

**Table S1.** Characteristics of studies (n = 82) included in the systematic review and meta-analysis of 5-HTTLPR and antidepressant response and tolerability in patients with psychiatric disorders.

Study (Author et al.)	Pubmed ID	Study Design	N	Age [Mean Years]	Sex [Female (%)]	Ancestry/ Race	Diagnosis	Antidepressant( s) Used	Other Drug(s) Used	SLC6A4 Variants Tested	Phenotype(s)	Phenotype(s) Measurement	Main Findings	Quality Score
Abdelmalik et al. (2009) [1]	18983505	Prospective Cohort Study	19	44.5	58	Not Available	Mood Disorder and/or Anxiety	Paroxetine	Depakine, Levothyroxin, Omeprazole	5-HTTLPR/ rs25531	Platelet Function	Bleeding Severity Scores	Paroxetine impairs platelet function by decreasing the levels of platelet serotonin and platelet $\beta$ -TG. These effects are mediated by 5HTTLPR, with pronounced effects in patients without La alleles	11
Akcali et al. (2008) [2]	18688140	Prospective CaseControl Study	264 CTTH=12 6 Healthy Controls=138	CTTH=38 Healthy Controls=23	CTTH=87 Healthy Controls=85	Not Available	CTTH	Amitriptyline, Citalopram, Sertraline	Not Available	5-HTTLPR, VNTR	Improvement in headache symptoms	VAS Scores	No statistically significant association between genotype and study outcome	12
AlOlaby et al. (2017) [3]	28242040	Prospective PlaceboControlled Study	51	46.1	11.8	Not Available	Children with Fragile X syndrome	Sertraline	Not Available	5-HTTLPR	Cognitive Improvement	MSEL Scores, CGI-I, VAS Scores, SPM Scores	Patients with the LL genotype showed a significant improvement in social participation scores relative to the placebo group	12
Basu et al. (2015) [4]	26261165	Prospective Cohort Study	55	35	42	North Indian	MDD	Escitalopram	Anxiolytics, sedatives and hypnotics allowed	5-HTTLPR	Depression Severity and side effects	MADRS, CGI, UKU Scale	No statistically significant association between genotype and study outcome	14
Baumer et al. (2006) [5]	16945343	Retrospecti ve Case Control Study	52	15.1	31	Caucasian (88.2%), Hispanic (5.9%), Multiracial (5.9%)	Bipolar and Subsyndromal Participants	Fluoxetine, Paroxetine, Sertraline, Citalopram, Fluvoxamine, Escitalopram,	Atypical antidepressant s: Bupropion, Venlafaxine, Trazadone, Serzone	5-HTTLPR	AIM Status	YMRS	All 3 participants with the SS genotype responded negatively to antidepressants	17
Billett et al. (1997) [6]	9322235	Retrospecti ve CaseControl Study	144	36.3	53	Not Available	OCD	Fluoxetine, Clomipramine, Fluvoxamine, Paroxetine, Sertraline	Not Available	5-HTTLPR	Severity of OCD Symptoms	3 Point Rating Scale	No statistically significant association between genotype and study outcome	11

Bishop <i>et al.</i> (2009) [7]	19204908	Naturalistic Prospective Study	115	29	76	Caucasian (92%), Hispanic (3%), Asian (2%), African	MDD	Citalopram, Escitalopram, Fluoxetine, Paroxetine, Sertraline, Fluvoxamine	Not Available	5-HTTLPR	Sexual WellBeing	CSFQ	Females with the LL genotype who were taking oral contraceptive medication had statistically significant lower	13
						American/Other (2%)							CSFQ scores than makes with the LL genotype. No relationship was observed in females who were not taking oral contraceptives	
Bloch <i>et al.</i> 2010 [8]	19995670	Prospective Placebo Controlled Study	32	41	25	Northern Israel Population	Schizophrenia or Schizoaffective Disorder	Bupropion	Placebo	5-HTTLPR	Smoking Behavior and Schizophrenia Severity	FTND, BPRs, PANSS	Male subjects with SS or SL genotype showed a reduction in cigarette consumption as a result of treatment	12
de Aguiar Ferreira <i>et al.</i> (2009) [9]	18534687	Retrospective Case Study	112	39	71	Caucasian (Brazilian)	Bipolar Disorder	Venlafaxine, SSRIs, Tricyclics	Mood stabilizers: Lithium, Sodium Divalproate, Carbamazepine, Oxcarbazepine, Lamotrigine	5-HTTLPR	AAM Status	Interviewed by psychiatrists and followed the DSM-IV criteria	S carriers (LS/SS genotypes) are more prone to have a manic/hypomanic episode associated with antidepressants	11
Denys <i>et al.</i> (2007) [10]	17503984	Prospective Parallelgroup Study	91	33.2	61	European Descent	OCD	Venlafaxine, Paroxetine	Not Available	5-HTTLPR	Antidepressant side effects	UKU Scale	Response in venlafaxine treated OCD patients is associated with the SL genotype	13
Di Bella <i>et al.</i> (2002) [11]	12082589	Prospective CaseControl Study	372	33.37	52	Caucasian (Italian Descent)	OCD	Fluvoxamine	Not Available	5-HTTLPR	Clinical Outcomes	Treatmentemergent adverse effects were assessed in each person visit	Participants with the SS genotype developed new or worsening insomnia and agitation	16

Dombrovski <i>et al.</i> (2010) [12]	19996755	Prospective Cohort Study	92	81 (Estimate)	62	75% Caucasian	Dementia	Citalopram	Risperidone	5-HTTLPR	Clinical Outcomes	NBR5, BPRS, UKU, MMSE, CIRS-G	Participants with the SS genotype had the shortest time- totreatment discontinuation. Excluding African American participants, participants with the SS or SL genotypes predicted greater adverse effects of citalopram. Participants with the SS or SL genotype taking risperidone predicted poorer early response of psychosis symptoms	13
Durham <i>et al.</i> (2004) [13]	12955294	Prospective Placebo-	217	69	53	Caucasian (95.4%), Black	MDD	Sertraline	Not Available	5-HTTLPR	Clinical Outcomes and	HAM-D, CGI-I	There was a significant increase in number of CGI-I	11
Controlled Study														
						(2.8%), Other (1.38%), Asian (0.46%)					Response Time	responders in the LL genotype group at weeks 1 and 2		
Frye <i>et al.</i> (2015) [14]	25611077	Retrospective CaseControl Study	295	Not Available	59	Caucasian	Bipolar	SSRIs	Not Available	5-HTTLPR, 5-HTTLPR/rs 25531, VNTR	AIM status	DSM-IV structured interviews	Bipolar I subtype was the only clinical risk factor associated with AIM	9
Garfield <i>et al.</i> (2014) [15]	24021217	Prospective PlaceboControlled Study	177	71	67	Not Available	GAD	Escitalopram	Low-dose benzodiazepines if already using for at least 2 months	HTTLPR/rs 25531	Clinical Outcomes	UKU	Greater dry mouth was observed in participants with the low expressing genotype. Greater sexual desire was observed in patients with the high expressing genotype	13
Gressier <i>et al.</i> (2014) [16]	25257397	Naturalistic Prospective Study	103	Nonmenopausal: 36.6 Menopausal: 60.8	72	Caucasian	Unipolar or Bipolar	Paroxetine, Fluoxetine, Escitalopram, Citalopram, Sertraline	Anxiolytics and hypnotics at minimal doses	5-HTTLPR	Clinical Outcomes	HAMD-17, CGI-I	In non- menopausal women, the L allele was associated with high antidepressant efficacy.	10

Han <i>et al.</i> (2008) [17]	18197080	Prospective Cohort Study	225	Not Available	0	Korean	Smokers	Bupropion	Not Available	5-HTTLPR, VNTR	Abstinence of Smoking	Assessed during visits	Participants with the LL genotype showed a higher abstinence rate than other participants	11
Higuchi <i>et al.</i> (2009) [18]	19649213	Prospective Cohort Study	80	52.4	65	Not Available	MDD	Milnacipran	Brotizolam	5-HTTLPR, VNTR	Antidepressant side effects	UKU	No statistically significant between genotype and study outcome	15
Hougardy <i>et al.</i> (2008) [19]	18279474	Naturalistic Prospective Study	43	48.4	74	Not Available	Patients taking Paroxetine for >4 weeks	Paroxetine	Not Available	5-HTTLPR	Bleeding time	PFA, Trough paroxetine levels, complete blood count	No statistically significant association between genotype and study outcome	11
Hu <i>et al.</i> (2007) [20]	17606812	Prospective CaseControl Study	2626	Depressed: 42.4 Control: 51.9	58	Caucasian (81.6%), Black (14.2%), Other (6%)	MDD	Citalopram	Not Available	5-HTTLPR	Clinical Outcomes	QIDS-C Score	The LA allele was associated with adverse effect burden in the entire sample	11
Huezo-Diaz <i>et al.</i> (2009) [21]	19567893	Prospective Cohort Study	810	Range: 19-72	63.5	Caucasian (European Descent)	MDD	Nortriptyline, Escitalopram	Hypnotics	5-HTTLPR, 5-HTTLPR/rs25531, STin2	Clinical Outcomes	MADRS, HRSD-17, selfreport BDI	Among participants taking Escitalopram, those carrying the long-allele improved more than the shortallele carriers	14
Ishiguro <i>et al.</i> (2011) [22]	21688171	Prospective Cohort Study	65	36	65	Japanese	PD	Paroxetine	Brotizolam, and Lorazepam	5-HTTLPR	Clinical Outcomes	PAS	Participants with the SS genotype showed improved clinical response after 2 weeks. No significant	12
difference in clinical response was observed at 4 weeks														
Joyce <i>et al.</i> (2005) [23]	15856721	Prospective Cohort Study	195	31	57	Not Available	MDD with Bipolar II, Melancholia, Atypical, Recurrent	Fluoxetine, Nortriptyline	Oral contraceptive, hypnotics	5-HTTLPR	Diurnal Variation	Amino acid ratio and revised spectrophotofluorimetric technique	Participants with reversed diurnal variation have significantly higher Trp:LNAA ratios, and are more likely to have the allele of the 5-HTTLPR	10

Kato <i>et al.</i> (2006) [24]	16874005	Prospective Cohort Study	100	43.7	44	Japanese	MDD	Paroxetine, Fluvoxamine	Not Available	5-HTTLPR	Clinical Outcomes	HAM-D	There were statistically significant greater number of responders among the L allele carriers at weeks 4 and 6	13
Kenna <i>et al.</i> (2009) [25]	19032576	Prospective Cohort Study	15	44.1	20	Not Available	Alcoholdependent	Sertraline	Ondansetron	5-HTTLPR	Alcohol Dependency Severity	Alcohol Consumption using TLFB	Participants taking Ondansetron with the LL genotype showed a significant improvement in drinking outcomes	12
Kenna <i>et al.</i> (2014) [26]	25212749	Prospective PlaceboControlled Study	49	43	39	Caucasian (53.1%), AfricanAmerican (28.6%), Hawaiian or Alaskan Multiethnic (10.2%), Hispanic (6.1%), American Indian (2%)	Non-treatment seeking alcohol dependent individuals	Sertraline	Ondansetron	5-HTTLPR, VNTR	Alcohol Dependency Severity	Alcohol Consumption using TLFB	No statistically significant association between genotype and study outcome.	15
Kranzler <i>et al.</i> (2011) [27]	21192139	Prospective PlaceboControlled Cohort Study	134	Range:1 8-65	19.5	Not Available	Alcohol Dependency	Sertraline	Not Available	5-HTTLPR	Alcohol Dependency Severity	Alcohol Consumption using TLFB, SIP, GGTP	In the LL genotype group, the effects of medication group varied by age of onset.	12
Kranzler <i>et al.</i> (2012) [28]	21981418	Prospective Case-Controlled Study	134	47.5	19	Caucasian (92%)	Alcohol Dependency	Sertraline	Not Available	5-HTTLPR	Alcohol Dependency Severity	Alcohol Consumption using TLFB	Late-onset alcoholic participants taking Sertraline with the LL genotype had fewer drinking days than the placebo group at the 3-month follow-up	10
Kranzler <i>et al.</i> (2013) [29]	23145795	Prospective Cohort Study	134	47.5	19	Caucasian (European Descent) (92%)	Alcohol Dependency	Sertraline	Not Available	5-HTTLPR	Alcohol Dependency Severity and Daily Mood	Daily surveys through IVR technology	Anxiety was a key moderator of the pharmacogenetic effects on drinking severity outcomes	12

Kronenberg <i>et al.</i> (2007) [30]	18315446	Prospective Cohort Study	74	7-18	45	Ashkenazi Background	MDD	Citalopram	Not Available	5-HTTLPR	Clinical Outcomes	K-SADS-PL, CGI-S, CGI-I, CDRS-R, SCARED	Participants with the SS genotype showed a poorer improvement in depressive symptoms, exhibited lower rates of agitation and had consistently higher scores of suicidality compared to the participants with SL or LL genotype	12
Lancôt <i>et al.</i> (2010) [31]	20515362	Prospective Cohort Study	90	39.9	44	Caucasian (52.2%), Other (34.4%), Asian (13.3%)	Traumatic Brain Injury with Major Depressive Episode	Citalopram	Not Available	5-HTTLPR, 5-HTTLPR/rs25531	Clinical Outcomes	HAMD	The SS genotype was significantly predictive of an adverse drug event index, accounting for 6.9% of the variance. The SL genotype had a higher adverse event index value compared to the SS group	12
Lee <i>et al.</i> (2010) [32]	20664233	Prospective Cohort Study	84	44.6	60	Korean	MDD	Venlafaxine	No other psychotropic drugs permitted	5-HTTLPR, 5-HTTVNTR	Clinical Outcomes	HAM-A, BAI, HAM-D, MADRS, BDI, Toronto side effect scale	Participants with the LL and LS genotype taking venlafaxine was associated with treatment response at week 4	13
Lee <i>et al.</i> (2018) [33]	29030421	Prospective PlaceboControlled Study	301	62.7	38	South Korean	Patients with acute stroke (within 21 days of onset). Patients with history of depression were excluded.	Escitalopram	Not Available	5-HTTLPR, 5-HTTVNTR	Depression Symptoms and Cognitive Function	mRS, NIHSS, MADRS, MoCA	No statistically significant association between genotype and study outcome	12
Lenze <i>et al.</i> 2010 [34]	21105279	Prospective PlaceboControlled Study	125	71.5	62	Caucasian	GAD	Escitalopram	Benzodiazepines	5-HTTLPR/rs25531	Clinical Outcomes	CGI-I, PSWQ, HAM-A	Escitalopram had no efficacy in the La-group but had moderate efficacy in the La+ group	13
Liu <i>et al.</i> (2018) [35]	29310115	Prospective CaseControl Study	244	45	60	Chinese	Patients with Globulus Pharyngeas with Anxiety and Depression	Amitriptyline, Paroxetine	Not Available	5-HTTLPR	Clinical Improvements and upper esophageal sphincter pressure	HAM-A, HAM-D	There was a significant association between the SS genotype and response to antidepressant treatment	14

Lohoff <i>et al.</i> (2013) [36]	22907732	Prospective Cohort Study	112	>18	Not Available	Caucasian (72%)	GAD	Venlafaxine	Benzodiazepine Anxiolytics, and Hypnotics	5-HTTLPR/rs 25531	Clinical Outcomes	HAM-A, CGI	Caucasian subjects who had the La/La genotype showed a significant reduction in HAM-A scores	12
														and better treatment response compared with S carriers at 6 months
Mandelli <i>et al.</i> (2009) [37]	19332357	Prospective Cohort Study	86	45.7	51	Caucasian (Italian population)	Bipolar I, Bipolar II, Cyclothymic Disorder	Conventional antidepressants	Mood Stabilizers, antipsychotics, sedative/anxiolytic drugs	5-HTTLPR, 5-HTTVNTR, 5-HTTLPR/rs 25531	Clinical Outcomes	HAMD	A high harm avoidance impaired outcome was associated with carriers of the S allele	13
Maron <i>et al.</i> (2009) [38]	19272758	Prospective PlaceboControlled Study	135	31.1	68	Not Available	MDD	Escitalopram	Hormonal contraceptives, Zolpidem, Zopiclone	5-HTTLPR, 5-HTTLPR/rs 25531	Clinical Outcomes	MADRS, HAM-D, CGI, BDI	Patients carrying the S allele may have increased risk for headaches, induced by escitalopram.	14
Masoliver <i>et al.</i> (2006) [39]	16395126	Prospective CaseControl Study	288	Not Available	Not Available	Not Available	Bipolar or Unipolar Disorder	Tricyclics, Monoamine oxidase inhibitors, SSRIs, Venlafaxine	Lithium	5-HTTLPR, 5-HTTVNTR	History of AIM	DSM-IV Criteria	Association analysis showed a higher rate of the SS genotype among patients with a history of AIM	11
Miguita <i>et al.</i> (2011) [40]	21625751	Prospective Cohort Study	41	20+	44	Not Available	OCD	Tricyclics, SRIs	Clomipramine	5-HTTLPR, 5-HTTVNTR	Clinical Outcomes	Y-BOCS	No statistically significant between genotype and study outcome	12
Monteleone <i>et al.</i> (2005) [41]	15940301	Prospective Naturalistic Study	47	>18 years	100	Caucasian	Bulimia	Fluoxetine, Paroxetine, Sertraline, Fluvoxamine, Citalopram, Escitalopram	Not Available	5-HTTLPR	Bulimia Severity	The eating disorder inventory-2, the bulimia investigation test Edinburgh, MADRS	Participants with the SS genotype were significantly more likely to be in the non-responder group than the participants with an SL or LL genotype	11
Murata <i>et al.</i> (2010) [42]	20075642	Prospective Cohort Study	56	45.9	57	Japanese	MDD, Anxiety Disorder, or pain disorder	Paroxetine	Tandospirone, Benzodiazepines, NonBenzodiazepines	5-HTTLPR, 5-HTTVNTR	Paroxetine Discontinuation Emergent Events	Qualitative Assessment of Symptoms	No statistically significant between genotype and study outcome	14

Murphy <i>et al.</i> (2004) [43]	15520364	Prospective Cohort Study	246	>65	52	Caucasian (92%)	MDD	Mirtazapine, Paroxetine	Not Available	5-HTTLPR	Clinical Outcomes	Adverse Event rating using a 3-point scale	Carriers of the S allele taking Paroxetine experienced more severe adverse events and had more discontinuations. Carriers of the S allele taking Mirtazapine had less severe adverse events and fewer discontinuations	12
Mushtaq <i>et al.</i> (2012) [44]	21962566	Prospective Cohort Study	226	41.4	55	Not Available	PTSD	Sertraline	Not Available	5-HTTLPR	Clinical Outcomes, Adverse Events	CAPS, IES[R], CGI-S	The improvement slope at 12 weeks was significantly steeper in the group with the LL genotype	15
compared to the LS and SS														
Najjar <i>et al.</i> (2015) [45]	26262902	Prospective Cohort Study	44	13.4	33	Caucasian (60%), African American (18%), Hispanic (16%), Asian (4%), African American/Hispanic (2%)	ASD	Escitalopram	Not Available	5-HTTLPR, 5-HTTLPR/rs25531	Sameness and Irritability Symptoms	RBS-R, ABCCV	No statistically significant association between genotype and study outcome	12
Ng <i>et al.</i> (2006) [46]	16580768	Prospective Cohort Study	45	41	38	Chinese (66.7%), Caucasian (33.3%)	MDD	Sertraline	Hypnotics (Zopiclone), Anxiolytics (Lorazepam)	5-HTTLPR	Clinical Outcomes	HDRS, CGI, LUNBERS	No statistically significant association between genotype and study outcome	11



Ng <i>et al.</i> (2013) [47]	24014145	Prospective Cohort Study	106	44	60	Caucasian (76%), Han Chinese (24%)	MDD	Escitalopram, Venlafaxine	Not Available	5-HTTLPR, 5-HTTVNTR	Clinical Outcomes	HDRS, UKU	Participants with the LL genotype was associated with significantly greater HDRS score reduction compared to the SS genotype among Caucasian subjects taking Escitalopram. Response rates were significantly higher for participants with the LL genotype than LS or SS.	11
Ng <i>et al.</i> (2016) [48]	27023264	Prospective Cohort Study	35	>18	Not Available	Not Available	MDD	Desvenlafaxine	Not Available	5-HTTLPR	Clinical Outcomes	HDRS, CGI, UKU	No statistically significant between genotype and study outcome	13
Owley <i>et al.</i> (2010) [49]	20020537	Prospective Cohort Study	58	9.75	17	Caucasian (83%), African American (10%), Asian (3%), Hispanic (3%)	ASD	Escitalopram	Not Available	5-HTTLPR	Clinical Outcomes	ABC-CV	No statistically significant between genotype and study outcome	13
Ozbek <i>et al.</i> (2014) [50]	25518026	Prospective Cohort Study	69	Range:2 1-59	0	Caucasian (Turkish)	Premature Ejaculation	Paroxetine	Not Available	5-HTTLPR	Clinical Outcomes	Intravaginal Ejaculatory Latency Time, International Index of Erectile Function Scores	Participants with the S allele were significantly more likely to belong to the responder group	12
Park <i>et al.</i> (2016) [51]	26508020	Prospective Cohort Study	24	39.5	58	Korean	PD	Escitalopram, Paroxetine, Sertraline, Venlafaxine	Not Available	5-HTTLPR	PD Severity	PDSS	Unable to analyze the relationship of genotype and outcome because of low statistical power	10
Perlis <i>et al.</i> (2003) [52]	14573314	Prospective Cohort Study	36	36	53	Caucasian (nonLatino)	MDD	Fluoxetine	Not Available	5-HTTLPR	Clinical Outcomes	HAMD-17	Patients with the S allele are at higher risk for developing insomnia or agitation with fluoxetine treatment	12

Perna <i>et al.</i> 2005 [53]	16034444	Prospective Cohort Study	92	34	55	Italian Descent	PD (with or without agoraphobia)	Paroxetine	Not Available	5-HTTLPR	PD Severity	PASS, FQ	Good responders were significantly more frequent among female LL and LS carriers	13
Peters <i>et al.</i> (2016) [54]	26303700	Retrospecti ve PlaceboControlled Cohort Study	175	80	46	Caucasian (70%), African American (16.6%), Other (6.9%), Asian (3.4%), Pacific Islander/Ha waiian (1.1%)	Alzheimer's Dementia	Citalopram	Placebo	5-HTTLPR	Clinical Outcomes	CGI-I, Hamilton Depression Scale	No statistically significant between genotype and study outcome	12
Popp <i>et al.</i> (2006) [55]	16515395	Retrospecti ve Cohort Study	109	49	61	Caucasian (97%), Turkish (1%), Libyan (1%)	MDD	Mirtazapine, Citalopram, Escitalopram, Sertraline, Venlafaxine, Paroxetine, Amitriptyline, Reboxetine, Trimipramine, Fluoxetine, Clomipramine, Opi Pramol, Tranlycypromin e	Doxepin,	5-HTTLPR, 5- HTTVNTR	Clinical Outcomes	CGI	Patients predominantly on HTT-blocking antidepressants with the SS genotype suffered more frequently from side effects	13
Putzhamme r <i>et al.</i> (2005) [56]	15322730	Prospective Cohort Study	62	Mean betwee n 40-45	69	Not Available	MDD	SSRIs, Tricyclics	Not Available	5-HTTLPR	Motor Activity	Mini- Motionlogger Actograph Basic	Nighttime motor activity was significantly higher in participants taking SSRIs with the LL genotype in comparison to the SL and SS genotype	13
Quaak <i>et al.</i> (2012) [57]	21658141	Prospective PlaceboControlled Study	214	51.5	51	Not Available	Current Daily Smokers	Bupropion, Nortriptyline	Not Available	5-HTTLPR, 5- HTTVNTR, 5-	Cessation of Smoking	Urinary Nicotine Values, Abstinence Rates	Participants with the LS or LL genotype who were treated with Bupropion showed increased	11
													levels of abstinence. Effects were not significant for those with the SS genotype	
										HTTLPR/rs 25531				

Rahikainen <i>et al.</i> (2017) [58]	28608626	Retrospective Matched Case Study	633 (Deceased Patients)	47	55.4	Not Available	Autopsies positive for Citalopram	Citalopram	Not Available	5-HTTLPR/rs 25531	Type of Death (Suicide)	Death Classification (violent of non-violent suicide)	There was a significant association between males with the SS genotype and violent suicide. The SS genotype was associated with repeated suicide attempts and violent suicide attempts	12
Rotberg <i>et al.</i> (2013) [59]	23510446	Prospective/Retrospective Cohort Study	83	13.9	55	Not Available	Depression or Anxiety Disorder of Moderate Severity	Citalopram	Not Available	5-HTTLPR	Clinical Outcomes	CGI	Participants with the S allele had lower response rates	16
Rousseva <i>et al.</i> (2003) [60]	12746735	CaseControl Study	305	26	44	Caucasian	Bipolar Affective Disorder	Tricyclics, SSRIs, Venlafaxine, Mirtazapine, Moclobemide, Nomifensine, Trazadone, Amineptine	Not Available	5-HTTLPR	History of AIM	Evaluated according to DSM-IV criteria	No statistically significant association between genotype and study outcome	13
Saeki <i>et al.</i> (2009) [61]	19259652	Prospective Cohort Study	27	34.3	78	Japanese	PD	Paroxetine	Brotizolam, and Lorazepam	5-HTTLPR	PD Severity, Plasma concentration of Paroxetine	PAS	There was a significant negative correlation between the percent reduction in PAS score and the plasma concentration of PAX in participants with the SS genotype	12
Sahraian <i>et al.</i> (2013) [62]	24130607	Prospective Cohort Study	104	Range: 18-65	75	Iranian (Fars background)	MDD	Citalopram	Alprazolam	5-HTTLPR	Clinical Outcomes	UKU, Selfreport Antidepressant Side Effect Checklist	L carriers were associated with an improved response to citalopram when compared to carriers of the SS genotype	14
Saiz-Rodríguez <i>et al.</i> (2018) [63]	29136336	Prospective Cohort Study	46	23	48	Caucasian	Healthy Volunteers	Sertraline	No other drugs allowed	5-HTTLPR	Plasma Concentration of Sertraline and ADRs	Liquid chromatographic/tandem mass spectrometric method	No statistically significant association between genotype and study outcome	11
Salem <i>et al.</i> (2017) [64]	27679962	Prospective CaseControl Study	80	34	0	Egyptian	Lifelong Premature Ejaculation	Paroxetine	Not Available	5-HTTLPR	Improvement in premature ejaculation		No statistically significant association between genotype and study outcome	11
Secher <i>et al.</i> (2009) [65]	19474754	Prospective Naturalistic Study	165	30-56	67	Danish Origin	Single Depressive Episode	Various Antidepressants	Not Available	5-HTTLPR	Weight Gain	UKU	No statistically significant	13

													association between	
													genotype and study outcome	
Serretti <i>et al.</i> (2001) [66]	11526473	Prospective PlaceboControlled Study	217	52.1	66	Not Available	MDD and/or Bipolar Disorder	Fluvoxamine	Pindolol, Flurazepam, Lithium	5-HTTLPR	Clinical Outcomes	Hamilton Rating Scale for Depression	5-HTTLPR polymorphism was not independently assessed from A218C tryptophan hydroxylase (TPH), therefore no relevant conclusion was made	17
Serretti <i>et al.</i> (2004) [67]	15274037	Retrospecti ve Cohort Study	221	50.6	66	Not Available	MDD and/or Bipolar Disorder	Fluvoxamine, Paroxetine	Flurazepam, Lithium	5-HTTLPR	Clinical Outcomes	HAMD	Carriers of the SS genotype showed a selective and slower improvement of depressive “core” and somatic anxiety symptoms when taking SSRI’s	17
Serretti <i>et al.</i> (2007) [68]	17157919	Retrospecti ve Cohort Study	281	48.6	68	Not Available	MDD, Bipolar Disorder Type I or Bipolar Disorder Type II	Fluvoxamine, Paroxetine, Sertraline	Flurazepam, Lithium	5-HTTLPR	Clinical Outcomes	HAMD	When participants with the SL and LL genotypes were pooled together and compared to the SS genotype, they showed a significantly better outcome	18
Silva <i>et al.</i> (2010) [69]	20010449	Prospective Cohort Study	49	30	73	Not Available	PD	Fluoxetine	Not Available	5-HTTLPR	Clinical Outcomes	OAS-M	Participants with the LL genotype had a significantly better response to Fluoxetine than participants carrying the S allele	11
Smits <i>et al.</i> (2007) [70]	17414739	Retrospecti ve Cohort Study	214	48.48	70	Caucasian (Netherland s Population)	MDD	Paroxetine, Fluoxetine, Fluvoxamine, Sertraline, Citalopram	Not Available	5-HTTLPR, 5- HTTVNTR	Clinical Outcomes and Adverse Events	6 Main classes of adverse events	Participants with the SS or SL genotype appeared to have an increased risk for adverse events (especially general adverse events such as dermatologic reactions, weight change and fatigue)	14

Staecker <i>et al.</i> (2014) [71]	24192302	Prospective Naturalistic Study	273	Range: 18-89	64	Caucasian	Psychiatric disorders that require antidepressant s	Citalopram, Fluoxetine, Paroxetine, Sertraline, Duloxetine, Venlafaxine, Reboxetine, Amitriptyline, Clomipramine, Imipramine, Trimipramine Mirtazapine	Doxepin, Benzodiazepi nes Zopiclone Zolpidem Clomethiazole Antihypertens ive drugs: ACE inhibitors Beta-blockers Angiotensin II receptor	5-HTTLPR, 5- HTTLPR/rs 25531, 5- HTTVNTR	Clinical Outcomes and Adverse Events	PD-S, CGI, DOTES	No statistically significant association between genotype and study outcome	13
									antagonists Calciumchannel blockers Diuretics Cardiac glycosides Thyroid drugs: Lthyroxine Kalium iodide Antidiabetic drugs: Insulin Metformin Repaglinide Glimepiride Pioglitazone					
Stein <i>et al.</i> (2006) [72]	16525856	Prospective Cohort Study	32	37.6	28	Caucasian (77%), Asian (8%), Other (8%), Black (6%), Indian/Alas kan Native/ First Nations (1%)	Social Anxiety Disorder	Paroxetine, Fluvoxamine	Not Available	5-HTTLPR	Clinical Outcomes	CGI-C	No statistically significant association between genotype and study outcome, however a statistical trend was found with LL carriers being more likely to respond than SS carriers	11
Stein <i>et al.</i> (2014) [73]	24154666	Prospective Cohort Study	346	35	34	Caucasian (77%), Asian (8%), Black (6%), Other (8%), American Indian/Alas ka Native (1%)	Social Anxiety Disorder	Sertraline	Not Available	5-HTTLPR	Clinical Outcomes	LSAS	No statistically significant association between genotype and study outcome	13

Strohmaier <i>et al.</i> (2011) [74]	21388237	Prospective Cohort Study	494	42	64	Not Available	MDD	Escitalopram, Nortriptyline	Hypnotics	5-HTTLPR	Clinical Outcomes, Sexual Dysfunction	MADRS, ASEC	No statistically significant association between genotype and study outcome	12
Sugie <i>et al.</i> (2005) [75]	16119478	Prospective PlaceboControlled Study	19	2-7	21	Japanese Population	ASD	Fluvoxamine	Not Available	5-HTTLPR	Clinical Outcomes, Side Effects	CGI	Fluvoxamine tended to be more effective in patients with the LL/LS genotype than those with the SS genotype. However, with respect to language use, a significant effectiveness was noted in the S allele	12
Takahashi <i>et al.</i> (2002) [76]	12208565	Prospective Cohort Study	54	51.2	59	Japanese	MDD	Fluvoxamine	Brotizolam	5-HTTLPR, 5- HTTVNTR	Clinical Outcomes, Nausea	MADRS, UKU	No statistically significant association between genotype and study outcome	12
Tomita <i>et al.</i> (2014) [77]	24858363	Prospective Cohort Study	51	46.3	69	Japanese	MDD	Paroxetine	Diazepam, Brotizolam, Sennoside	5-HTTLPR	Clinical Outcomes, Plasma Concentration	MADRS, UKU, Liquid Chromatograp hy	In the SS group, the paroxetine plasma concentration was significantly negatively correlated with improvement in MADRS at week 6 while the SL and LL group was significantly positively correlated. In the SS group, only the paroxetine plasma concentration showed a significant association with improvement in MADRS at week 6. However, in the SL and LL group, the paroxetine plasma concentration was not significantly associated with improvement in MADRS at week 6	14

Wilkie <i>et al.</i> (2009) [78]	18253134	Prospective Cohort Study	166	43.42	69	Caucasian	Unipolar Depression	Paroxetine, Citalopram, Imipramine, Lofepramine, Phenelzine	Not Available	5-HTTLPR, 5-HTTVNTR	Clinical Outcomes	HAMD	Participants with the S allele were significantly associated with both remission and response	13
Won <i>et al.</i> (2012) [79]	23095326	Prospective Cohort Study	115	46	86	Korean	MDD	Escitalopram	Lorazepam	5-HTTLPR	Clinical Outcomes	UKU, HAMD, CGI	The therapeutic response was better in S allele carriers than participants with the LL genotype	14
Wong <i>et al.</i> (2008) [80]	18311688	Prospective CaseControl Study	23	Mean between n 32-36	0	Not Available	Alcohol Dependency	Citalopram	Not Available	5-HTTLPR	Clinical Outcomes, ACTH Blood Levels	VAS, SSS	No statistically significant association between genotype and study outcome	12
Yevtushenko <i>et al.</i> (2010) [81]	19800133	Prospective Cohort Study	102	36.9	76	Caucasian	Panic Disorder	Sertraline, Paroxetine	Not Available	5-HTTLPR	Frequency of Panic Attacks	HADS, CGI	No statistically significant association between genotype and study outcome	14
Zanardi <i>et al.</i> (2001) [82]	11543734	Prospective Cohort Study	155	51.97	70	Not Available	MDD and/or Bipolar Disorder	Fluvoxamine	Pindolol, Flurazepam, Lithium	5-HTTLPR	Clinical Outcomes	HAMD-21	The S allele was significantly associated with poorer response to fluvoxamine treatment	13

\*Abbreviations used: ABC-CV, Aberrant Behavioral Checklist-Community Version; ASEC, Antidepressant Side-Effect Checklist; ASD, Autism Spectrum Disorder; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; BPRS, Brief Psychiatric Rating Scale; CAPS, Clinician-Administered PTSD Scale; CDRS-R, Children's Depression Rating Scale-Revised; CGI-I, Clinical Global Impression Scale- Improvement; CGI-S, Clinical Global Impression Severity; CIRS-G, Cumulative Illness Rating Scale adapted for Geriatrics; CSFQ,

Changes in Sexual Function Questionnaire; CTH, Chronic Tension-Type Headache; DOTES, Dosage Record and Treatment Emergent Symptoms; FTND, Fagerstrom Test of Nicotine Dependence; FQ, Fear Questionnaire; GGTP, Concentration of F-glutamyl-transpeptidase; HADS, Hospital Anxiety and Depression Subscales; HAM-A, The Hamilton Anxiety Rating Scale; HAM-D, Hamilton Depression Rating Scale; IES[R], Impact of Event Scale-Revised; IVR, Interactive Voice Response Technology; K-SADS-PL, Hebrew version of the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version; LUNTERS, Liverpool University Neuroleptic Side Effect Rating Scale; MADRS, Montgomery-Asberg Depression Rating Scale; MMSE, Mini Mental Status Examination; MoCA, Montreal Cognitive Assessment; MSEL, Mullen Scales of Early Learning; NIHSS, National Institute of Health Stroke Scale; OAS-M, Overt Aggression Scale Modified; PANSS, Positive and Negative Syndrome Scale; PASS, Panic Associated Symptom Scale; PD-S, Paranoid Depression Scale; PDSS, Panic Disorder Severity Scale; PFA, Platelet Function Analyser; PSWQ, Penn State Worry Questionnaire; QIDS-C, 16-item Quick Inventory of Depressive Symptomatology Clinician Rated; RBS-R, Repetitive Behavior Scale-Revised; SCARED, Screen for the Child Anxiety Related Emotional Disorders; SIP, Short Index of Problems; SPM, Sensory Processing Measures; SSS, Serotonin Syndrome Scale; TLFB, Timeline Follow-Back; UKU, Udvalg for Kliniske Undersogelser; VAS, Visual Analog Scale; YMRS, Young Mania Rating Scale.



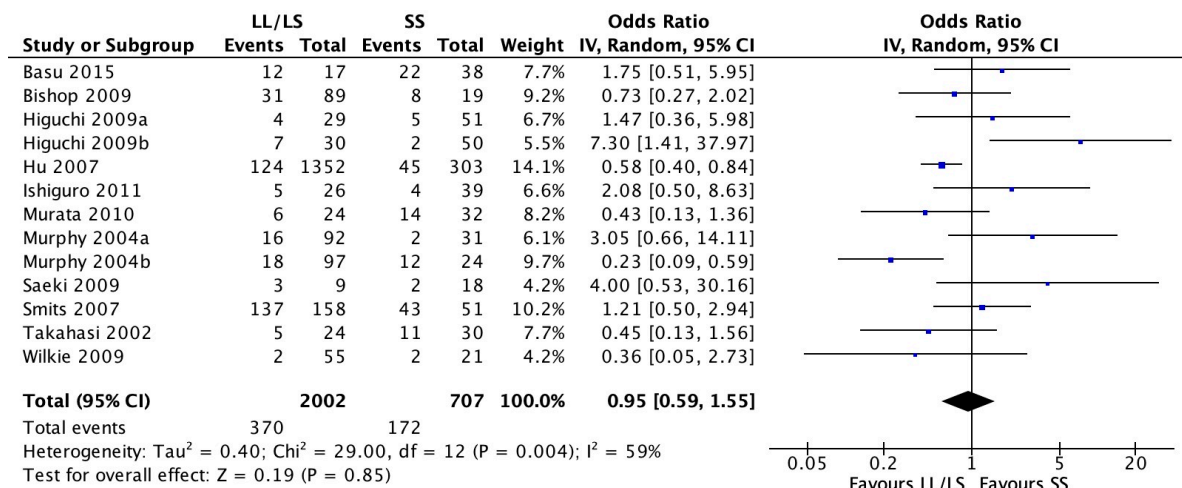


Zanardi et al. (2001)	YES	YES	NO	YES	155	NO	YES	PROSPECTIVE COHORT STUDY	YES	YES	NO	NO	NO	YES	YES	NO	NO	YES	YES	NO	NO	NO	N/A	N/A	YES	YES	YES	13
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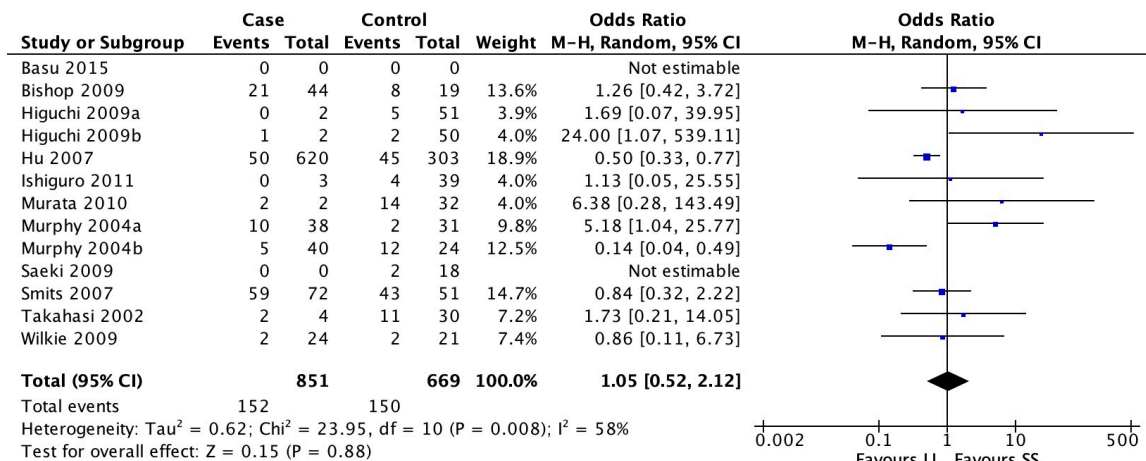
**Supplementary Table S3.** Reported prevalence of ADRs among studies in the tolerability metaanalysis

Study	Subjects Reporting ADR/Total Subjects	Prevalence (%)
Basu 2015 [4]	34/55	61.8
Bishop 2009 [7]	85/108	78.7
Higuchi 2009a [18]	9/80	11.3
Higuchi 2009b [18]	9/80	11.3
Hu 2007 [20]	169/1655	10.2
Ishiguro 2011 [22]	9/65	5.5
Murata 2010 [42]	20/56	35.7
Murphy 2004a [43]	18/123	78.3
Murphy 2004b [43]	30/121	24.8
Saeki 2009 [61]	5/27	18.5
Smits 2007 [70]	180/209	86.1
Takahasi 2002 [76]	16/54	29.6
Wilkie 2009 [78]	4/76	5.3

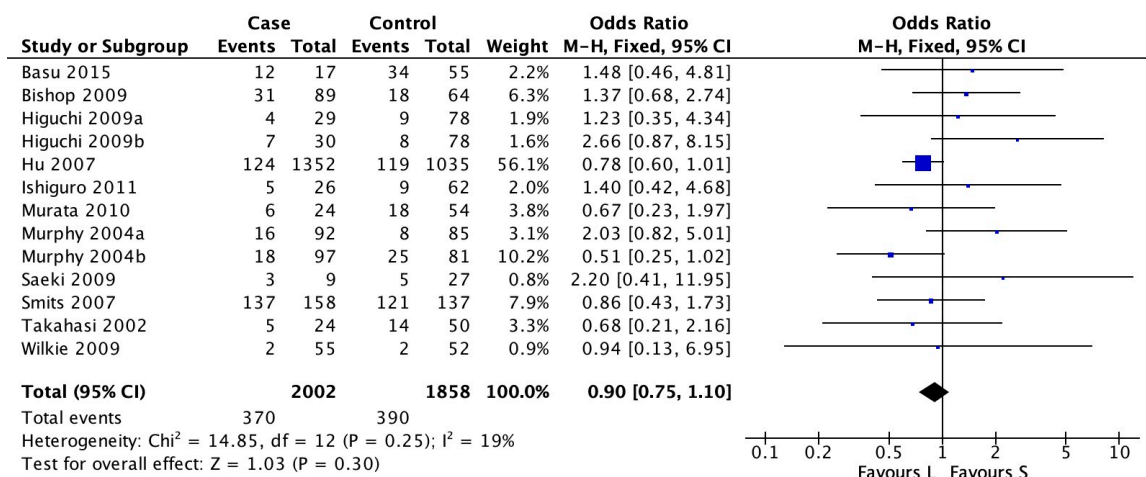
(A)



(B)

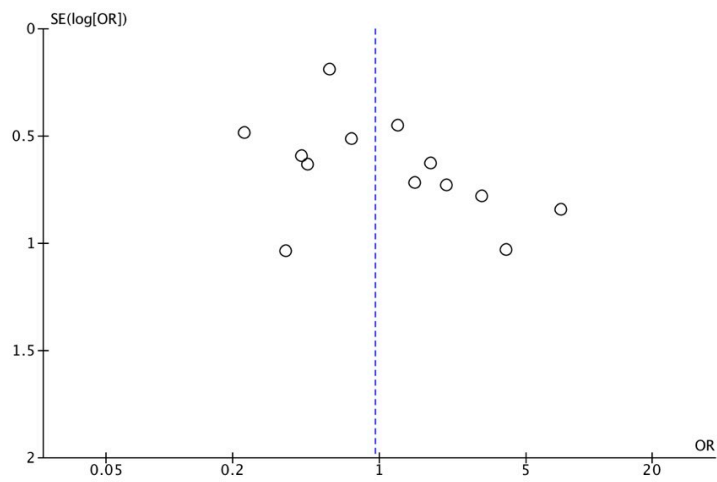


(C)

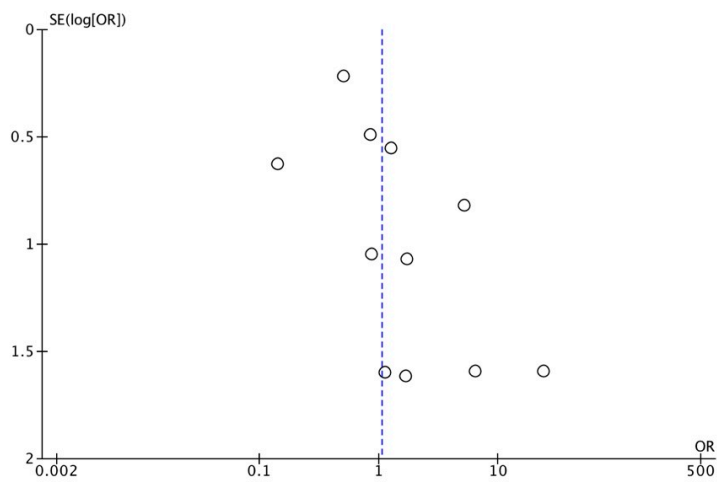


**Figure S1.** Forest plots of 5-HTTLPR polymorphisms and adverse drug reactions in all studies by genotype comparisons. (A) LL/LS vs. SS (B) LL vs. SS (C) L vs. S.

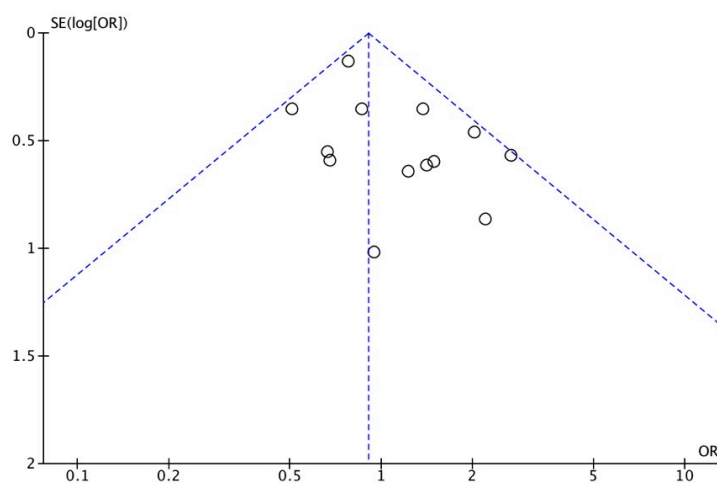
(A)



(B)



(C)



**Figure S2.** Funnel plots of 5-HTTLPR polymorphisms and adverse drug reactions in all studies by genotype comparisons. (A) LL/LS vs. SS (B) LL vs. SS (C) L vs. S

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