

## Supplementary Online Content

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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	%			
<b>Drugs started after randomization</b>	<b>46</b>	<b>34.3</b>	<b>59</b>	<b>44.4</b>	<b>105</b>	<b>39.3</b>	<b>0.10</b>
<b>Adrenergic Drugs</b>	<b>4</b>	<b>3.0</b>	<b>5</b>	<b>3.8</b>	<b>9</b>	<b>3.4</b>	<b>0.75</b>
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	
<b>Opiates</b>	<b>22</b>	<b>16.4</b>	<b>19</b>	<b>14.3</b>	<b>41</b>	<b>15.4</b>	<b>0.73</b>
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	
<b>Psycho-Stimulants</b>	<b>0</b>	<b>0.0</b>	<b>2</b>	<b>1.5</b>	<b>2</b>	<b>0.7</b>	<b>0.25</b>
Methylphenidate	0	0.0	2	1.5	2	0.7	
<b>Muscle Relaxant</b>	<b>2</b>	<b>1.5</b>	<b>4</b>	<b>3.0</b>	<b>6</b>	<b>2.2</b>	<b>0.45</b>
Baclofen	2	1.5	2	1.5	4	1.5	
Cyclobenzaprine	1	0.7	2	1.5	3	1.1	
<b>Antidepressants</b>	<b>12</b>	<b>9.0</b>	<b>15</b>	<b>11.3</b>	<b>27</b>	<b>10.1</b>	<b>0.55</b>
<b>Other Antidepressants</b>	<b>3</b>	<b>2.2</b>	<b>3</b>	<b>2.3</b>	<b>6</b>	<b>2.2</b>	<b>1.00</b>
Bupropion	3	2.2	3	2.3	6	2.2	
<b>Serotonin Reuptake Inhibitors</b>	<b>9</b>	<b>6.7</b>	<b>13</b>	<b>9.8</b>	<b>22</b>	<b>8.2</b>	<b>0.38</b>
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	
<b>Tricyclic Antidepressants</b>	<b>1</b>	<b>0.7</b>	<b>1</b>	<b>0.8</b>	<b>2</b>	<b>0.7</b>	<b>1.00</b>
Doxepin	1	0.7	1	0.8	2	0.7	
<b>Mood Stabilizers</b>	<b>10</b>	<b>7.5</b>	<b>6</b>	<b>4.5</b>	<b>16</b>	<b>6.0</b>	<b>0.44</b>
<b>Antimanic Agents</b>	<b>10</b>	<b>7.5</b>	<b>6</b>	<b>4.5</b>	<b>16</b>	<b>6.0</b>	<b>0.44</b>
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	%	
<b>Anxiolytics, Sedatives, and Hypnotics</b>	<b>20</b>	<b>14.9</b>	<b>32</b>	<b>24.1</b>	<b>52</b>	<b>19.5</b>	<b>0.07</b>
<b>Benzodiazepine-Like Anxiolytic Sedative</b>	<b>11</b>	<b>8.2</b>	<b>19</b>	<b>14.3</b>	<b>30</b>	<b>11.2</b>	<b>0.13</b>
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	
<b>Non-Benzodiazepine-Like Sedatives</b>	<b>4</b>	<b>3.0</b>	<b>10</b>	<b>7.5</b>	<b>14</b>	<b>5.2</b>	<b>0.11</b>
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	
<b>Serotonin Antagonists</b>	<b>5</b>	<b>3.7</b>	<b>9</b>	<b>6.8</b>	<b>14</b>	<b>5.2</b>	<b>0.29</b>
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	
<b>Benzodiazepine Receptor Agonist</b>	<b>1</b>	<b>0.7</b>	<b>0</b>	<b>0.0</b>	<b>1</b>	<b>0.4</b>	<b>1.00</b>
Eszopiclone	1	0.7	0	0.0	1	0.4	
<b>Other</b>	<b>3</b>	<b>2.2</b>	<b>5</b>	<b>3.8</b>	<b>8</b>	<b>3.0</b>	<b>0.50</b>
<b>Antiarrhythmic agents</b>	<b>2</b>	<b>1.5</b>	<b>1</b>	<b>0.8</b>	<b>3</b>	<b>1.1</b>	<b>1.00</b>
Lidocaine	2	1.5	1	0.8	3	1.1	
<b>Anti-Migrane</b>	<b>0</b>	<b>0.0</b>	<b>2</b>	<b>1.5</b>	<b>2</b>	<b>0.7</b>	<b>0.25</b>
Zolmitriptan	0	0.0	2	1.5	2	0.7	
<b>Anti-Parkinson</b>	<b>0</b>	<b>0.0</b>	<b>1</b>	<b>0.8</b>	<b>1</b>	<b>0.4</b>	<b>0.50</b>
Pramipexole	0	0.0	1	0.8	1	0.4	
<b>Dietary Supplement</b>	<b>1</b>	<b>0.7</b>	<b>1</b>	<b>0.8</b>	<b>2</b>	<b>0.7</b>	<b>1.00</b>
Omega-3 Fatty Acid	1	0.7	1	0.8	2	0.7	
<b>Hormone Replacement</b>	<b>0</b>	<b>0.0</b>	<b>1</b>	<b>0.8</b>	<b>1</b>	<b>0.4</b>	<b>0.50</b>
Levothyroxine	0	0.0	1	0.8	1	0.4	
<b>Antipsychotics</b>	<b>1</b>	<b>0.7</b>	<b>3</b>	<b>2.3</b>	<b>4</b>	<b>1.5</b>	<b>0.37</b>
<b>Second Generation Antipsychotics</b>	<b>1</b>	<b>0.7</b>	<b>1</b>	<b>0.8</b>	<b>2</b>	<b>0.7</b>	<b>1.00</b>
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	
<b>Other Antipsychotics</b>	<b>0</b>	<b>0.0</b>	<b>3</b>	<b>2.3</b>	<b>3</b>	<b>1.1</b>	<b>0.12</b>
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
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
<b>Adrenergic Drugs</b>	<b>0</b>	98	107
	<b>1</b>	36	26
<b>Antidepressants</b>	<b>0</b>	24	21
	<b>1</b>	85	79
	<b>2</b>	23	31
	<b>3</b>	2	2
<b>Anxiolytics, Sedatives, and Hypnotics</b>	<b>0</b>	51	48
	<b>1</b>	66	58
	<b>2</b>	15	20
	<b>3</b>	2	6
	<b>4</b>	.	1
<b>Mood Stabilizers</b>	<b>0</b>	103	99
	<b>1</b>	29	30
	<b>2</b>	2	4
<b>Muscle Relaxant</b>	<b>0</b>	120	123
	<b>1</b>	14	10
<b>Opiates</b>	<b>0</b>	109	100
	<b>1</b>	21	25
	<b>2</b>	4	8
<b>Other</b>	<b>0</b>	111	113
	<b>1</b>	21	20
	<b>2</b>	2	.
<b>Psycho-Stimulants</b>	<b>0</b>	132	130
	<b>1</b>	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

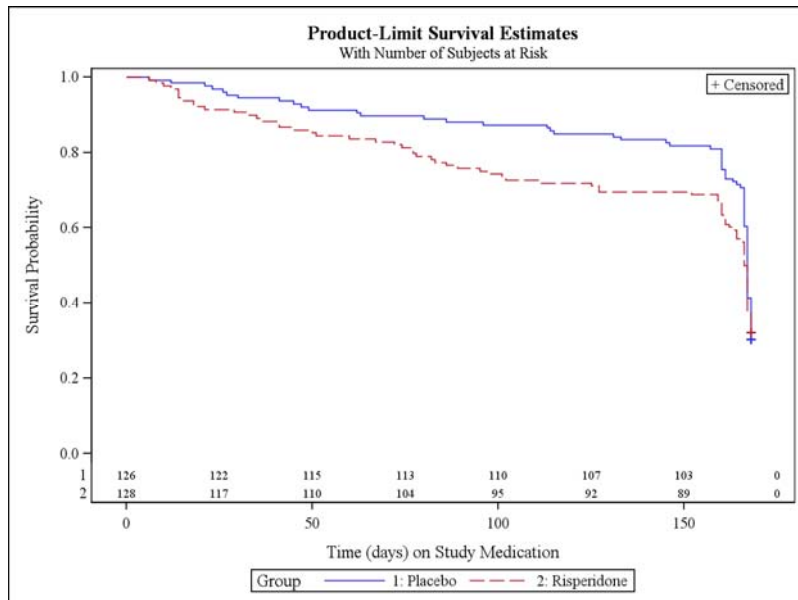


**eTable 5. Adverse Events\***

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

