

Supplementary Online Content

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eTable 1. Follow-up Drugs Started After Randomization

eTable 2. Baseline Medications

eTable 3. Number of Different Drugs From Each Major Class Each Patient Is Taking at Baseline

eTable 4. Baseline Medication Combinations

eTable 5. Adverse Events

eFigure 1. Product-Limit Survival Estimates With Number of Subjects at Risk

eFigure 2. Percentage of Veterans at Each CAPS Severity Level at 24 Weeks, by Treatment

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

eTable 1. Follow-up Drugs Started After Randomization

	Placebo		Risperidone		Total		p-value
	N=	134	N=	133	Patients	%	
	Patients	%	Patients	%			
Drugs started after randomization	46	34.3	59	44.4	105	39.3	0.10
Adrenergic Drugs	4	3.0	5	3.8	9	3.4	0.75
Atenolol	0	0.0	2	1.5	2	0.7	
Metoprolol	3	2.2	2	1.5	5	1.9	
Propranolol	1	0.7	1	0.8	2	0.7	
Opiates	22	16.4	19	14.3	41	15.4	0.73
Codeine	1	0.7	1	0.8	2	0.7	
Fentanyl	3	2.2	0	0.0	3	1.1	
Hydrocodone (With Or Without Acetaminophen)	13	9.7	10	7.5	23	8.6	
Methadone	1	0.7	0	0.0	1	0.4	
Morphine	3	2.2	2	1.5	5	1.9	
Oxycodone (With Or Without Acetaminophen)	4	3.0	7	5.3	11	4.1	
Tramadol	3	2.2	2	1.5	5	1.9	
Psycho-Stimulants	0	0.0	2	1.5	2	0.7	0.25
Methylphenidate	0	0.0	2	1.5	2	0.7	
Muscle Relaxant	2	1.5	4	3.0	6	2.2	0.45
Baclofen	2	1.5	2	1.5	4	1.5	
Cyclobenzaprine	1	0.7	2	1.5	3	1.1	
Antidepressants	12	9.0	15	11.3	27	10.1	0.55
Other Antidepressants	3	2.2	3	2.3	6	2.2	1.00
Bupropion	3	2.2	3	2.3	6	2.2	
Serotonin Reuptake Inhibitors	9	6.7	13	9.8	22	8.2	0.38
Citalopram	3	2.2	1	0.8	4	1.5	
Duloxetine	2	1.5	3	2.3	5	1.9	
Fluoxetine	2	1.5	4	3.0	6	2.2	
Paroxetine	1	0.7	0	0.0	1	0.4	
Sertraline	2	1.5	4	3.0	6	2.2	
Venlafaxine	2	1.5	3	2.3	5	1.9	
Tricyclic Antidepressants	1	0.7	1	0.8	2	0.7	1.00
Doxepin	1	0.7	1	0.8	2	0.7	
Mood Stabilizers	10	7.5	6	4.5	16	6.0	0.44
Antimanic Agents	10	7.5	6	4.5	16	6.0	0.44
Divalproex Or Valproic Acid	5	3.7	4	3.0	9	3.4	
Gabapentin	3	2.2	2	1.5	5	1.9	
Lamotrigine	2	1.5	1	0.8	3	1.1	
Topiramate	2	1.5	0	0.0	2	0.7	

eTable 1. Follow-up Drugs Started After Randomization (continued)

	Placebo		Risperidone		Total		p-value
	N=	134	N=	133	Patients	%	
Anxiolytics, Sedatives, and Hypnotics	20	14.9	32	24.1	52	19.5	0.07
Benzodiazepine-Like Anxiolytic Sedative	11	8.2	19	14.3	30	11.2	0.13
Alprazolam	1	0.7	0	0.0	1	0.4	
Clonazepam	3	2.2	5	3.8	8	3.0	
Diazepam	2	1.5	2	1.5	4	1.5	
Lorazepam	6	4.5	4	3.0	10	3.7	
Temazepam	0	0.0	2	1.5	2	0.7	
Zolpidem	3	2.2	8	6.0	11	4.1	
Midazolam	3	2.2	1	0.8	4	1.5	
Non-Benzodiazepine-Like Sedatives	4	3.0	10	7.5	14	5.2	0.11
Buspirone	1	0.7	0	0.0	1	0.4	
Diphenhydramine (With Or Without Acetaminophen)	1	0.7	3	2.3	4	1.5	
Hydroxyzine	2	1.5	7	5.3	9	3.4	
Serotonin Antagonists	5	3.7	9	6.8	14	5.2	0.29
Cyproheptadine	1	0.7	0	0.0	1	0.4	
Mirtazapine (<30 Mg Daily)	2	1.5	2	1.5	4	1.5	
Nefazodone (<100 Mg Daily)	0	0.0	1	0.8	1	0.4	
Quetiapine	1	0.7	2	1.5	3	1.1	
Trazodone (<100 Mg Daily)	2	1.5	4	3.0	6	2.2	
Benzodiazepine Receptor Agonist	1	0.7	0	0.0	1	0.4	1.00
Eszopiclone	1	0.7	0	0.0	1	0.4	
Other	3	2.2	5	3.8	8	3.0	0.50
Antiarrhythmic agents	2	1.5	1	0.8	3	1.1	1.00
Lidocaine	2	1.5	1	0.8	3	1.1	
Anti-Migrane	0	0.0	2	1.5	2	0.7	0.25
Zolmitriptan	0	0.0	2	1.5	2	0.7	
Anti-Parkinson	0	0.0	1	0.8	1	0.4	0.50
Pramipexole	0	0.0	1	0.8	1	0.4	
Dietary Supplement	1	0.7	1	0.8	2	0.7	1.00
Omega-3 Fatty Acid	1	0.7	1	0.8	2	0.7	
Hormone Replacement	0	0.0	1	0.8	1	0.4	0.50
Levothyroxine	0	0.0	1	0.8	1	0.4	
Antipsychotics	1	0.7	3	2.3	4	1.5	0.37
Second Generation Antipsychotics	1	0.7	1	0.8	2	0.7	1.00
Aripiprazole	0	0.0	1	0.8	1	0.4	
Olanzapine	1	0.7	1	0.8	2	0.7	
Ziprasidone	0	0.0	1	0.8	1	0.4	
Other Antipsychotics	0	0.0	3	2.3	3	1.1	0.12
Chlorpromazine	0	0.0	2	1.5	2	0.7	
Perphenazine	0	0.0	1	0.8	1	0.4	

eTable 2. Baseline Medications. A description of the number of medications within each drug class prescribed to patients assigned to placebo and risperidone at baseline. Individual patients contribute a single data point to each medication class.

			TREAT		
			Placebo	Risperidone	
			N	N	
Major	Minor	Generic			
Antidepressants	Serotonin Reuptake Inhibitors	CITALOPRAM	35	29	
		DULOXETINE	3	5	
		ESCITALOPRAM	2	2	
		FLUOXETINE	12	21	
		PAROXETINE	8	6	
		SERTRALINE	28	15	
		VENLAFAXINE	10	16	
	Other Antidepressants	BUPROPION	33	43	
	Tricyclic Antidepressants	AMITRIPTYLINE	2	5	
		DESIPRAMINE	1	.	
		DOXEPIN	.	2	
		IMIPRAMINE	.	1	
		NORTRIPTYLINE	3	2	
	Mood Stabilizers	Antimanic Agents	CARBAMAZEPINE	1	1
			DIVALPROEX or VALPROIC ACID	8	1
GABAPENTIN			16	15	
LAMOTRIGINE			3	5	
TOPIRAMATE			4	4	
Lithium		LITHIUM	1	2	

eTable 2. Baseline Medications (continued)

			TREAT		
			Placebo	Risperidone	
			N	N	
Major	Minor	Generic			
Anxiolytics, Sedatives, and Hypnotics	Benzodiazepine- Like Anxiolytic Sedative	ALPRAZOLAM	1	2	
		CLONAZEPAM	11	13	
		DIAZEPAM	5	5	
		LORAZEPAM	5	4	
		TEMAZEPAM	6	9	
		TRIAZOLAM	1	.	
		ZOLPIDEM	13	19	
	Non- Benzodiazepine- Like Sedatives	BUSPIRONE	9	6	
		CHLORPHENIRAMINE	1	1	
		CYPROHEPTADINE	.	1	
		DIPHENHYDRAMINE +/- ACETAMINOPHEN	6	9	
		HYDROXYZINE	8	8	
		MIRTAZAPINE < 30mg daily	12	17	
		NEFAZODONE < 100mg daily	1	.	
		RAMELTEON	1	1	
		QUETIAPINE < 25mg daily	3	.	
		TRAZODONE < 100mg daily	23	27	
			ATENOLOL	22	15
	Adrenergic Drugs		CARVEDILOL	1	.
		METOPROLOL	9	5	
		NADOLOL	.	1	
		PROPRANOLOL	3	4	
		TIMOLOL	1	1	
		CODEINE	1	.	
Opiates		FENTANYL	1	2	
		HYDROCODONE +/- ACETAMINOPHEN	10	18	
		METHADONE	2	4	
		MORPHINE	.	6	
		OXYCODONE	4	2	
		PROPOXYPHENE	.	1	
		TRAMADOL	11	8	

eTable 2. Baseline Medications (continued)

			TREAT	
			Placebo	Risperidone
			N	N
Major	Minor	Generic		
		BACLOFEN	2	2
Muscle Relaxant		CYCLOBENZAPRINE	12	8
Psycho-Stimulants		AMPHETAMINE/DEXTROAMPHETAMINE	1	.
		DEXTROAMPHETAMINE	1	1
		METHYLPHENIDATE	.	2
Other	Antiarrhythmic agents	LIDOCAINE	3	1
	Antidiabetic Agents	PIOGLITAZONE	2	2
	Anti-Migrane	SUMATRIPTAN	3	.
	Anti-Migrane	ZOLMITRIPTAN	6	5
	Anti-Parkinson	PRAMIPEXOLE	.	1
	Anti-Parkinson	ROPINIROLE	3	1
	Dietary Supplement	OMEGA-3 FATTY ACID	7	7
	Hormone Replacement	LEVOTHYROXINE	2	3

eTable 3. Number of different drugs from each Major Class each patient is taking at Baseline. A description of the number of medications within each drug class prescribed to patients assigned to placebo and risperidone at baseline. Individual patients contribute a single data point to each medication class.

	Frequency Count	TREAT	
		Placebo N	Risperidone N
Adrenergic Drugs	0	98	107
	1	36	26
Antidepressants	0	24	21
	1	85	79
	2	23	31
	3	2	2
Anxiolytics, Sedatives, and Hypnotics	0	51	48
	1	66	58
	2	15	20
	3	2	6
	4	.	1
Mood Stabilizers	0	103	99
	1	29	30
	2	2	4
Muscle Relaxant	0	120	123
	1	14	10
Opiates	0	109	100
	1	21	25
	2	4	8
Other	0	111	113
	1	21	20
	2	2	.
Psycho-Stimulants	0	132	130
	1	2	3

eTable 4. Baseline Medication Combinations (chi square = 1.73, df=8, p=0.988).

	Placebo (percent)		Risperidone (percent)		Total (percent)	
No medications at baseline	5	3.73%	8	6.02%	13	4.87%
No Serotonin Reuptake Inhibitor (SRI) ± other psychotropic medications	33	24.63%	34	25.56%	67	25.09%
SRI only	11	8.21%	10	7.52%	21	7.87%
SRI ± another antidepressant (AA)	3	2.24%	4	3.01%	7	2.62%
SRI ± AA ± sedative-hypnotics/anxiolytics (SH)	19	14.18%	20	15.04%	39	14.61%
SRI ± AA ± SH ± mood stabilizers (MS)	6	4.48%	7	5.26%	13	4.87%
SRI ± AA ± SH ± MS ± pain medications (PM)	18	13.43%	18	13.53%	36	13.48%
SRI ± AA ± SH ± MS ± PM ± anti-adrenergic agents (AAA)	18	13.43%	14	10.53%	32	11.99%
SRI ± AA ± SH ± MS ± PM ± AAA ± other CNS medications	21	15.67%	18	13.53%	39	14.61%
Total	134	100.00%	133	100.00%	267	100.00%

The entry criteria for this study specified that patients had to be on SRI medication unless, on the basis of at least two prior trials of SRI's, either the patient refused to try another SRI or the study physician determined that SRI's presented a significant medical or psychiatric risk for the patient.

Medications within each category:

SRI: citalopram, duloxetine, escitalopram, fluoxetine, paroxetine, sertraline, venlafaxine

Another antidepressant: bupropion, amitriptyline, desipramine, doxepin, imipramine, nortriptyline

Sedative-hypnotics: alprazolam, clonazepam, diazepam, lorazepam, temazepam, triazolam, zolpidem, busprione, chlorpheniramine, diphenhydramine ± acetaminophen, hydroxyzine, ramelteon, cyproheptadine, mirtazapine <30mg daily, nefazodone <100mg daily, quetiapine <25mg daily, trazodone <100mg daily

Mood stabilizer: carbamazepine, divalproex or valproic acid, gabapentin, lamotrigine, topiramate, lithium

Pain medication: codeine, fentanyl, hydrocodone ± acetaminophen, methadone, oxycodone, propoxyphene, tramadol

Anti-adrenergic agents: atenolol, carvedilol, metoprolol, nadolol, propranolol, timolol

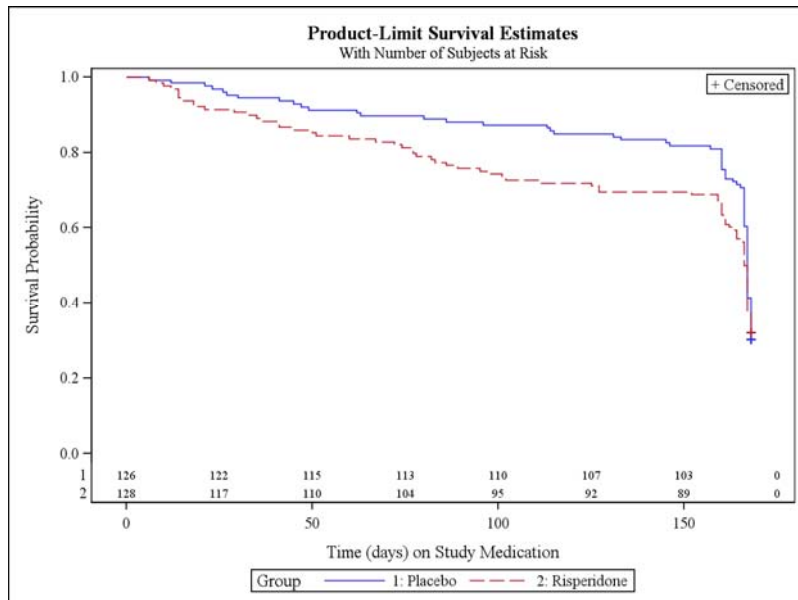
Other: baclofen, cyclobenzaprine, amphetamine, dextroamphetamine, methylphenidate, lidocaine, pioglitazone, sumatriptan, zolmitriptan, pramipexole, ropinirole, omega-3-fatty acid, levothyroxine

eTable 5. Adverse Events*

Body System and Preferred Term	Placebo		Risperidone		Total		p-value
	N=	134	N=	133	Patients	%	
All Adverse Events	97	73.5	109	83.2	206	77.2	0.08
Nervous system disorders	57	43.2	69	52.7	126	47.9	0.14
Somnolence	2	1.5	13	9.9	15	5.7	0.00
Disturbance in attention	2	1.5	9	6.9	11	4.2	0.03
Gastrointestinal disorders	37	28.0	41	31.3	78	29.7	0.59
Salivary hypersecretion	1	0.8	13	9.9	14	5.3	0.00
Investigations	26	19.7	39	29.8	65	24.7	0.06
Weight increased	3	2.3	20	15.3	23	8.7	0.00
Psychiatric disorders	23	17.4	42	32.1	65	24.7	0.01
Libido decreased	0	0.0	8	6.1	8	3.0	0.00
General disorders and administration site conditions	18	13.6	31	23.7	49	18.6	0.04
Fatigue	0	0.0	18	13.7	18	6.8	0.00
Respiratory, thoracic and mediastinal disorders	4	3.0	20	15.3	24	9.1	0.00
Dyspnoea	0	0.0	8	6.1	8	3.0	0.00
Nasal congestion	0	0.0	6	4.6	6	2.3	0.01

* Adverse events presented here are coded using the Medical Dictionary for Regulatory Activities (MedDRA v.13.0; <http://www.meddrasso.com>). The table reflects only the MedDRA **System Organ Classes** where events occurred in more than 5% of all participants. Overall, there were 1499 adverse events in all **System Organ Classes**.

eFigure 1. Product-Limit Survival Estimates With Number of Subjects at Risk



eFigure 2. Percentage of Veterans at Each CAPS Severity Level at 24 Weeks, by Treatment

