

SUPPLEMENT

Lowest Score Strategy for Simulated Treatment Recommendation in PReDICT Sample. As an alternate treatment recommendation strategy, we determined the treatment for which the predicted HAMD-Outcome was lowest for each individual and considered this the “recommended” treatment. We then used ANOVAs to compare the true HAMD-Outcome values among individuals who were randomized to receive their recommended treatment versus the other two non-recommended treatments. The means of each group are plotted in **Supplementary Figure 1A** and values are available in **Supplementary Table 5**. For all three treatment conditions, individuals who received the recommended treatment had significantly lower HAMD-Outcome than those who did not, and the effect sizes were in the medium to large range. Critically, the observed HAMD-Outcome did not differ by recommended treatment group ($F = 1.71, p = .18$) nor by actual treatment group (mean HAMD-Outcome scores: CBT 9.4, escitalopram 8.1, duloxetine 7.7, $F = 1.71, p = .18$). However, there was strong evidence of moderation of treatment by recommended treatment type ($F = 8.741, p = .0000013$). Thus, patients’ responses to treatment were not sensitive to the type of treatment they received nor to the type of treatment they were recommended, only to whether the treatment they received matched the recommended treatment. Combining across groups, participants who received the recommended treatment ($N = 79$) and those who did not ($N = 169$) had significantly different HAMD-Outcome scores (means of 5.3 and 9.8, respectively, $t = 6.6, p = 2.131E-10$, Cohen’s $d = .79$).

Next, we examined the remission (HAMD-Outcome ≤ 7) rates across the groups (see **Supplementary Figure 1B**). In each case, remission rates were higher for those who received the recommended treatment. Combining across the groups, patients who received their recommended treatment had better outcomes compared to those who did not receive their recommended treatment in a chi-square test (72% vs 44%, $p = 00001$). The matched-to-recommendation outcomes were superior

to the overall remission rates within the actual treatment groups: escitalopram (47%), CBT (42%), duloxetine (55%), and study-wide (48%). Thus, matching to the recommended treatment improved remission rates by 24%, converting to a number needed to assess of 5.

Lowest Score Strategy in PET-Predictor Sample. We applied the same strategy to the PET-Predictor Sample. The mean HAMD-Outcome scores and test statistics from independent-sample t-tests for these groups are available in **Supplementary Table 6** and plotted in **Supplementary Figure 2A**. Using this strategy, those for whom the analysis recommended CBT and received it did not perform significantly better than those who did not, but those recommended ADM and received it did perform better than those who did not. The effect size ($d=0.773$) was large comparing within Recommend ADM. Combining across groups, the HAMD-Outcome scores of those who got the recommended treatment ($M = 7.4$, $SD = 4.9$) compared with those who did not ($M = 9.5$, $SD = 5.2$) did not differ significantly ($p = .07$) but the difference had a moderate effect size (Cohen's $d = .416$). For comparison, without considering recommended treatments, the mean HAMD-Outcome in the PET-Predictor CBT group was 9.5, the mean HAMD-Outcome in the medication group was 8.5, and the study-wide mean HAMD-Outcome was 9.0.

We then examined remission rates among the groups (see **Figure 2B**). For individuals recommended CBT and ADM, remission rates were higher for those receiving the recommended treatment compared to those who did not. Combining across groups and using this strategy, individuals who received the recommended treatment had a non-significantly higher remission rate than those who did not (56% vs 42%, $p = .31$). For comparison, the PET-Predictor remission rates by treatment type (without considering recommended treatment) were as follows: CBT (47%), escitalopram (44%), and study-wide (45%). Thus, although sample size rendered these differences nonsignificant, this strategy yielded a 11% absolute improvement in remission rate, which translates to a number needed to assess of 9.1, identical to the PReDICT study result.

Prediction of Response Outcomes

Following the same approach used for prediction of remission, we also examined outcome of response (defined as $\geq 50\%$ reduction in HAM-D score baseline to week 12) across groups using Strategies A2 and B2 in the PReDICT and PET-Predictor samples.

Using the Maximum Youden Strategy in the PReDICT Sample, response rates were also higher for those who received the recommended treatment (see **Supplementary Figure 3**). Participants who received the recommended treatment had higher response rates (73% vs 45%, $p = .00004$) than those who did not. This led to a study-wide absolute improvement in response rate of 13%, who translates to a number needed to assess of 7.7 for response.

In the PET-Predictor sample, there were sizeable differences in response rates between those who received the recommended treatment and those who did not (see **Supplementary Figure 4**). Combining across treatments and comparing with a chi-square test, those who got their recommended treatment responded at much higher rates than those who did not (83% vs 44%, $p = .003$). This represented a 25% absolute improvement for response rates over random assignment, which translates to a number needed to assess of 4.

Supplementary Tables

Supplementary Table 1: Top ten loading items for each component of the best fitting model for each treatment

Duloxetine 1 104 Total Items	Duloxetine 2 19 Total Items	CBT 62 Total Items	Escitalopram 53 Total Items
↓Self-Criticalness (BDI)	↑Guilt (BDI)	↓Loss of Pleasure (BDI)	↓Family/Home Disruption (SDS)
↓Feeling sad (QIDS-SR)	↑Falling asleep (QIDS-SR)	↓Depressed Mood (HAMD)	↑Mood (QLESQ)
↑Family hit marks (CTQ)	↑Family/Home Disruption (SDS)	↑Overall life satisfaction (QLESQ)	↑Social Disruption (SDS)
↑Overall sense of wellbeing (QLESQ)	↓Overall sense of wellbeing (QLESQ)	↓Reported Sadness (MADRS)	↓Sadness (BDI)
↑Wore dirty clothes (CTQ)	↓Overall life satisfaction (QLESQ)	↓Emotionally abused (CTQ)	↑Overall life satisfaction (QLESQ)
↓Family Strength (CTQ)	↑Sadness (BDI)	↓Depressed Mood (HAMA)	↑Social Relationships (QLESQ)
↓Daily Functioning (QLESQ)	↑Loss of Interest In Sex (BDI)	↓Punishment Feelings (BDI)	↓Depressed Mood (HAMD)
↑Emotionally abused (CTQ)	↑Energy Level (QIDS-SR)	↑Leisure Time Activities (QLESQ)	↓Feeling sad (QIDS-SR)
↓Energy Level (QIDS-SR)	↑Feeling Slowed (QIDS-SR)	↓Guilt (HAMD)	↑Daily Functioning (QLESQ)
↓Depressed Mood (HAMA)	↓Work (QLESQ)	↑Living situation (QLESQ)	↓Feeling Slowed (QIDS-SR)

Supplementary Table 2: Loadings of All Items on PLSR-Derived Predictor Variables

Item	Dul 1	Dul 2	CBT	Escitalopram
Sex				
Number of Suicide Attempts	-0.109			
Number MDD Episodes				
Current Anxiety Disorder				
Lifetime Substance Use				
FamHx Mood				
FamHx MDD				
FamHx Bipolar				
FamHx Psychiatric Any	-0.1			
Education Level	0.147		-0.11	
Weight				
Age				
Married				
CTQ				
Not enough to eat	-0.122			
Someone took care of me	0.105		-0.156	
Family Insults	-0.138			
Parents Intoxicated	-0.136		0.106	
Family made me special	0.112			
Wore dirty clothes	-0.192			
Felt loved	0.114		-0.134	-0.14
Parents wished wasn't born	-0.151			
Got hit by family	-0.111			
Nothing I wanted to change			-0.132	
Family hit marks	-0.203			
Punished with belt	-0.164			
Family looked out			-0.139	-0.11
Family hurtful	-0.16		0.103	
Physically abused	-0.148		0.132	
Perfect Childhood	0.158		-0.145	
Beated, other noticed	-0.103			
Family hated	-0.11		0.113	
Family close			-0.111	-0.101
Sexual touch	-0.133	-0.107	0.114	
Threatened into sex	-0.128	-0.107	0.125	
Best Family	0.138		-0.15	-0.111

Made to do sexual things	-0.117		0.107	
Someone molested	-0.113		0.121	
Emotionally abused	-0.176		0.175	0.1
Took to doctor	0.168			
Sexually abused			0.125	
Family Strength	0.19		-0.137	-0.117
Klein				
Childhood Physical Abuse	-0.131		0.102	
Childhood Neglect				
Family Sexual Abuse	-0.1		0.112	
Non-family Sexual Abuse				
Guardian died				
Parents Divorced				
Separated from Parents				
BDI				
Sadness	0.141	-0.129		0.17
Pessimism	0.148		0.138	0.11
Past Failure	0.138		0.112	0.128
Loss of Pleasure	0.118		0.178	0.11
Guilt	0.108	-0.158	0.156	0.121
Punishment Feelings	0.14		0.169	0.129
Self-Dislike	0.108			0.102
Self-Criticalness	0.215		0.101	0.118
Suicidal Thoughts	0.127	-0.1		0.128
Crying				
Agitation	-0.13			
Loss of Interest	-0.137			0.128
Indecisiveness	-0.149			0.128
Worthlessness				0.138
Loss of Energy	0.153		0.101	0.119
Changes in Sleep	0.114			
Irritability	0.124		0.159	0.127
Changes in Appetite	-0.131		0.12	0.111
Concentration	-0.103			
Fatigue	0.108		0.114	
Loss of Interest In Sex	0.131	-0.125		0.11
Sheehan Disability Scale				
Work/School Disruption	0.156	-0.105		0.138
Have not worked Unrelated				
Social Disruption	0.159	-0.104	0.133	0.181
Family/Home Disruption	0.131	-0.143		0.183
QLESQ				

Physical health			-0.125	
Mood	-0.122			-0.183
Work	-0.162	0.11		
Household Activities	0.145			-0.142
Social Relationships	-0.111		-0.13	-0.165
Family Relationships	-0.119			-0.14
Leisure Time Activities	-0.109		-0.169	-0.125
Daily Functioning	0.187		-0.143	-0.157
Sexual Drive	-0.106	0.106	-0.137	-0.106
Economic Status			-0.134	
Living situation	0.145		-0.167	
Ability to get around	0.166			
Vision	0.152		-0.1	
Overall sense of wellbeing	-0.196	0.14	-0.143	-0.13
Medication				
Overall life satisfaction	-0.153	0.132	-0.175	-0.166
QIDS-SR				
Falling asleep	0.116	-0.151		
Sleep during night	0.13			
Waking too early	0.146		0.105	
Sleeping too much				
Feeling sad	0.206	-0.109		0.159
Decreased appetite	-0.137		0.127	
Increased appetite	0.122			
Decreased weight				
Increased weight	0.125			
Concentration	0.122	-0.182		0.106
View of self			0.142	0.135
Thoughts of Death	0.117		0.111	
General Interest	0.113			0.14
Energy Level	0.176	-0.124		0.142
Feeling Slowed	0.124	-0.111		0.152
Restlessness	-0.14			0.105
MADRS				
Apparent Sadness	-0.15		0.131	
Reported Sadness	0.161	-0.1	0.175	0.149
Inner tension	0.116			
Reduced Sleep	0.123			
Reduced appetite	-0.14			
Concentration			0.125	
Lassitude	-0.156		0.106	
Inability to feel	0.124		0.153	0.136
Pessimistic thoughts			0.114	0.117

Suicidal thoughts	0.129		0.123	
HAMD				
Depressed Mood	0.135		0.176	0.163
Guilt			0.169	0.124
Suicide	0.143		0.131	
Insomnia Initial	0.11			
Middle Insom				
Delayed Insom				
Work and Interests	0.135		0.114	0.109
Retardation				
Agitation	-0.113			
Anxiety Psychic				
Anxiety Somatic				
Somatic Gastro	-0.113			
Somatic General				
Genital Symptoms	-0.105			
Hypochondriasis	0.142			
Weight Loss				
Diurnal Variation A	-0.138			
Diurnal Variation B	-0.125			
Depersonal/Dereal				0.112
Paranoid				
Obsessional				
Helplessness	-0.146		0.165	0.115
Hopelessness			0.118	0.125
Worthlessness				
HAMA				
Anxious mood				
Tension	0.169		0.109	0.107
Fears				
Insomnia Initial	0.139			
Intellectual	0.141		0.114	
Depressed Mood	0.176		0.174	0.149
Somatic (muscular)	0.149			
Somatic (sensory)				
Cardiovascular	0.147			
Respiratory				
Gastrointestinal	0.162			0.108
Genitourinary				
Autonomic				
Behavior at interview	-0.121			

Note: Cells are color coordinated to indicate strength and direction of loading. Darker color indicates stronger loading. Green color indicates that higher scores on this item predict better treatment response (lower HAMD-Outcome). Red color indicates that higher scores on this item predict worse treatment response (higher HAMD-Outcome).

Supplementary Table 3: Means and Test Statistics for Comparing HAMD-Outcome Using Strategy B in PReDICT Sample

	Randomized Treatment Group N, M(SE)			ANOVA F	ANOVA p	Eta-Squared
Recommended Treatment	CBT	Duloxetine	Escitalopram			
Recommended CBT	<i>N = 7</i> <i>M(SE) = 3.5(2.1)</i>	N = 21 M(SE) = 11.2(1.2)	N = 4 M(SE) = 14.3(2.8)	6.23	0.002	0.257
Either	<i>N = 26</i> <i>M(SE) = 7.4(1.1)</i>	<i>N = 17</i> <i>M(SE) = 8.2(1.4)</i>	<i>N = 32</i> <i>M(SE) = 9.5(1.0)</i>	1.03	0.357	0.025
Recommended ADM	N = 39 M(SE) = 11.8(0.9)	N = 46 M(SE) = 5.9(0.8)	N = 56 M(SE) = 6.8(0.8)	13.06	0.000004	0.175

Note: Italicized cells are individuals who received the recommended treatment.

Supplementary Table 4: Means and Test Statistics for Comparing HAMD-Outcome Using Strategy B in PET-Predictor Sample

	Randomized Treatment Group N, M		T-test t	P	Cohen's d
Recommended Treatment	CBT	Escitalopram			
Recommend CBT	<i>N = 7</i> <i>M = 6.8</i>	N = 16 M = 11.5	2.14	.02	.97
Recommend ADM	N = 25 M = 10.3	<i>N = 16</i> <i>M = 5.5</i>	3.27	.001	1.05

Note: Individuals in the Either Category are considered to have received the recommended treatment

Note: Italicized cells are individuals who received the recommended treatment.

Supplementary Table 5: Means and Test Statistics for Comparing HAMD-Outcome Using Strategy A in PReDICT Sample

	Randomized Treatment Group N, M(SE)			ANOVA F	ANOVA p	Eta-Squared
Lowest Predicted HAMD-Outcome	CBT	Duloxetine	Escitalopram			
Recommended CBT	<i>N = 23, M(SE) = 5.3(1.2)</i>	<i>N = 22, M(SE) = 9.7(1.2)</i>	<i>N = 30, M(SE) = 8.1(1.0)</i>	3.73	0.029	0.094
Recommended Duloxetine	<i>N = 27, M(SE) = 10.6(1.1)</i>	<i>N = 33, M(SE) = 4.6(1.0)</i>	<i>N = 39, M(SE) = 9.2(0.9)</i>	9.41	0.0001	0.151
Recommended Escitalopram	<i>N = 22, M(SE) = 12.2(1.2)</i>	<i>N = 29, M(SE) = 9.7(1.1)</i>	<i>N = 23, M(SE) = 6.2(1.2)</i>	6.54	0.002	0.165

Note: Italicized cells are individuals who received the recommended treatment.

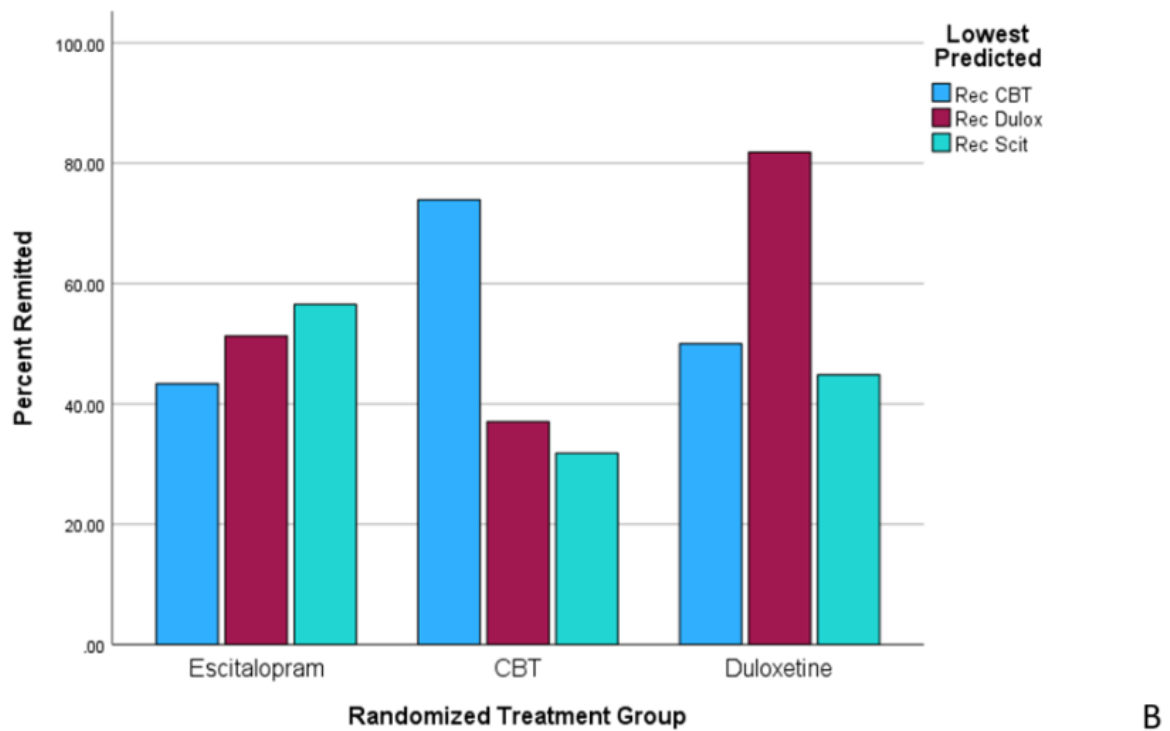
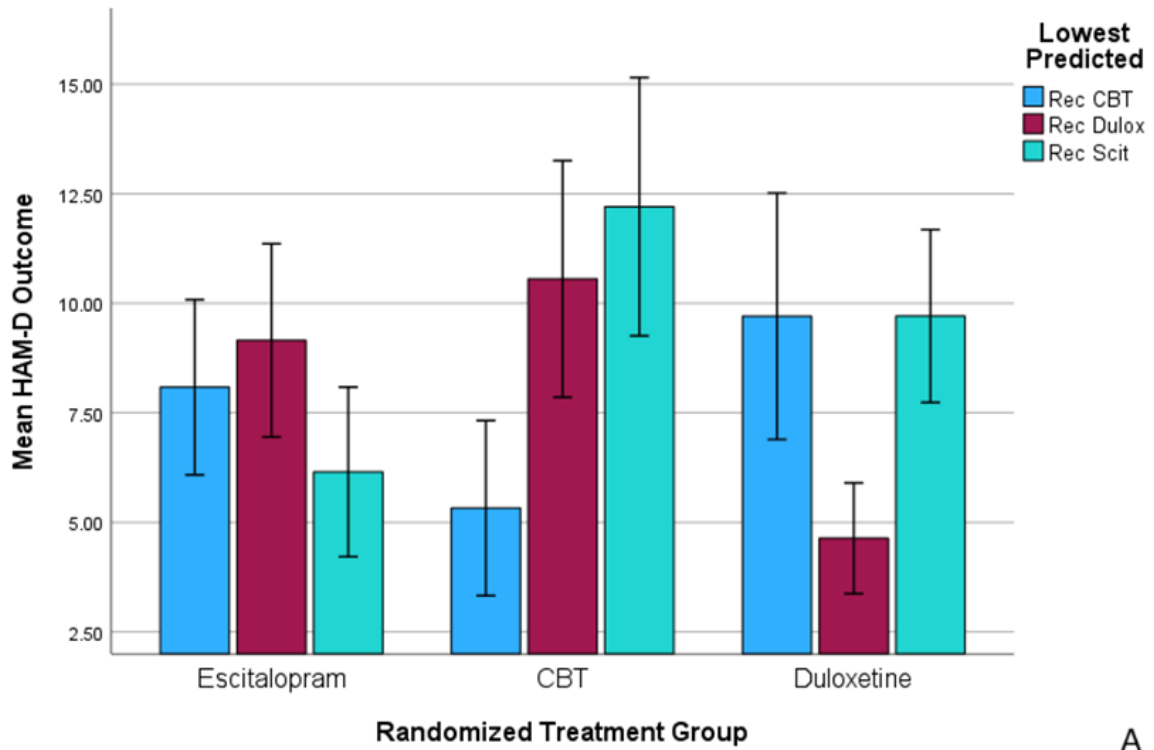
Supplementary Table 6: Means and Test Statistics for Comparing HAMD-Outcome Using Strategy A in PET-Predictor Sample

	Randomized Treatment Group N, M(SE)		T-test t	p	Cohen's d
Lowest Predicted HAMD-Outcome	CBT	Escitalopram			
Recommended CBT	<i>N = 10</i> <i>M(SE) = 8.2(1.7)</i>	<i>N = 26</i> <i>M(SE) = 9.0(1.0)</i>	0.443	0.33	0.165
Recommended ADM	<i>N = 22</i> <i>M(SE) = 10.1(1.1)</i>	<i>N = 6</i> <i>M(SE) = 6.1</i>	1.68	0.05	0.773

Note: Italicized cells are individuals who received the recommended treatment.

Supplementary Figure 1:

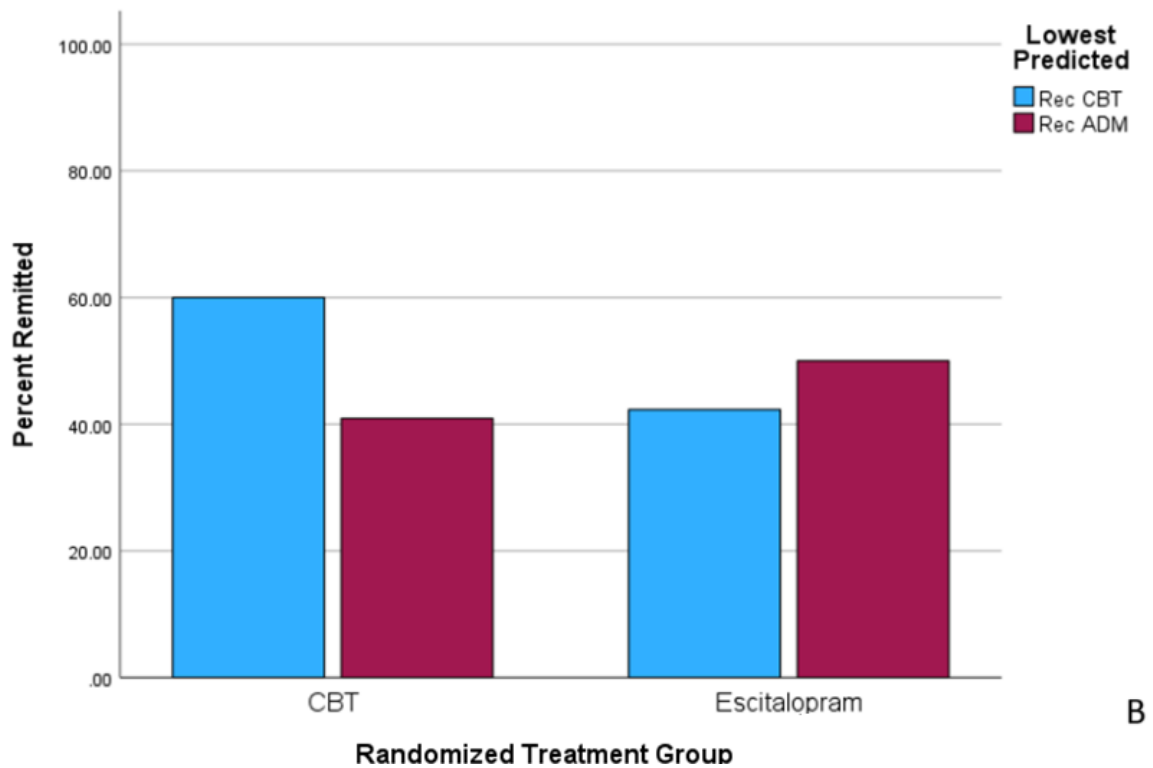
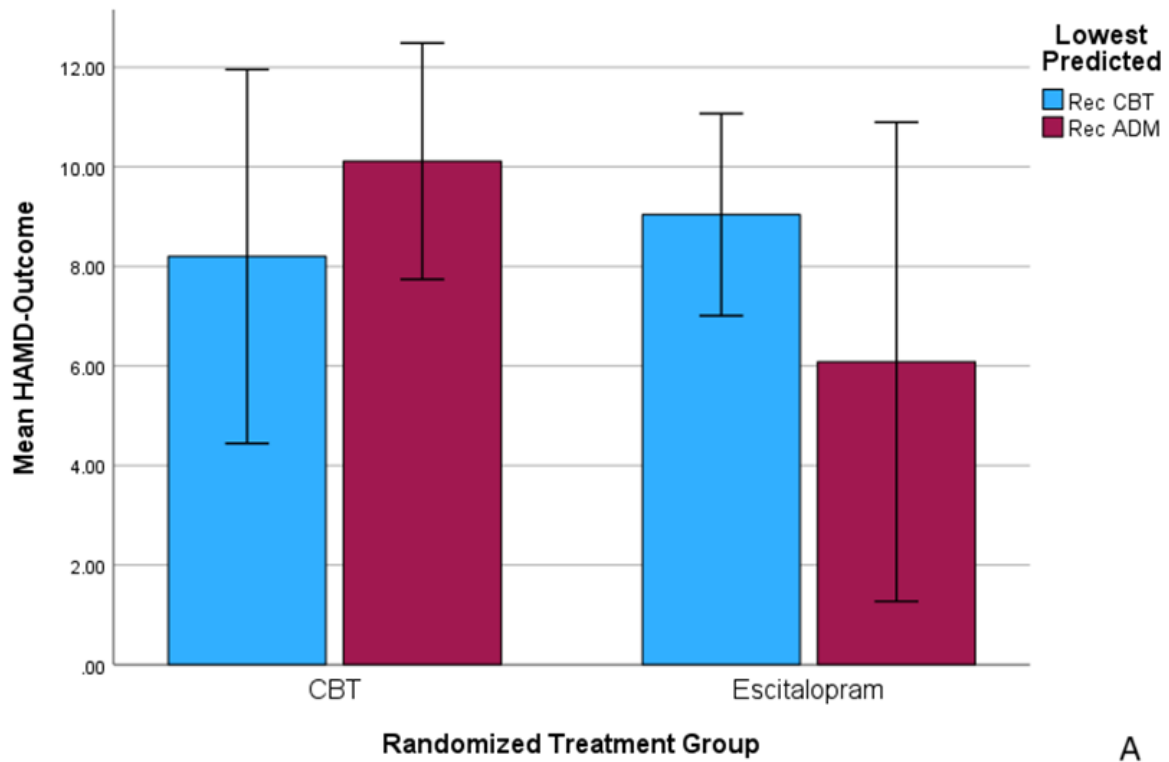
Mean HAM-D Outcome and Remission Rate by Treatment Group and Recommended Treatment Using Lowest Predicted Strategy in PREdict



- a) Mean end of treatment depression severity (HAMD-Outcome) by treatment and recommendation group. Error bars represent 95% confidence intervals.
- b) Percent remitted by treatment and recommendation group

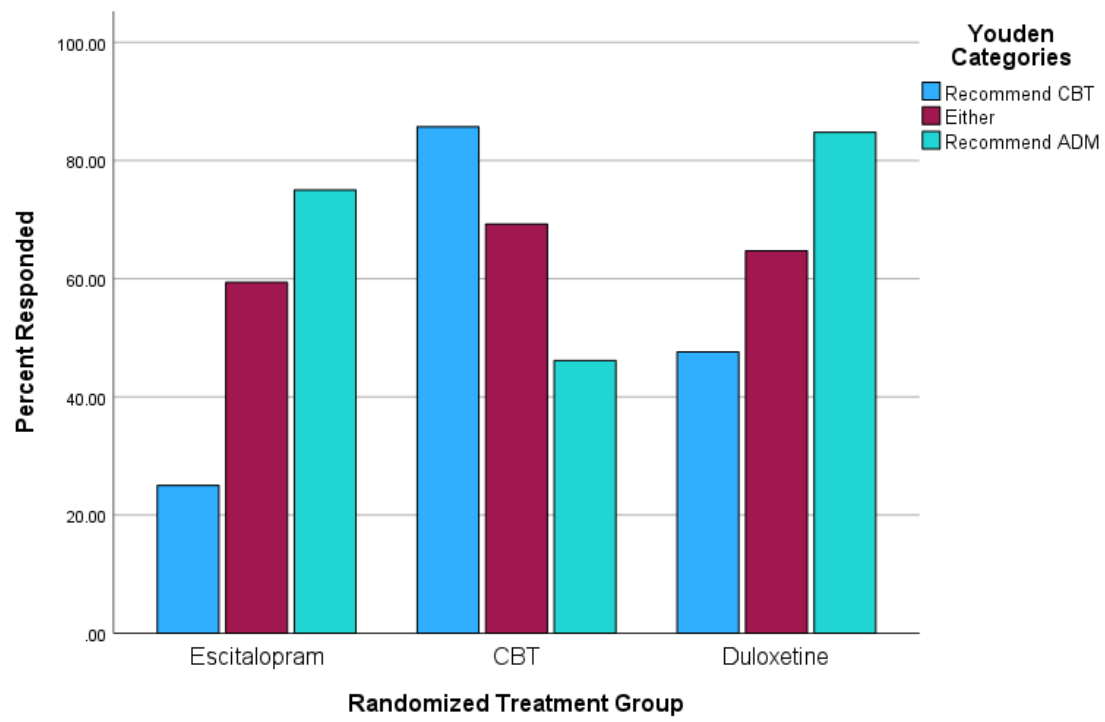
Supplementary Figure 2:

Mean HAMD-Outcome and Remission Rate by Treatment Group and Recommended Treatment Using Lowest Predicted Strategy in PET-Predictor



- a) Mean end of treatment depression severity (HAMD-Outcome) by treatment and recommendation group. Error bars represent 95% confidence intervals.
- b) Percent remitted by treatment and recommendation group

Supplementary Figure 3: Response Rates in PReDICT



Supplementary Figure 4: Response Rates in PET-Predictor

