Significantly more patients on paroxetine withdrew due to adverse events (16 vs. 8)	No differences	Fair
Baldwin et al., 2006 <sup>[100]</sup>	325	8 weeks	Escitalopram 10-20 Paroxetine 20-40	NR	No differences	No differences	Fair
Ventura et al.,	215	8 weeks	Escitalopram 10	NR	Higher rate of diarrhea with	No differences	Fair

2007 <sup>[65]</sup>			Sertraline 50-200		sertraline (23 vs. 13)		
Dalery and Honig, 2003 <sup>[101]</sup>	184	6 weeks	Fluoxetine 20 Fluvoxamine 100	NR	No differences	No differences	Fair
Rapaport et al., 1996 <sup>[12]</sup>	100	7 weeks	Fluoxetine 20-80 Fluvoxamine 100-150	NR	Higher rates of nausea (43 vs. NR) and vomiting (13 vs. 4) with fluoxetine Higher rate of insomnia (36 vs. 28) with fluvoxamine	No differences	Fair
Cassano et al., 2002 <sup>[102]</sup>	242	52 weeks	Fluoxetine 20-60 Paroxetine 20-40	33 vs. 28	Significantly more severe adverse events with fluoxetine (13 vs. 5)	Higher rate of serious adverse events with fluoxetine (9 vs. 4)	Fair
Chouinard et al., 1999 <sup>[103]</sup>	203	12 weeks	Fluoxetine 20-80 Paroxetine 20-50	NR	Higher rates of nausea (37 vs. 32) and abnormal ejaculation (24 vs. 12) with paroxetine Higher rates of diarrhea (19 vs. 12) and weight loss (12 vs. 3) with fluoxetine	No differences	Fair
DeWilde et al., 1993 <sup>[104]</sup>	100	6 weeks	Fluoxetine 20-60 Paroxetine 20-40	58 vs. 43	No differences	No differences	Fair
Fava et al., 1998 <sup>[28]</sup>	128	12 weeks	Fluoxetine 20-80 Paroxetine 20-50	NR	Higher rate of insomnia (29 vs. 20) with paroxetine	Higher rate of sexual side effects with paroxetine (25 vs. 7); higher rates of cardiovascular AEs (11 vs. 5) with fluoxetine	Fair
Gagiano et al., 1993 <sup>[105]</sup>	90	6 weeks	Fluoxetine 20-60 Paroxetine 20-40	87 vs. 96	Higher rate of insomnia (20 vs. 11) with fluoxetine Higher rate of headache (53 vs. 47) with paroxetine	No differences	Fair
Schöne and Ludwig 1993 <sup>[106]</sup>	108	6 weeks	Fluoxetine 20-60 Paroxetine 20-40	NR	Higher rate of vomiting with paroxetine (15 vs. 8) Higher rate of diarrhea with fluoxetine (12 vs. 2)	No differences	Fair
Tignol, 1993 <sup>[107]</sup>	178	6 weeks	Fluoxetine 20 Paroxetine 20	NR	Higher rate of nausea with fluoxetine (10 vs. 4)	No differences	Fair
Fava et al., 2002 <sup>[69, 82, 108]</sup>	284	10-16 Weeks	Fluoxetine 20-60 Paroxetine 20-60 Sertraline 50-200	NR	Higher rate of diarrhea with sertraline than paroxetine (26 vs. 20); higher rate of insomnia with paroxetine and sertraline than fluoxetine (23 vs. 23 vs. 17); higher rate of somnolence with sertraline than fluoxetine or paroxetine	Higher rate of sexual dysfunction with paroxetine	Fair

(16 vs. 11 vs. 10)							
	284	26-32 weeks	Fluoxetine 20-60 Paroxetine 20-60 Sertraline 50-200	NR	Higher rate of significant mean weight gain with paroxetine compared to fluoxetine and sertraline (25.5 vs. 6.8 vs. 4.2)	No differences	Fair
Kroenke et al., 2001 <sup>[109]</sup>	601	36 weeks	Fluoxetine 20 Paroxetine 20 Sertraline 50	NR	No differences	No differences	Fair
Bennie et al., 1995 <sup>[66]</sup>	286	6 weeks	Fluoxetine 20-40 Sertraline 50-100	60 vs. 56	No differences	No differences	Fair
Boyer et al., 1998 <sup>[110]</sup>	242	180 days	Fluoxetine 50-150 Sertraline 20-60	51 vs. 58	No differences	No differences	Fair
Newhouse et al., 2000 <sup>[71, 72]</sup>	236	12 weeks	Fluoxetine 20-40 Sertraline 50-100	89 vs. 88	Higher rate of diarrhea with sertraline (22 vs. 16)	No differences	Fair
Sechter et al., 1999 <sup>[73]</sup>	234	24 weeks	Fluoxetine 20-60 Sertraline 50-150	NR	Higher rate of nausea with sertraline (23 vs. 17)	No differences	Fair
Van Moffaert et al., 1995 <sup>[111]</sup>	165	8 weeks	Fluoxetine 20 Sertraline 50	54 vs. 48	No differences	No differences	Fair
Kiev and Feiger, 1997 <sup>[112]</sup>	60	7 weeks	Fluvoxamine 50-150 Paroxetine 20-50	97 vs. 100	Higher rates of headache (57 vs. 40), nausea (47 vs. 37), dizziness (27 vs. 20), and diarrhea (30 vs. 13) with paroxetine Higher rate of somnolence (40 vs. 30) with fluvoxamine	Higher rates of impotence (21 vs. 14) and ejaculatory abnormality (21 vs. 7) with paroxetine	Fair
Nemeroff et al., 1995 <sup>[31]</sup>	95	7 weeks	Fluvoxamine 50-150 Sertraline 50-200	NR	Higher rates of headache (33 vs. 27), insomnia (35 vs. 27), and diarrhea (24 vs. 14) with sertraline Higher rates of nausea (31 vs. 22), and somnolence (25 vs. 17) with fluvoxamine	Higher rate of sexual dysfunction (28 vs. 10) with sertraline	Fair
Rossini et al., 2005 <sup>[113]</sup>	93	7 weeks	Fluvoxamine 150 Sertraline 200	NR	No differences	No differences	Fair
Aberg-Wistedt et al., 2000 <sup>[30]</sup>	353	8 weeks	Paroxetine 20-40 Sertraline 50-150	NR	NR	NR	Fair
	353	24 weeks	Paroxetine 20-40 Sertraline 50-150	NR	Higher rates of diarrhea (35 vs. 16) and nausea/vomiting (53 vs. 44) with sertraline	Higher rates of decreased libido in males (13 vs. 4) with sertraline Higher rates of ejaculation disorder (14 vs. 5), decreased	

						libido in females (9 vs. 2), and anorgasmia (6 vs. 1) with paroxetine	
<b>SSRIs vs. SSNRIs and SNRIs</b>							
Leinonen et al., 1999 <sup>[114]</sup>	270	8 weeks	Citalopram 20-60 Mirtazapine 15-60	71 vs. 66	Higher rate of nausea (20 vs. 10) with citalopram Higher rate of weight gain (15 vs. 5) with mirtazapine	No differences	Fair
Allard et al., 2004 <sup>[115]</sup>	150	22 weeks	Citalopram 10-20 Venlafaxine 75-100	43 vs. 62	No differences	No differences	Fair
Nierenberg et al., 2007 <sup>[116]</sup>	684	8 weeks	Escitalopram 10 Duloxetine 60	81 vs. 86	Higher rates of nausea with duloxetine (24 vs. 12)	No differences	Fair
Goldstein et al., 2002 <sup>[117]</sup>	173	8 weeks	Fluoxetine 20 Duloxetine 40-120	NR	Higher rates of headache (33 vs. 20), diarrhea (30 vs. 14), and nausea (18 vs. 13) with fluoxetine Higher rates of insomnia (20 vs. 9) and dizziness (16 vs. 6) with duloxetine	No differences	Fair
Alves et al., 1999 <sup>[57]</sup>	87	12 weeks	Fluoxetine 20-40 Venlafaxine 75-150	51 vs. 56	Higher rates of dizziness (10 vs. 2), nausea (33 vs. 28), and vomiting (15 vs. 2) with venlafaxine Higher rate of insomnia (11 vs. 5) with fluoxetine	No differences	Fair
Bielski et al., 2004 <sup>[51]</sup>	198	8 weeks	Escitalopram 20 Venlafaxine 225	68 vs. 85	Higher rates of nausea (24 vs. 6) and somnolence (17 vs. 9) with venlafaxine	Higher rate of ejaculation disorder (23 vs. 7) with venlafaxine; mean changes in vital signs significantly higher with venlafaxine	Fair
Montgomery et al., 2004 <sup>[52]</sup>	293	8 weeks	Escitalopram 10-20 Venlafaxine 75-150	67 vs. 71	Higher rate of nausea with venlafaxine (data NR)	No differences	Fair
Hong et al., 2003 <sup>[76]</sup>	133	6 weeks	Fluoxetine 20-40 Mirtazapine 15-45	58 vs. 71	Higher rates of dizziness (20 vs. 14) and weight gain (8 vs. 3) with mirtazapine Higher rate of nausea (12.1 vs. 0) with fluoxetine	No differences	Fair
Versiani et al., 2005 <sup>[79]</sup>	297	8 weeks	Fluoxetine 20-40 Mirtazapine 15-60	45 vs. 50	Higher rate of weight gain (7 vs. 1) with mirtazapine Higher rate of nausea (24 vs. 16) with fluoxetine	No differences	Fair

Wheatley et al., 1998 <sup>[77]</sup>	133	6 weeks	Fluoxetine 20-40 Mirtazapine 15-60	NR	Higher rates of somnolence (18 vs. 13) and weight gain (12 vs. 0) with mirtazapine Higher rates of headache (18 vs. 9) and nausea (10 vs. 3) with fluoxetine	No differences	Fair
Costa e Silva et al., 1998 <sup>[59]</sup>	382	8 weeks	Fluoxetine 20-40 Venlafaxine 75-225	65 vs. 69	Higher rates of nausea (29 vs. 19), dizziness (8 vs. 3), and somnolence (8 vs. 2) with venlafaxine	No differences	Fair
De Nayer et al., 2002 <sup>[60]</sup>	146	12 weeks	Fluoxetine 20-40 Venlafaxine 75-150	67 vs. 56	Higher rate of nausea (29 vs. 21) for venlafaxine	No differences	Fair
Dierick et al., 1996 <sup>[47]</sup>	314	8 weeks	Fluoxetine 20 Venlafaxine 75-150	56 vs. 63	Higher rates of nausea (28 vs. 14) with venlafaxine	No differences	Fair
Tylee et al., 1997 <sup>[48]</sup>	341	12 weeks	Fluoxetine 20 Venlafaxine 75	72 vs. 81	Higher rates of nausea (35 vs. 18) and vomiting (13 vs. 5) with venlafaxine Higher rate of headache (17 vs. 11) with fluoxetine	No differences	Fair
Nemeroff et al., 2005 <sup>[62]</sup>	308	6 weeks	Fluoxetine 20-60 Venlafaxine 75-225	NR	Higher rates of nausea (40 vs. 22), headache (36 vs. 24), insomnia (22 vs. 15), dizziness (13 vs. 8), and vomiting (11 vs. 5) with venlafaxine	No differences	Fair
Rudolph et al., 1999 <sup>[49]</sup>	301	8 weeks	Fluoxetine 20-60 Venlafaxine 75-225	NR	Higher rates of nausea (36 vs. 20), dizziness (26 vs. 6), and infection (13 vs. 5) with venlafaxine Higher rate of diarrhea (19 vs. 14) with fluoxetine	No differences	Fair
Schatzberg et al. 2006 <sup>[63]</sup>	300	8 weeks	Fluoxetine 20-60 Venlafaxine 37,5-225	94 vs. 92	Higher rates of nausea (45 vs. 23) and headache (26 vs. 18) with venlafaxine	No differences	Fair
Silverstone et al., 1999 <sup>[53]</sup>	368	12 weeks	Fluoxetine 20-60 Venlafaxine 75-225	NR	Higher rates of dizziness (38 vs. 18), nausea (41 vs. 32), and insomnia (32 vs. 25) with venlafaxine	No differences	Fair
Tzanakaki et al., 2000 <sup>[64]</sup>	109	6 weeks	Fluoxetine 60 Venlafaxine 225	46 vs. 49	Higher rates of dizziness (6 vs. 0) and insomnia (13 vs. 2) with venlafaxine Higher rates of nausea (15 vs. 6) and vomiting (6 vs. 0) with	No differences	Fair

					fluoxetine		
Detke et al., 2004 <sup>[118]</sup>	367	8 weeks	Paroxetine 20 Duloxetine 80 Duloxetine 120	NR	Higher rate of nausea (23.6 vs. 11.6 vs. 5.4) with duloxetine 80 and paroxetine Higher rates of somnolence (7.5 vs. 5.8 vs. 2.1) with duloxetine 120 and paroxetine	No differences	Fair
Perahia et al., 2006 <sup>[119]</sup>	392	8 weeks	Paroxetine 20 Duloxetine 80 Duloxetine 120	NR	No differences	No differences	Fair
Benkert et al., 2003 <sup>[81, 120]</sup>	275	6 weeks	Paroxetine 20-40 Mirtazapine 15-45	63 vs. 68	Higher rate of weight gain (15 vs. 4) with mirtazapine Higher rate of nausea (11 vs. 4) with paroxetine	Higher rate of orgasmic dysfunction (14 vs. 3) with paroxetine	Fair
Schatzberg et al., 2002 <sup>[80]</sup>	255	8 weeks	Paroxetine 20-40 Mirtazapine 15-45	83 vs. 80	Higher rate of weight gain (11 vs. 0) with mirtazapine Higher rates of nausea (19 vs. 6) and headache (25 vs. 16) with paroxetine	No differences	Fair
McPartlin et al., 1998 <sup>[55]</sup>	361	12 weeks	Paroxetine 20 Venlafaxine XR 75	70 vs. 70	Higher rate of dizziness (17 vs. 10) with venlafaxine	No differences	Fair
Ballus et al., 2000 <sup>[50]</sup>	84	12 weeks	Paroxetine 20-40 Venlafaxine 75-150	NR	NR	NR	Fair
		24 weeks	Paroxetine 20-40 Venlafaxine 75-150	79 vs. 68	Higher rates of nausea (28 vs. 9) and vomiting (15 vs. 2) with venlafaxine Higher rates of diarrhea (9 vs. 0), headache (40 vs. 18), weight gain (21 vs. 15), and severe AEs (21 vs. 10) with paroxetine	No differences	
Behnke et al., 2003 <sup>[29]</sup>	345	8 weeks	Sertraline 50-150 Mirtazapine 30-45	68 vs. 64	Higher rates of diarrhea (10 vs. 6) and nausea (23 vs. 7) with sertraline Higher rates of somnolence (20 vs. 8) and weight gain (9 vs. 2) with mirtazapine	Greater improvement in sexual functioning shown by CSFQ scores with mirtazapine	Fair
Mehtonen et al., 2000 <sup>[61]</sup>	147	8 weeks	Sertraline 50-100 Venlafaxine 75-150	NR	Higher rate of diarrhea (14 vs. 8) with sertraline Higher rates of dizziness (13 vs. 7) and nausea (36 vs. 29) with venlafaxine	No differences	Good
Shelton et al.,	160	8 weeks	Sertraline 50-150	NR	No differences	No differences	Fair

2006 <sup>[54]</sup>			Venlafaxine 75-225				
Sir et al., 2005 <sup>[56]</sup>	163	8 weeks	Sertraline 50-150 Venlafaxine XR 75-225	NR	Higher rates of headache (44 vs. 32), insomnia (35 vs. 27), and dizziness (33 vs. 26) with sertraline	Statistically significantly greater increase in heart rate (standing: 4.1 vs. 0.4), systolic (supine: 0.8 vs. -3.0 mm Hg) and diastolic (supine: 3.1 vs. -1.4 mm Hg) blood pressure with venlafaxine	Good
<b>SSRIs vs. other second-generation antidepressants</b>							
Coleman et al., 2001 <sup>[16]</sup>	456	8 weeks	Fluoxetine 20-60 Bupropion SR 150-400	NR	Higher rate of nausea (12 vs. 21) with bupropion SR Higher rate of somnolence (11 vs. 3) with fluoxetine	Significantly more sexual adverse events with fluoxetine (orgasm dysfunction: 33 vs. 15)	Fair
Feighner et al., 1991 <sup>[26]</sup>	123	6 weeks	Fluoxetine 20-80 Bupropion SR 225-450	NR	NR	Higher rate of sexual dysfunction (impotence) with fluoxetine (7.6 vs. NR)	Fair
Rush et al., 1998 <sup>[121]</sup>	125	8 weeks	Fluoxetine 20-40 Nefazodone 200-500	NR	Higher rates of headache (48 vs. 56), nausea (25 vs. 36), and dizziness (8 vs. 22) with nefazodone Higher rates of diarrhea (26 vs. 16) and insomnia (11 vs. 6) with fluoxetine.	Higher rate of impotence (11 vs. 0) with fluoxetine	Fair
Beasley Jr et al., 1991 <sup>[84]</sup>	126	6 weeks	Fluoxetine 20-60 Trazodone 100-400	NR	Higher rates of somnolence (20 vs. 45), dizziness (6.2 vs. 21.3) and headache (28 vs. 22) with trazodone Higher rate of insomnia (9 vs. 3) with fluoxetine	No differences	Fair
Perry et al., 1989 <sup>[87]</sup>	40	6 weeks	Fluoxetine 20-60 Trazodone 50-400	43 vs. 37 (2+ events)	Higher rates of somnolence (37 vs. 19) and dizziness (21 vs. 14) with trazodone Higher rate of diarrhea (14 vs. 0) with fluoxetine	No differences	Fair
Kennedy et al. 2006 <sup>[122]</sup>	141	8 weeks	Paroxetine 20-40 Bupropion SR 150-300	NR	NR	Worsening of sexual functioning in men on paroxetine but not in women. No changes in sexual functioning in patients on bupropion	Fair
Weihls et al., 2000 <sup>[123]</sup>	100	6 weeks	Paroxetine 10-40 Bupropion SR 100-300	NR	Significantly higher rates of somnolence (27 vs. 6) and diarrhea (21 vs. 6) with	No differences	Fair



					paroxetine Higher rate of headache (35 vs. 19) with bupropion SR		
Baldwin et al., 1996 <sup>[124]</sup>	206	8 weeks	Paroxetine 20-40 Nefazodone 200-600	78 vs. 84	Higher rate of headache (35 vs. 25) and dizziness (17 vs. 9) with nefazodone Higher rate of somnolence with paroxetine (24 vs. 16)	No differences	Fair
Hicks et al., 2002 <sup>[125]</sup>	40	8 weeks	Paroxetine 20-40 Nefazodone 400-600	NR	Higher rates of dizziness (25 vs. 15) and somnolence (40 vs. 25) with nefazodone Higher rate of gastrointestinal side effects (i.e., upset stomach, diarrhea, nausea or vomiting) with paroxetine (65 vs. 40)	Higher rate of sexual dysfunction (20 vs. 0) with paroxetine Higher rates of suicidality (5 vs. 0) with nefazodone	Fair
Kasper et al., 2005 <sup>[86]</sup>	108	6 weeks	Paroxetine 20-40 Trazodone 150-450	26.4 vs. 34.5	Higher rate of headache with trazodone (8 vs. 07) Higher rate of nausea with paroxetine (11 vs. 2)	No differences	Fair
Coleman et al., 1999 <sup>[15]</sup>	364	8 weeks	Sertraline 50-200 Bupropion SR 150-400	NR	Higher rate of diarrhea with sertraline(18 vs. 12) Higher rate of headache with bupropion SR (34 vs. 27)	Significantly more sexual adverse events with sertraline (39 vs. 13)	Fair
Croft et al., 1999 <sup>[14]</sup>	360	8 weeks	Sertraline 50-200 Bupropion SR 150-400	NR	Significantly higher rates of nausea (21 vs. 18), diarrhea (27 vs. 7), insomnia (18 vs. 13), and somnolence (17 vs. 3) with sertraline. Higher rate of headache with sertraline (40 vs. 34)	Sertraline treatment was more often associated with sexual dysfunction compared with bupropion SR (sexual desire disorder: 28 vs. 19, significantly more orgasmic dysfunction >40 vs. NR )	Fair
Kavoussi et al., 1997 <sup>[27, 70]</sup>	248	16 weeks	Sertraline 50-200 Bupropion SR 100-300	NR	Significantly higher rates of nausea (30 vs. 10), diarrhea (22 vs. 3), and somnolence (13 vs 2) with sertraline	Significantly higher rate of sexual adverse events with sertraline (men: 61 vs. 10; women 41 vs.7)	Fair
Segraves et al, 2000 <sup>[13]</sup>	248	16 weeks	Sertraline Burpopion SR	NR	NR	Significantly more sexual adverse events with sertraline (sexual arousal disorder, orgasm dysfunction, or premature ejaculation (men only); men: 63 vs 15; women: 41 vs. 7)	Fair
Ferguson et al, 2001 <sup>[126]</sup>	105	8 weeks	Sertraline Nefazodone	97 vs. 100	No differences	Higher reemergence rates of sexual dysfunction for	Fair

Feiger et al., 1996 <sup>[32]</sup>	160	6 weeks	Sertraline 50-200 Nefazodone 100-600	95 vs. 96	Higher rate of diarrhea with sertraline (20 vs. 9) Higher rates of dizziness (32 vs. 7) and nausea (32 vs. 27) with nefazodone	sertraline (76 vs. 26) Sertraline had more adverse effects on sexual dysfunction	Fair
Munizza et al., 2006 <sup>[127]</sup>	122	6 weeks	Sertraline 50-100 Trazodone 150-450	54 vs. 45	No differences	No differences	Fair
<b>SNRIs vs. SNRIs</b>							
Guelfi et al., 2001 <sup>[78]</sup>	157	8 weeks	Mirtazapine 45-60 Venlafaxine 225-375	74.4 vs. 65.8	Higher rate of weight gain with mirtazapine (10 vs. 5)	No differences	Fair
<b>SNRIs vs. other second-generation antidepressants</b>							
Halikas et al., 1995 <sup>[75]</sup>	150	6 weeks	Mirtazapine 5-35 Trazodone 40-280	NR	Higher rates of headache (20 vs. 14) and dizziness (27 vs. 22) with trazodone	Higher rate of cardiovascular adverse events (palpitations + tachycardia) with trazodone (24 vs. 6)	Fair
van Moffaert et al., 1995 <sup>[128]</sup>	200	6 weeks	Mirtazapine 24-72 Trazodone 150-450	NR	Higher rates of somnolence with trazodone (Day 14: 21 vs. 10; day 42: 13 vs. 5)	No differences	Fair
Thase et al., 2006 <sup>[129]</sup>	348	12 weeks	Venlafaxine XR 150-225 Bupropion XL 300-450	NR	Higher rates of nausea (26 vs. 15) and somnolence (7 vs. 1) for venlafaxine	Significantly greater sexual functioning scores for bupropion	Fair
Cunningham et al., 1994 <sup>[85]</sup>	225	6 weeks	Venlafaxine 75-200 Trazodone 150-400	NR	Significantly higher rates of somnolence (61 vs. 43), dizziness (36 vs. 17), and weight gain (NR) with trazodone Significantly higher rates of weight loss (NR) and nausea (44 vs. 19) with venlafaxine	No differences	Fair
<b>Other second-generation antidepressants vs. other second-generation antidepressants</b>							
Weisler et al., 1994 <sup>[88]</sup>	124	6 weeks	Bupropion 225-450 Trazodone 150-400	NR	Significantly higher rate of somnolence (45 vs. 8), with trazodone Higher rates of diarrhea (12 vs. 5) and dizziness (30 vs. 21) with trazodone Higher rates of headache (34 vs. 23) and insomnia (15 vs. 5.0) with bupropion Statistically significant difference in mean weight change (+2.5 lbs vs. -1.2 lbs)	NR	Fair

CSFQ: Changes in Sexual Functioning Questionnaire; NR: not reported; SR, sustained release; SNRI, serotonin-norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors; XR, extended release.

**Table S4: Study characteristics, main findings, and quality ratings of observational studies and open-label trials**

Study	Design, Interventions	N	Results	Quality Rating
<b>General Tolerability and Discontinuation</b>				
Mackay et al., 1997, 1999 <sup>[42, 43]</sup>	Prescription event monitoring, Fluoxetine, fluvoxamine, nefazodone, paroxetine, venlafaxine	> 60,000	Venlafaxine had highest rate of nausea and vomiting; paroxetine highest rate of sexual side effects; among SSRIs, most overall adverse events with fluvoxamine	N/A
Meijer et al., 2002 <sup>[74]</sup>	Observational study Sertraline vs. SSRIs	1,251	Significantly more diarrhea with sertraline	Fair
<b>Suicidality (Self-harm; Suicide Attempts; Completed Suicides)</b>				
Didham et al., 2005 <sup>[19]</sup>	Retrospective cohort study, citalopram, fluoxetine, paroxetine	> 57,000	Significant association between self-harm and SSRIs; no differences in risk among drugs	Fair
Jick et al., 2004 <sup>[20]</sup>	Case-control study; fluoxetine, paroxetine	159,810	No differences in risk among drugs	Fair
Jick et al., 1995 <sup>[21]</sup>	Retrospective cohort study, nested case-control study, fluoxetine, trazodone, first-generation antidepressants	172,598	Significantly higher risk of suicide for fluoxetine and mianserin compared to dothiepin	Fair
Khan et al., 2003 <sup>[22]</sup>	Retrospective cohort study, bupropion, citalopram, fluoxetine, mirtazapine, nefazodone, paroxetine, venlafaxine	48,277	No differences in the rates of suicides	Fair
Martinez et al. 2005 <sup>[18]</sup>	Case-control study, citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, TCAs	146,095	No differences in risk of suicide or non-fatal self-harm between SSRIs and TCAs or among individual SSRIs	Fair
Rubino et al. 2007 <sup>[23]</sup>	Retrospective cohort study, citalopram, fluoxetine, venlafaxine	219,088	Significantly higher rates of suicide for venlafaxine than for citalopram and fluoxetine	Fair
<b>Sexual Dysfunction (Lack of sexual desire, pleasure, arousal, and orgasm)</b>				
Clayton et al., 2002 <sup>[25]</sup>	Cross-sectional survey, Bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, venlafaxine	6,297	Highest risk for paroxetine, lowest risk for bupropion	Fair
Kennedy et al., 2000 <sup>[130]</sup>	Prospective cohort study, paroxetine, sertraline, venlafaxine; moclobemide	174	No differences	Fair
Landen et al., 2005 <sup>[131]</sup>	Cross-sectional study Citalopram, paroxetine	119	No differences	Fair
Montejo et al, 2001 <sup>[24]</sup>	Prospective cohort study, Citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, venlafaxine	1,022	Highest incidence of sexual dysfunction for citalopram, paroxetine, and venlafaxine; lowest for mirtazapine and nefazodone	Fair
Philipp et al, 2000 <sup>[132]</sup>	Prospective cohort study, Fluoxetine, fluvoxamine, paroxetine, sertraline; moclobemide	268	No difference among SSRIs	Fair
<b>Cardiovascular Events</b>				
Thase et al., 2005 <sup>[83]</sup>	Post-hoc data analysis Fluoxetine, paroxetine, duloxetine	1,873	Greater change in heart rate for duloxetine than for fluoxetine and paroxetine	N/A
<b>Seizures</b>				
Dunner et al., 1998 <sup>[35]</sup>	Uncontrolled, open-label trial Bupropion	3,100	Rate of seizures for bupropion within reported range of other antidepressants	Fair
Johnston et al., 1991 <sup>[34]</sup>	Uncontrolled, open-label trial	3,341	Rate of seizures for bupropion within range of other antidepressants	Fair
<b>Other Adverse Events</b>				
Buckley et al.,	Post-marketing surveillance	47,329	Highest rate of fatal toxicity for	N/A

2005 <sup>[37]</sup>		venlafaxine		
Kirby et al, 2002 <sup>[133]</sup>	Retrospective cohort study, 199 SSRIs, venlafaxine		Higher rate of hyponatremia in patients on SSRIs and venlafaxine	Fair
Mackay et al., 1999 <sup>[134]</sup>	Postmarketing surveillance	11, 834	Incidence of serotonin syndrome in patients treated with nefazodone was 0.4 per 1000 patient-months	N/A
Thapa et al, 1998 <sup>[38]</sup>	Retrospective cohort study, 2,428 Fluoxetine, paroxetine, sertraline, trazodone		No differences in the risk of falls	Fair
Whyte et al., 2003 <sup>[36]</sup>	Prospective observational SSRI, TCAs, venlafaxine	538	Seizures more common in venlafaxine overdose than TCAs or SSRI overdose	Good

N/A: not applicable; NR: not reported; RCT: randomized controlled trial; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants.

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