



## **Supplementary Material**

**Article Title:** Treatment of Major Depressive Disorder Using Botulinum Toxin A: A 24-Week Randomized, Double-Blind, Placebo-Controlled Study

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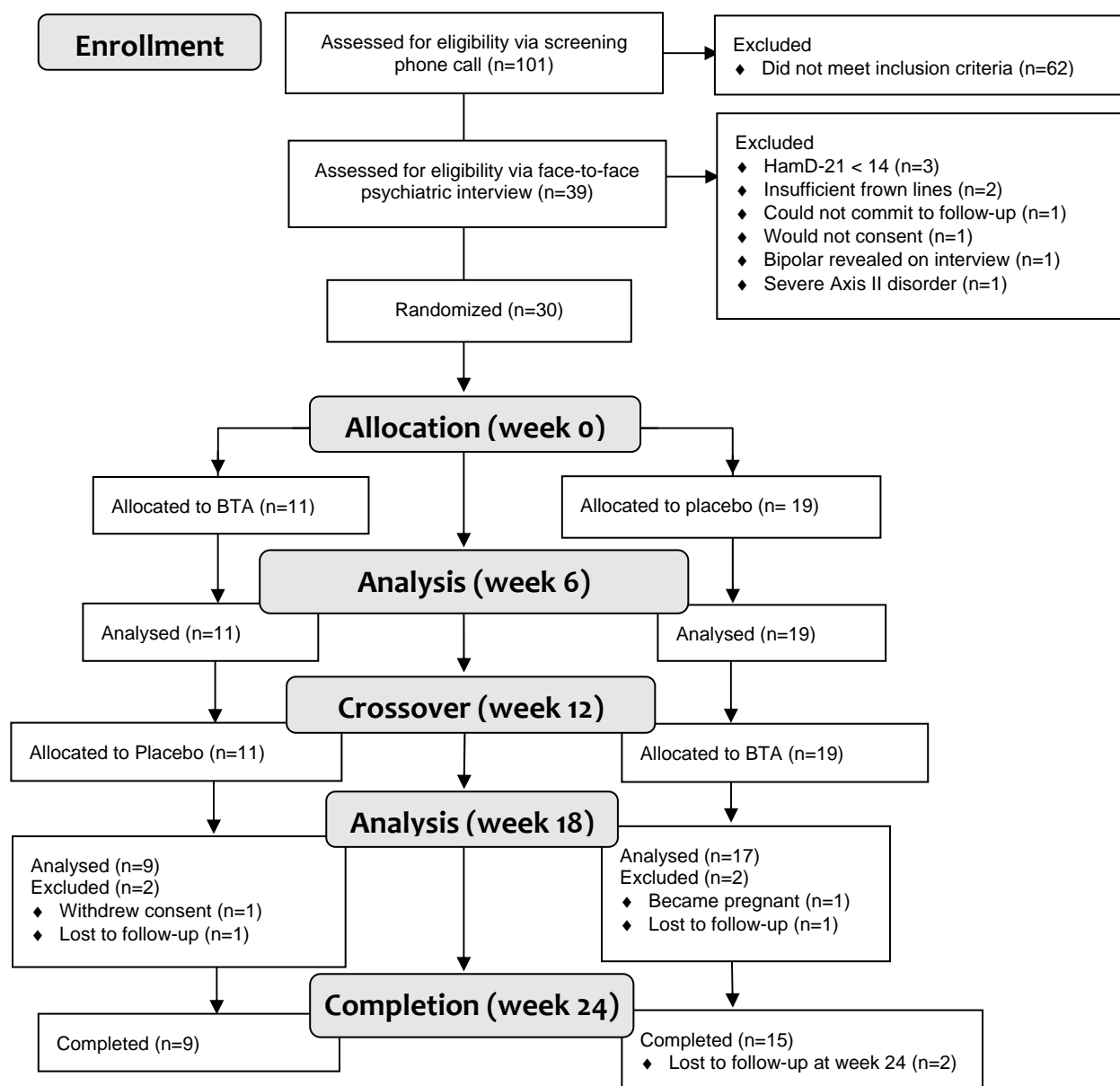
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# Supplementary eFigure 1: CONSORT Diagram- Treatment of MDD using BTA



Supplementary eTable 1: Baseline characteristics of study participants									
	Total (N=30)		Placebo (N=19)		BTA First (N=11)		Test		Significance
<b>Demographic data</b>	N	%	N	%	N	%			
Women	28	93%	17	89%	11	100%	Fisher's exact		0.39
Living alone	9	30%	5	26%	4	36%	Fisher's exact		0.53
<b>Severity of depression <sup>a</sup></b>									
Mild (296.31)	5	17%	4	21%	1	9%	Fisher's exact		0.38
Moderate (296.32)	9	30%	7	37%	2	18%	Fisher's exact		0.26
Severe (296.33)	16	53%	8	42%	8	73%	Fisher's exact		0.11
	Mean	SD	Mean	SD	Mean	SD	Df <sup>b</sup>		
Age	49.47	9.79	50.00	9.49	48.55	10.70	t=0.37	28	0.71
Education, years	14.93	2.56	15.16	2.61	14.55	2.54	t=0.63	28	0.54
Duration of MDD, years (mean)	18.05	12.43	18.05	13.96	16.09	9.73	t=0.45	28	0.66
<b>Objective Rating Scores (mean)</b>									
HAM-D 17	20.83	7.58	20.16	7.34	22.00	8.20	t=0.61	28	0.55
HAM- D 21	25.23	7.70	23.68	7.11	27.91	8.29	t=1.40	28	0.17
BDI	25.07	9.65	23.68	9.56	27.45	9.77	t=1.02	28	0.32
PHQ-9	14.43	4.62	13.47	4.88	16.09	3.78	t=1.63	28	0.11
<b>Frowning Scores</b>									
CSS-GFL	2.60	0.46	2.53	0.51	2.73	0.34	t=1.28	28	0.21
0-10 scale	7.92	1.50	7.66	1.63	8.36	1.19	t=1.36	28	0.18
<b>Number of psychiatric medications</b>	1.47	0.82	1.47	0.84	1.45	0.82	t=0.06	28	0.95

Supplementary eTable 1: The study groups did not differ in age, living situation, duration of MDD, number of psychotropic medications, or depression rating scores according to absolute Ham-D21, Ham-D17, BDI, and PHQ-9 rating.

a. Severity of Depression according to Ham D: 14-18 mild, 19-22 moderate, >23 severe

b. For Welch-test, uncorrected degrees of freedom (df) are reported.

Supplementary eTable2: Individual Demographic and Medication Profiles for 30 Patients												
Subject Number	Sex	Age	Diagnoses (ICD-9 code)	Duration of MDD (years)	# of episodes	Length of most recent episode (months)	Education (years)	Living Alone	Ham-D response to BTA	# of psychiatric meds	Psychiatric Medications x duration	Confounding factors
PLACEBO FIRST												
1	F	48	MDD, moderate (296.32)	10	4	2	16	No	Yes	0		
2	F	64	MDD, severe (296.33), Dysthymia (300.4)	50	Don't know	Ongoing	18	Yes	No	1	Fluoxetine 20 mg qam x 20 years	
3	F	52	MDD, moderate (296.32)	15	2	6	16	Yes	No	1	Venlafaxine 37.5 mg qam x 7 months	
4	M	43	MDD, mild (296.31)	10	6	6	12	Yes	No	3	Bupropion XL 450 mg qam x 12 years, Duloxetine 120 mg qam x 2 years, Methylphenidate 20 mg qam x 6 years	
5	F	56	MDD, moderate (296.32)	8	6	12	18	No	No	1	Venlafaxine 150 mg qam x 5 years	
6	F	54	MDD, mild (296.31)	12	>10	4	16	No	No	1	Bupropion 150 mg qam x 4 months	
7	F	43	MDD, severe (263.33)	4			12	No	Yes	0		
8	F	56	MDD, severe (296.33), Dysthymia (300.4)	30	>10	Ongoing	12	No	No	2	Duloxetine 90 mg x 3 years, Lamotrigine 100 mg x 2 years	
9	F	61	MDD, severe (296.23), Dysthymia (300.4)	56	1	Ongoing	16	Yes	No	2	Duloxetine 90 mg qday x 10 years, Trazodone 50 mg qhs x 6 years	
10	F	52	MDD, severe (263.33)	8	4	12	18	No	No	0		
11	F	32	MDD, moderate (296.32)	15	4	2	12	No	No	2	Escitalopram 20mg qam x 7 months, Nortriptyline 50 mg qam x 7 months	
12	F	65	MDD, moderate (296.32)	12	Don't know	Ongoing	16	No	No	1	Sertraline 50 mg qam x 13 years	
13	F	36	MDD, severe (263.33)	6	2	12	18	Yes	No	3	Bupropion XL 150 qam x 4 years, Duloxetine 90 mg x 5 years, Trazodone 200 qhs x 6 years	
14	F	47	MDD, severe (296.33), Dysthymia (300.4)	10	Don't know	Ongoing	18	No	No	2	Bupropion XL 300 mg qam x 8 years, Escitalopram 10 mg qam x 11 years	
15	F	35	MDD, severe (296.23), Dysthymia (300.4)	18	1	Ongoing	12	No	N/A	3	Venlafaxine XR 375 qam x 5 years, Bupropion XL 300 mg qam x 5 years, Eszopiclone 3 mg qhs x 4 years	Week 12- pregnant. Excluded from crossover.
16	M	54	MDD, severe (263.33)	20	4	12	18	No	N/A	2	Venlafaxine SR 300 mg qday x 2 years	Week 6- added aripiprazole 5 mg qam. Week 18- dropout
17	F	59	MDD, mild (296.31)	14	>10	Ongoing	16	No	Yes	2	Bupropion XL 300 mg qam x 3 months, Fluoxetine 10 mg qam x 13 years	Week 3- stopped fluoxetine
18	F	45	MDD, severe (263.33)	25	Don't know	1	12	No	No	1	Fluoxetine 10 mg qday x 16 years	
19	F	48	MDD, mild (296.31)	20	Don't know	Ongoing	12	No	Yes	1	Venlafaxine 150 mg qam x 19 years	
MEAN		50		18		7	15			1.47		

Supplementary eTable2: Individual Demographic and Medication Profiles for 30 Patients												
Subject Number	Sex	Age	Diagnoses (ICD-9 code)	Duration of MDD (years)	# of episodes	Length of most recent episode (months)	Education (years)	Living Alone	Ham-D response to BTA	# of psychiatric meds	Psychiatric Medications x duration	Confounding factors
BTA FIRST												
20	F	55	MDD, severe (263.33)	20	>10	4	12	Yes	No	0	None	
21	F	57	MDD, mild (296.31)	20	>10	2	16	No	No	2	Fluoxetine 40 qday x 22yrs, Bupropion XL 300 qday x 8yrs	Week 15- sister died
22	F	60	MDD, severe (263.33)	6	9	2	12	No	No	1	Duloxetine 60 mg qam x 5 yrs	
23	F	46	MDD, severe (263.33)	10	Don't know	12	18	Yes	Yes	1	Lamotrigine 100mg qday x 1 yr	
24	F	24	MDD, moderate (296.22), Anorexia Nervosa in remission (V11.8)	1	1	9	16	Yes	No	2	Venlafaxine XR 225 qday x 4 yrs, Mirtazapine 15 mg qhs x 1 yr	Week 3- increased mirtazapine 30 mg. Week 24- stopped mirtazapine.
25	F	44	MDD, severe (263.33), Post Traumatic Stress Disorder (309.81)	30	>10	Ongoing	16	No	Yes	1	Paroxetine 40 mg qday x 6 months.	
26	F	57	MDD, moderate (296.32)	23	5	2	18	Yes	Yes	2	Bupropion XL 150 qd x 5 yrs, Sertraline 100 qd x 2yrs	Week 3-started a new job
27	F	57	MDD, severe (296.33), Dysthymia (300.4)	20	>10	Ongoing	12	No	No	1	Fluoxetine 40 qday x20 yrs	
28	F	42	MDD, severe (296.33), Dysthymia (300.4)	2	4	1	12	No	Yes	1	Escitalopram 20 mg x 2 yrs	
29	F	40	MDD, severe (296.33), Dysthymia (300.4), Polysubstance/alcohol abuse, in remission (304.83)	25	>10	Ongoing	16	No	Yes	3	Fluoxetine 90mg qday x 12 yrs, Quetiapine 100 qhs x 2yrs, Clonazepam 0.5 qhs x 1 yr	
30	F	52	MDD, severe (263.33)	20	>10	12	12	No	Yes	2	Gabapentin 1200 qhs x 4 yrs, Bupropion XL 150 mg qam x 6 months	
MEAN		49		16			15			1.45		
<b>Supplementary eTable 2:</b> Data collection based on individual characteristics of each participant. Confounding factors are listed, including 3 patients that made medication changes during the study. One of these 3 patients was a responder (patient 17), which occurred 12 weeks after stopping her antidepressant and 3 weeks after BTA injection. Timing suggests response was not due to medication change (i.e. medication change less likely to be a confounding factor). Abbreviations: ICD-The International Classification of Diseases, #- number, MDD- Major Depressive Disorder, qday- every day; qhs- every night, qam- every morning, BTA- botulinum toxin A												

Supplementary eTable 3: Main effects of ANOVA models with random intercepts							
		Cell Means Model, % Change					
		BDI		HAMD-21		PHQ-9	
Group	Week	Estimate	p-value	Estimate	p-value	Estimate	p-value
BTA First	0	0.0	--	0.0	--	0.0	--
	3	-37.6	<.0001	-37.0	<.0001	-31.7	0.0008
<b>6 wks post BTA</b>	<b>6</b>	<b>-41.9</b>	<b>&lt;.0001</b>	<b>-42.4</b>	<b>&lt;.0001</b>	<b>-35.2</b>	<b>0.0002</b>
	12	-41.3	<.0001	-41.4	<.0001	-48.5	<.0001
	15	-33.5	0.0002	-27.4	0.0022	-36.2	0.0004
	18	-37.8	<.0001	-32.4	0.0003	-55.8	<.0001
<b>24 wks post BTA</b>	<b>24</b>	<b>-58.3</b>	<b>&lt;.0001</b>	<b>-46.6</b>	<b>&lt;.0001</b>	<b>-61.0</b>	<b>&lt;.0001</b>
BTA Second	0	0.0	--	0.0	--	0.0	--
	3	-14.7	0.0191	-14.4	0.0219	-13.9	0.0491
<b>6 wks post Placebo</b>	<b>6</b>	<b>-11.9</b>	<b>0.0574</b>	<b>1.8</b>	<b>0.7728</b>	<b>-9.1</b>	<b>0.1956</b>
	12	-13.3	0.0334	-0.9	0.8913	-7.1	0.3152
	15	-30.2	<.0001	-33.0	<.0001	-36.3	<.0001
<b>6 wks post BTA</b>	<b>18</b>	<b>-35.8</b>	<b>&lt;.0001</b>	<b>-34.9</b>	<b>&lt;.0001</b>	<b>-25.2</b>	<b>0.0006</b>
	24	-41.4	<.0001	-39.6	<.0001	-41.6	<.0001
		Weeks since BTA Model, % Change					
		BDI		HAMD-21		PHQ-9	
Time effect	0	0.0	--	0.0	--	0.0	--
	3	-14.7	0.0162	-14.4	0.0181	-13.9	0.0442
	6	-11.9	0.0513	1.8	0.7660	-9.1	0.1855
	12	-13.3	0.0292	-0.9	0.8879	-7.1	0.3042
	15	-7.3	0.5499	-10.5	0.3907	-18.5	0.1815
	18	-5.7	0.6383	9.2	0.4496	0.8	0.9525
	24	-13.4	0.2821	1.0	0.9353	-0.1	0.9941
Weeks since BTA	0	0.0	--	0.0	--	0.0	--
	3	-23.0	0.0180	-22.6	0.0186	-17.7	0.1080
	6	-30.1	0.0021	-44.2	<.0001	-26.1	0.0186
	12	-28.0	0.0041	-40.6	<.0001	-41.5	0.0002
	15	-26.2	0.0957	-16.9	0.2810	-17.7	0.3218
	18	-32.1	0.0414	-41.7	0.0083	-56.7	0.0017
	24	-44.9	0.0051	-47.6	0.0029	-60.9	0.0009

Supplementary eTable3: Statistical analysis based on repeated measures 2-way ANOVA model. Two different ANOVA models were used: 1. cell means model; 2. time-since-BTA model. The data emphasized in text is highlighted.