



Supplementary Material

Article Title: Clinical and Genetic Predictors of Delayed Remission After Multiple Levels of Antidepressant Treatment: Toward Early Identification of Depressed Individuals for Advanced Care Options

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Supplementary eTable 1. Estimated median time to remission with 95% confidence interval estimates of important comorbid psychiatric symptoms in STAR*D data (n = 1953)

Variable	Category (events, n)	% Nonremitters	Median time to complete remission in weeks (95% CIE)	Hazard Ratio	Log-Rank test p-value
Dysthymic symptoms	0 - 1 (250, 350)	28.6	10.0 (9.1, 12.1)	Reference	<0.0001
	2 - 4 (370, 493)	24.9	11.7 (9.8 - 12.7)	0.98	
	> 4 (659, 1077)	38.8	14.6 (13.9, 15.7)	0.65	
PTSD symptoms	0 (395, 540)	26.9	10.3 (9.3, 12.0)	Reference	<0.0001
	1 - 9 (620, 897)	30.9	12.5 (12.0, 13.0)	0.84	
	> 9 (259, 476)	45.6	18.3 (15.9, 21.0)	0.53	
Eating disorder symptoms	0 (516, 772)	33.2	12.4 (11.7, 13.1)	Reference	0.0008
	1 - 3 (359, 506)	29.1	12.7 (11.7, 13.7)	0.98	
	> 3 (406, 647)	37.2	14.0 (12.9, 15.1)	0.79	
OCD symptoms	0 (675, 941)	28.3	12.0 (10.4, 12.6)	Reference	<0.0001
	1 - 3 (489, 755)	35.2	13.3 (12.6, 14.4)	0.80	
	> 3 (116, 230)	49.6	20.1 (15.3, 24.0)	0.54	
Panic disorder symptoms	0 (494, 681)	27.5	11.9 (10.0, 12.4)	Reference	<0.0001
	1 - 3 (435, 630)	31	12.8 (12.3, 13.9)	0.86	
	> 3 (351, 613)	42.7	15.1 (13.9, 18.0)	0.64	
Psychotic symptoms	0 (967, 1372)	29.5	12.1 (11.9, 12.7)	Reference	<0.0001
	1 (189, 305)	38	13.9 (12.6, 15.0)	0.81	
	> 1 (126, 251)	49.8	20.9 (17.0, 24.1)	0.54	
Agoraphobia symptoms	0 (647, 879)	26.4	11.6 (10.0, 12.1)	Reference	<0.0001
	1 - 3 (325, 493)	34.1	12.9 (11.7, 14.1)	0.81	
	> 3 (304, 545)	44.2	18.0 (15.4, 20.9)	0.56	
Social phobia symptoms	0 - 3 (579, 811)	28.6	11.7 (10.0, 12.1)	Reference	<0.0001
	4 - 9 (373, 567)	34.2	12.9 (12.1, 14.0)	0.81	
	> 9 (325, 541)	39.9	15.7 (14.0, 17.9)	0.65	
GAD symptoms	0 - 3 (280, 377)	25.7	11.6 (9.4, 12.7)	Reference	<0.0001
	4 - 6 (297, 409)	27.4	11.7 (10.0, 12.4)	0.96	
	> 6 (702, 1134)	38.1	14.4 (13.6, 15.0)	0.66	
Somatization symptoms	0 (388, 499)	22.2	9.7 (9.1, 11.4)	Reference	<0.0001
	1 - 3 (596, 904)	34.1	13.3 (12.6, 14.1)	0.71	
	> 3 (287, 507)	43.4	17.9 (14.7, 20.9)	0.52	
Alcohol use disorder symptoms	0 (985, 1481)	33.5	12.9 (12.3, 13.7)	Reference	0.917
	1 or more (295, 446)	33.9	12.9 (12.3, 14.1)	1.01	
Any substance use disorder symptoms	0 (1180, 1748)	32.5	12.7 (12.1, 13.0)	Reference	0.0151
	1 or more (100, 175)	42.9	16.6 (14.0, 21.3)	0.78	
Any personality disorder	No (880, 1328)	33.7	12.9 (12.1, 13.4)	Reference	0.007
	Yes (11, 31)	64.5	24.0 (13.9, --)	0.45	

Supplementary eTable 2. Estimated median time to remission with 95% confidence interval estimates of SNPs with *p*-value < 0.2 in the limited STAR*D data (n = 1953)

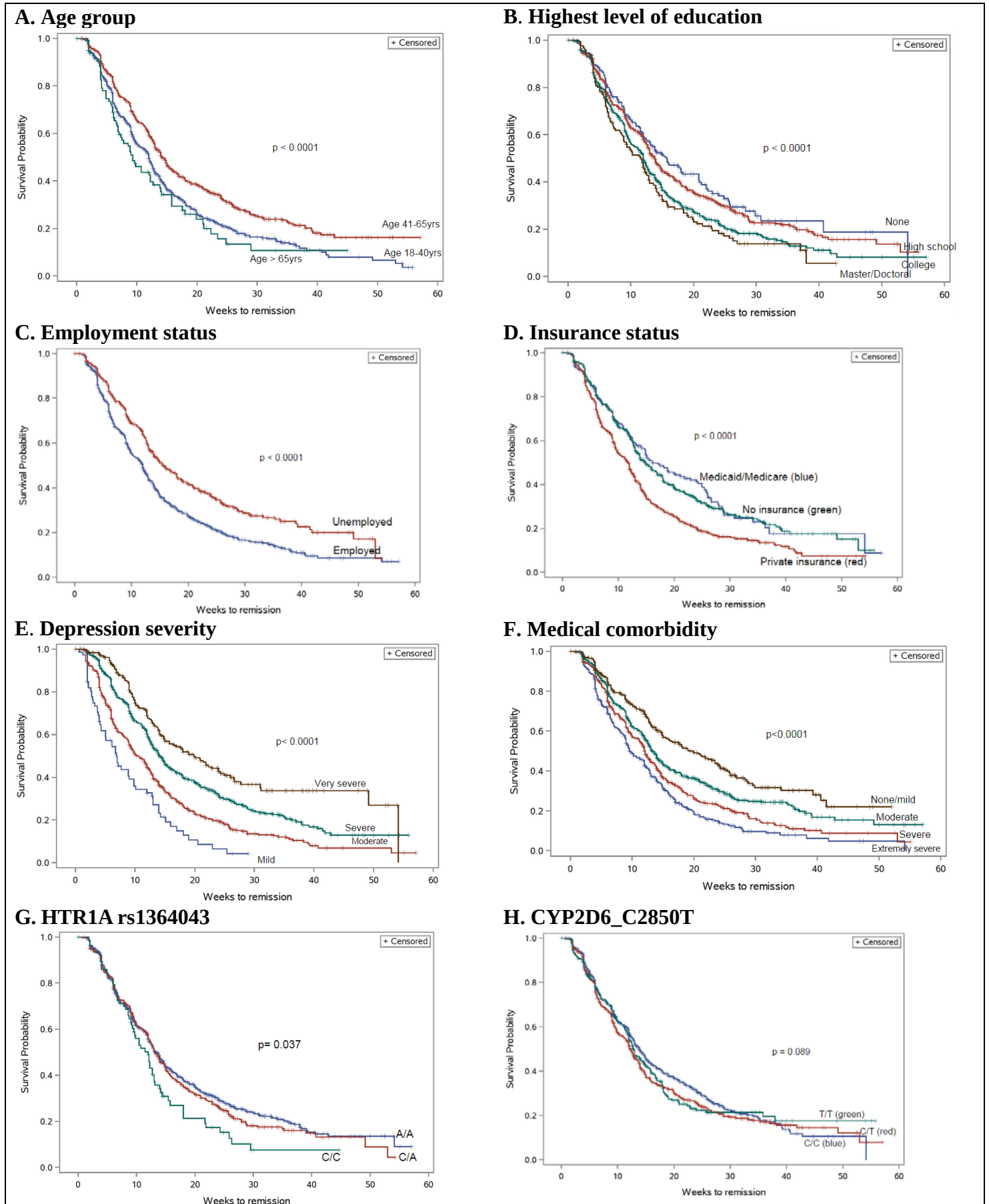
	SNPs*	Category (events, n)	% Nonremitters	Median time to complete remission in weeks (95% CIE)	Hazard Ratio	Log-Rank test p-value
HTR1A	rs1364043	A/A (684, 1070)	36.1	13.3 (12.6, 14.1)	0.71	0.0367
		C/A (408, 595)	31.4	13.0 (12.4, 14.1)	0.76	
		C/C (61, 80)	23.7	12.0 (9.1, 13.0)	Reference	
HTR2A	rs731245	C/C (294, 439)	33.0	13.1 (12.4, 14.1)	0.90	0.164
		C/T (502, 790)	36.5	13.0 (12.4, 14.0)	0.88	
		T/T (332, 471)	29.5	12.3 (11.3, 13.9)	Reference	
	rs2770296	A/A (632, 983)	35.7	13.6 (12.9, 14.7)	0.81	0.126
		G/A (421, 637)	33.9	12.9 (12.0, 14.0)	0.83	
		G/G (102, 130)	21.5	11.3 (8.9, 12.1)	Reference	
	rs927544	C/C (94, 126)	25.4	11.8 (8.9, 12.9)	1.20	0.17
		C/T (405, 584)	30.7	12.7 (12.0, 14.0)	1.08	
		T/T (624, 974)	35.9	13.0 (12.4, 13.9)	Reference	
	rs1923882	A/A (89, 126)	29.4	12.4 (10.3, 14.9)	1.05	0.154
		G/A (396, 611)	35.4	14.0 (13.0, 14.9)	0.90	
		G/G (686, 1018)	32.6	12.6 (12.0, 13.0)	Reference	
TPH2	rs2129575	G/G (651, 969)	32.8	12.9 (12.1, 13.9)	0.93	0.103
		G/T (407, 630)	35.4	13.9 (12.7, 15.0)	0.83	
		T/T (91, 131)	30.5	12.6 (9.7, 14.9)	Reference	
	rs2171363	A/A (258, 422)	38.9	13.0 (12.3, 14.7)	0.87	0.141
		A/G (560, 854)	34.4	13.1 (12.4, 14.3)	0.89	
		G/G (341, 483)	29.4	12.7 (11.9, 14.0)	Reference	
	rs17110747	A/A (35, 48)	27.1	13.0 (11.1, 14.9)	1.25	0.202
		A/G (275, 393)	30.0	12.6 (1.3, 13.9)	1.10	
		G/G (932, 1428)	34.7	13.0 (12.6, 13.9)	Reference	
MOA-A	rs1465108	A/A (207, 342)	39.5	14.1 (12.7, 16.1)	0.90	0.045
		G/A (291, 420)	30.7	12.4 (11.9, 13.0)	1.12	
		G/G (561, 842)	33.4	13.0 (12.3, 14.0)	Reference	
CYP2D6	_2D6_C2850T	C/C (544, 839)	35.2	13.9 (13.0, 14.9)	0.91	0.089
		C/T (531, 780)	31.9	12.3 (11.6, 12.9)	1.04	
		T/T (195, 300)	35.0	12.7 (12.0, 14.7)	Reference	
CYP2C19	_2C19_star3	A/A (1267, 1909)	33.6	13.0 (12.4, 13.6)	2.46	0.062
		A/C (4, 12)	66.7	40.4 (9.3.-)	Reference	
CYP3A4	_3A4_rs2740574	A/A (1041, 1525)	31.7	12.7 (12.1, 13.4)	1.36	0.017
		A/G (147, 241)	39.0	13.0 (11.7, 14.9)	1.22	
		G/G (83, 155)	46.5	14.1 (12.7, 20.9)	Reference	
CYP3A5	_3A5_rs776746	A/A (98, 175)	44.0	14.0 (13.0, 17.0)	0.75	0.016
		A/G (248, 388)	36.1	13.3 (12.4, 15.7)	0.91	
		G/G (925, 1357)	31.8	12.6 (12.0, 13.1)	Reference	
MDR1	_MDR1_rs2032582	G/G (505, 805)	37.3	13.9 (12.7, 14.7)	0.86	0.107
		G/T (516, 753)	31.5	12.7 (12.0, 13.9)	0.96	
		T/T (246, 359)	31.5	12.6 (11.1, 13.1)	Reference	
	_MDR1_C3435T	C/C (371, 582)	36.3	13.1 (12.3, 14.3)	0.88	0.184

		T/C (596, 905)	34.1	12.9 (12.3, 14.0)	0.89	
		T/T (307, 434)	29.3	12.4 (11.0, 13.6)	Reference	
PK-deletion variants	_2D6_1863ins	-/+ (1, 1)	--	--	--	--
		+/+ (1266, 1915)	--	--	--	--
SLC6A4	rs16965628	C/C (978, 1434)	31.8	12.6 (12.0, 13.0)	1.06	0.052
		G/C (166, 281)	40.9	14.7 (12.9, 16.6)	0.87	
		G/G (24, 37)	35.1	14.8 (9.3, 20.4)	Reference	
	rs2066713	C/C (397, 620)	36.0	14.0 (12.7, 15.0)	0.80	0.036
		C/T (489, 720)	32.1	12.6 (12.0, 13.1)	0.90	
		T/T (166, 235)	29.4	11.4 (9.6, 13.9)	Reference	
	rs140700	A/A (6, 10)	40.0	13.9 (3.0, 17.6)	1.05	0.016
		A/G (157, 218)	28.0	12.0 (9.4, 12.9)	1.28	
		G/G (796, 1263)	37.0	13.9 (12.9, 14.3)	Reference	

Supplementary eTable 3. Models comparisons

	Model 1. Sociodemographics only	Model 2. Clinical variables only	Model 3. Genetic variables only	Model 4. Demographic + clinical	Model 5. Demographic + clinical + genetic
Age	0.021			0.028	0.01
Gender	0.0063			ns	ns
Education level	0.0002			0.017	0.008
Employment	0.015			0.004	0.005
Insurance type	0.055			ns	ns
Medical comorbidity		<0.0001		0.0012	0.0005
Depression severity		<0.0001		<0.0001	<0.0001
Prior psychotropic exposure		ns		ns	ns
PTSD		0.055		0.02	0.02
GAD		ns		ns	ns
Dysthymia		0.005		0.01	0.02
Somatization symptoms		0.03		ns	ns
Agoraphobia		0.01		ns	ns
Any personality disorder		0.04		ns	ns
HTR1A rs1364043			0.048		0.02
CYP2D6_C2850T			0.0013		0.0003
MOA-A rs1465108			0.026		ns
AUC, %	62.9	68.1	56.2	68.7	70.1
Sensitivity, %	97.3	89.3	100.0	89.8	87.6
Specificity, %	7.8	24.3	0.0	20.2	23.5

Supplementary eFigure 1 (A – H). Kaplan-Meier plots of time to remission in weeks and key baseline characteristics



Supplementary eFigure 2. Predictors and Time to remission.

2a. Showing the dose-response relationship between number of comorbid psychiatric symptoms and increased time to remission.

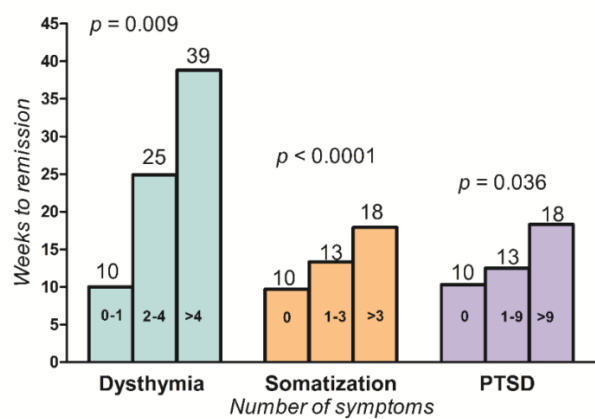


Figure 2b. Showing the association serotonin 5HT1A receptor marker and and increased risk of non-remission.

