Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Walkup JT, Albano AM, Piacentini J, et al. Cognitive behavioral therapy, sertraline, or a combination in childhood anxiety. N Engl J Med 2008;359:2753-66. DOI: 10.1056/NEJMoa0804633.

(PDF updated December 19, 2008.)

This supplementary table presents mild (i.e., not functionally impairing), moderate, and severe AEs that occurred in 3% or more of the participants in any treatment group. Statistical testing is limited to pairwise contrasts between the sertraline only group vs. the placebo group, and the sertraline only group vs. the cognitive behavioral therapy group. Statistical testing was also conducted on the number of AE elicitation opportunities among the four treatment groups.

No AEs were identified more frequently in the sertraline only group as compared to the placebo group. Significantly fewer AEs were identified in a number of categories when comparing the cognitive-behavioral therapy group to the sertraline only group. There were significantly more AE elicitation opportunities in the combination treatment group as compared to sertraline only, cognitive behavioral therapy only and placebo groups.

Given the lack of any AE differences between the sertraline only and placebo group, the lower number of AEs in the cognitive behavioral therapy group as compared to the sertraline only group is difficult to interpret. As noted in the main paper, the increased rate of some AEs in the combination condition maybe related to significantly greater opportunities to elicit adverse events (see Table below). It is also possible that parental, patient and/or clinician expectancies for side effects may have contributed differentially to the adverse event reporting in the combination treatment group and the cognitive-behavioral therapy only group due to the open nature of the treatment provided.

Proportion of Participants Who Experienced a Mild, Moderate, and Severe Adverse Event (AE) by Treatment Condition Across 12 Weeks of Acute Treatment, N (%)*

	COMB (N = 140)		SRT (N = 133)		CBT (N = 139)		PBO (N = 76)		Total (N = 488)		SRT vs PBO	SRT vs CBT
	N	%	N	%	N	%	N	%	N	%	P-value†	P-value†
Physical Adverse Events*												
Headaches	62	44.29	49	36.84	44	31.65	21	27.63	176	36.07	0.17	0.37
Cold Symptoms	40	28.57	32	24.06	40	28.78	17	22.37	129	26.43	0.78	0.38
Gastric Distress	51	36.43	**34**	**25.56**	**21**	**15.11**	20	26.32	126	25.82	0.90	**0.03**
Sore Throat	24	17.14	17	12.78	20	14.39	13	17.11	74	15.16	0.39	0.70
Body Ache	15	10.71	**21**	**15.79**	**11**	**7.91**	9	11.84	56	11.48	0.43	**0.04**
Insomnia	21	15.00	**24**	**18.05**	**4**	**2.88**	7	9.21	56	11.48	0.08	**<0.001**
Diarrhea	22	15.71	13	9.77	7	5.04	11	14.47	53	10.86	0.31	0.13
Vomiting	18	12.86	7	5.26	12	8.63	7	9.21	44	9.02	0.27	0.27
Fever	9	6.43	12	9.02	13	9.35	10	13.16	44	9.02	0.35	0.92
Dermatologic Problems	19	13.57	12	9.02	8	5.76	4	5.26	43	8.81	0.33	0.30
Cough	10	7.14	12	9.02	11	7.91	5	6.58	38	7.79	0.53	0.74

Nausea	12	8.57	12	9.02	7	5.04	7	9.21	38	7.79	0.96	0.20
Fatigue	14	10.00	**13**	**9.77**	**0**	**0.00**	11	14.47	38	7.79	0.31	**<0.001**
Interrupted Sleep	20	14.29	9	6.77	3	2.16	3	3.95	35	7.17	0.40	0.06
Appetite Decrease	16	11.43	**11**	**8.27**	**2**	**1.44**	4	5.26	33	6.76	0.42	**0.01**
Allergies	15	10.71	6	4.51	6	4.32	6	7.89	33	6.76	0.36§	0.94
Upper Respiratory Infection	8	5.71	5	3.76	12	8.63	5	6.58	30	6.15	0.50§	0.10
Accidental Injury	8	5.71	8	6.02	9	6.47	2	2.63	27	5.53	0.33§	0.88
Ear Pain	11	7.86	6	4.51	8	5.76	1	1.32	26	5.33	0.43§	0.64
Dental Problems	7	5.00	9	6.77	4	2.88	3	3.95	23	4.71	0.54§	0.13
Dizziness	7	5.00	**8**	**6.02**	**1**	**0.72**	4	5.26	20	4.10	0.83	**0.02§**
Sinus Infections	4	2.86	3	2.26	7	5.04	3	3.95	17	3.48	0.67§	0.22§
Sedation	1	0.71	**9**	**6.77**	**0**	**0.00**	3	3.95	13	2.66	0.54§	**0.001§**
Chest Pain	7	5.00	0	0.00	1	0.72	1	1.32	9	1.84	0.36§	1.00§
Enuresis	4	2.86	4	3.01	0	0.00	0	0.00	8	1.64	0.30§	0.06§
Sweating	4	2.86	4	3.01	0	0.00	0	0.00	8	1.64	0.30§	0.06§
Nose Bleed	6	4.29	1	0.75	1	0.72	0	0.00	8	1.64	1.00§	1.00§
Bruising	5	3.57	2	1.50	0	0.00	0	0.00	7	1.43	0.54§	0.24§
Total N Reporting Above Physical AEs‡	114	81.43	97	72.93	93	66.91	53	69.74	357	73.16	NA	NA
Psychiatric Adverse Events*												
Increased Motor Activity	21	15.00	**12**	**9.02**	**2**	**1.44**	5	6.58	40	8.20	0.53	**0.005**
Disinhibition	19	13.57	**9**	**6.77**	**2**	**1.44**	3	3.95	33	6.76	0.54§	**0.03**
Irritability	7	5.00	**12**	**9.02**	**4**	**2.88**	6	7.89	29	5.94	0.78	**0.03**
Restless/Fidgety	14	10.00	**9**	**6.77**	**2**	**1.44**	4	5.26	29	5.94	0.77§	**0.03**
Disobedient/Defiant	12	8.57	7	5.26	3	2.16	2	2.63	24	4.92	0.49§	0.21§
Anxiety/Nervousness	6	4.29	5	3.76	2	1.44	5	6.58	18	3.69	0.50§	0.27§
Habits/Mannerisms/Rituals	12	8.57	5	3.76	1	0.72	0	0.00	18	3.69	0.16§	0.11§
Depression	2	1.43	8	6.02	3	2.16	3	3.95	16	3.28	0.75§	0.11
Emotional Outburst	1	0.71	5	3.76	6	4.32	4	5.26	16	3.28	0.73§	0.82
Hostility	7	5.00	4	3.01	3	2.16	2	2.63	16	3.28	1.00§	0.72§
Agitation	10	7.14	2	1.50	2	1.44	0	0.00	14	2.87	0.54§	1.00§
Tremor	7	5.00	5	3.76	1	0.72	0	0.00	13	2.66	0.16§	0.11§
Early Morning Awakening	7	5.00	3	2.26	1	0.72	0	0.00	11	2.25	0.56§	0.36§
Impulsivity	6	4.29	3	2.26	1	0.72	1	1.32	11	2.25	1.00§	0.36§

Concentration Difficulty	1	0.71	**5**	**3.76**	**0**	**0.00**	2	2.63	8	1.64	1.00§	**0.03§**
Apathy/Disinterest	1	0.71	4	3.01	2	1.44	0	0.00	7	1.43	0.30§	0.44§
Total N Reporting Above Psychiatric AEs‡	68	48.57	43	32.33	21	15.11	24	31.58	156	31.97	NA	
Harm Related Adverse Events**												
Suicidal Ideation	12	8.57	5	3.76	9	6.47	2	2.63	28	5.74	1.00§	0.31
Aggression	9	6.43	2	1.50	3	2.16	0	0.00	14	2.87	0.54§	1.00§
Self-Injurious Behavior	3	2.14	2	1.50	1	0.72	1	1.32	7	1.43	1.00§	0.61§
Homicidal Ideation	0	0.00	2	1.50	0	0.00	0	0.00	2	0.41	0.54§	0.24
Suicidal Behavior	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	NA	NA
Total N Reporting any Harm-related AEs‡	21	15.00	10	7.52	13	9.35	3	3.95	47	9.63	NA	

Average No. of AE Reporting Opportunities				P-Value
Mean (SD)	12.8 (3.95)	9.9 (3.63)	10.6 (1.96)	9.68 (4.24)	§§
Range	1-22	0-14	1-14	0-14	

COMB = Combination treatment group; SRT = Sertraline treatment group; CBT = cognitive behavior therapy treatment group; PBO = Placebo treatment group.

Bold P-value indicates a statistically significant difference (P<0.05) in pairwise contrast between sertraline and CBT

* Unless noted otherwise, adverse events occurring in at least 3% or greater of the participants in any treatment condition are reported.

† Unless noted otherwise, differences in the number of adverse events between SRT and PBO, and SRT and CBT groups were evaluated using Pearson's chi-square statistic.

‡ Note: any given participant could have had more than one adverse event.

§ The P-value reported is based on Fisher's exact test because the expected number of events in any given cell was less than five.

** All harm related adverse events are reported (i.e., not limited to only those occurring in at least 3% of the patients).

§§ Statistical comparisons of adverse event reporting opportunities: COMB vs. SRT: $t = 6.92$, $P < 0.001$; COMB vs. CBT: $t = 5.37$, $P < 0.001$; COMB vs. PBO: $t = 6.32$, $P < 0.001$.