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# Supplementary Material

**Article Title:** Varenicline for Smoking Cessation in Bipolar Disorder: A Randomized, Double-Blind, Placebo-Controlled Study

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## List of Supplementary Material for the article



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| **Supplementary eTable 1 Serious Adverse Events (SAE)** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| ID | Age/ Gender/ Race | Description | Varenicline or Placebo | Relationship to Study Medicine | Study Phase | Start and Stop Dates of SAE and Outcome | Smoking Status at time of SAE | Actions Taken |
| 102 | 55/F/C | Subject exposed to significant stressor (terminally ill brother in hospital). Became very anxious and requested admission to hospital. Denied suicidal/homicidal ideation. Subject had taken only 1 dose of study medication. SAE Terminology: Exacerbation of Anxiety | Varenicline | Unlikely Discussed and confirmed at DSMB meeting 03/12/10 | Phase 1 | 03/12/2010-03/20/2010, Resolved | Smoking at same rate | Study medication stopped. Subject terminated from study and hospitalized. Discharged in 8 days with previous psychotropic medications and mirtazapine was added. |
| 104 | 48/F/C | After 6 days of study medication, subject developed red, raised maculopapular rash on arms, shoulders and inner thighs. Was also receiving lamotrigine (started 3 months prior to study) SAE Terminology: Development of Rash | Varenicline | Possible Discussed and confirmed with DSMB 06/14/10 | Phase 1 | 06/10/2010-06/14/2010, Resolved - 06/23/2010 | Smoking at same rate | Study medication stopped. Subject terminated from study. Lamotrigine was discontinued |
| 10 | 42/M/C | After receiving an eviction notice, subject became very agitated, began using crack cocaine, heroin, and alcohol, became hostile and expressing homicidal intentions toward roommate. Hospitalized on involuntary commitment. SAE Terminology: Agitation, hostility, alcohol abuse, drug abuse. | Varenicline | Possible Discussed and confirmed via e-mail with DSMB on 08/04/10 | Phase 1 | 7/29/2010-08/4/2010, Resolved | Quit for 3 weeks | Study medication stopped. Hospitalized. Discharged in 6 days on previous psychotropic medication regimen. |
| 17 | 53/F/C | Subject with history of asthma and COPD. Subject experienced severe breathing difficulty and was admitted to the University hospital | Varenicline | Unlikely Discussed and confirmed at DSMB meeting | Phase 1 | 10/12/2010-11/03/2010, Resolved | Smoking at reduced rate | Continued on study medication in the hospital and upon discharge. |

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| | | and treated with steroids, antibiotics, and breathing treatments.<br>SAE Terminology: Hypoxia, asthma with COPD with acute exacerbation | | 10/27/10 | | | | Completed study. Did not quit. |
| 105 | 56/F/C | Subject contacted via phone after no show for Visit 4. Subject was incoherent and speech was slurred. Admitted to drinking vodka and unsure if she had taken more medications than prescribed. 911 (ambulance) was called and subject admitted to community hospital<br>SAE Terminology: Hospitalization related to alcohol intoxication | Placebo | Unlikely. Discussed and determined at the DSMB meeting 12/22/10 | Phase 1 | 12/22/2010-12/25/2010, Resolved | Smoking at same rate | Study medication stopped and subject terminated from study.<br>Hospitalized.<br>Discharged on previous psychiatric medication regimen. |
| 40 | 24/F/C | Contacted by subject's mother that subject was experiencing tremors, heaviness in left arm and grogginess.<br>SAE Terminology: Tremulousness, grogginess, upper left arm weakness. | Varenicline | Unlikely<br>Discussed and determined by DSMB Meeting 06/22/2011 | Phase 1 | 06/07/2011-06/13/2011 Resolved | Smoking at a reduced rate | Seen by emergency room MD and by endocrinology.<br>Diagnosis - Reactive hypoglycemia.<br>Subject withdrew from study. |
| 46 | 45/F/C | Shortness of breath and worsening of asthma symptoms. Admitted to University hospital where she was treated with antibiotics; steroids and breathing treatments.<br>SAE Terminology: Exacerbation of asthma | Placebo | Unlikely<br>Confirmed and decision made to continue subject in study at DSMB meeting 02/29/12 | Phase 1 | 02/25/2012-02/26/2012, Resolved | Smoking at a reduced rate | Subject continued on study medication in hospital and continued in study.<br>Hospitalized and discharged. |

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| 52 | 27/F/AA | Laboratory work done at end of treatment phase reported a positive pregnancy test (previous 3 pregnancy tests –were all negative). SAE Terminology: Pregnancy | Placebo | Unlikely Confirmed at DSMB meeting on 08/08/2012 | Phase 1 | 08/07/2012, Resolved | Smoking at reduced rate | Study medication had already been stopped. Subject terminated from study. Subject counseled to stop smoking. |
| 51 | 61/M/C | Subject hospitalized for c/o gastro intestinal complaints as well as breathing difficulty and nasal congestion. SAE Terminology: Pneumonia | Varenicline | Unlikely Discussed and confirmed at DSMB meeting 09/26/2012 | Phase 2 | 08/23/2012-8/27/2012, Resolved | Quit for nearly 12 weeks | Patient was off study medication for 19 days. Subject continued and completed study. Hospitalized and discharged |
| 54 | 51/F/AA | Subject went to the hospital after experiencing chest pain and numbness in left hand. Enzymes for myocardial infarction – negative. Pain and numbness subsided. Subject discharged next day. SAE Terminology: Chest pain, left hand numbness | Placebo | Possible Discussed and determined at DSMB meeting on 12/19/2012 | Phase 2 | 12/16/2012-12/17/2012, Resolved | Smoking at a reduced rate | Subject was off study medication for 46 days. Subject continued in study. |

Footnote: Phase 1: 12 weeks of Treatment with Varenicline or Placebo, Phase 2: Follow Up (weeks 12 through 24)

**Supplementary eTable 2 – Details of Neuropsychiatric Adverse Events – Depressed Mood**

| ID | Rx | MADRS Baseline | MADRS Scores /Visit #s /# of Days | Episode Of Depression | Specific Rx for Depressive Episode | Quit Status | Severity | Relationship to Study Drug | Study Meds Action Taken |
|---|---|---|---|---|---|---|---|---|---|
| 1 | V | 4 | MADRS = 10<br>Visits 7 ( to 8) # Days 11 | No | No | No | 1 | 3 | 1 |
| 5 | V | 8 | MADRS = 5 to 10<br>Visits 10 ( to 15) # Days 35 | No | No | Yes | 1 | 3 | 1 |
| 21 | V | 8 | MADRS = 10<br>Visit 14 # Days 11 | No | No | Yes | 1 | 3 | 1 |
| 30 | V | 3 | MADRS = 19<br>Visits 11 (to 12) # Days 14 | Yes | Yes, sertraline started | No | 2 | 3 | 1 |
| 40 | V | 2 | MADRS = 18<br>Visits 6 (to 7) # Days 14 | Yes | Yes, Duloxetine increased 60 to 90 mg | No | 2 | 3 | 4 |
| 41 | V | 1 | MADRS = 16<br>Visit 8 # Days 21 | Yes | Yes, escitalopram added | Yes | 2 | 3 | 1 |
| 42 | V | 8 | MADRS = 19<br>Visits post 14 (to 17) # Days 21 | Yes | Yes,↑therapy visits | No | 3 | 3 | 1 |
| 45 | V | 4 | MADRS = 15<br>Visits 9 (to 10) # Days 5 | No | No | No | 2 | 3 | 1 |
| 31 | P | 1 | MADRS = 9<br>Visit 16 # Days 9 | No | No | No | 2 | 4 | 1 |
| 46 | P | 1 | MADRS = 16<br>Visits 12(to 14) # Days 14 | Yes | Yes, lamotrigine increased | No | 3 | 3 | 1 |

V = Varenicline, P = Placebo

Severity → 1 = mild, 2 = moderate, 3 = marked
Relationship → 1 = certain, 2 = probable/likely, 3 = possible, 4 = unlikely
Action Taken → 1 = none, 2 = drugs decreased, 3 = drugs stopped temp, 4 = drugs stopped permanently

**Supplementary eTable 3 – Vital Signs [a]**

| Vital Sign | Baseline | | 12 Weeks | | 24 Weeks | |
|---|---|---|---|---|---|---|
| | Varenicline Mean (SD) n = 31 | Placebo Mean (SD) n= 29 | Varenicline Mean (SD) n = 29 | Placebo Mean (SD) n = 25 | Varenicline Mean (SD) n = 23 | Placebo Mean (SD) n = 20 |
| Blood Pressure | | | | | | |
| Systolic (mm/hg) | 126.2 (15.3) | 125.00 (17.9) | 123.4 (11.5) | 119.6 (13.4) | 123.7 (11.8) | 128.9 (12.7) |
| Diastolic (mm/hg) | 80.2 (9.6) | 79.0 (8.6) | 79.4 (8.2) | 78.6 (11) | 78.7 (8.8) | 79.6 (8.6) |
| Resting Pulse (beats/min) | 79.2 (8.1) | 75.5 (10.2) | 82.8 (9.4) | 78.1 (12.3) | 82.6 (9.3) | 81.6 (11.5) |
| Respiratory Rate (rate/min) | 18.5 (4) | 18.8 (2.2) | 18.7 (2) | 18.2 (1.9) | 19.0 (1.9) | 18.7 (1.5) |
| Temperature (◦F) | 97.8 (0.6) | 98.0 (0.7) | 97.7 (0.5) | 97.7 (0.7) | 97.5 (0.5) | 97.8 (0.5) |
| Body Weight (lbs) | 199.2 (47.4) | 202.7 (42) | 196.8 (47) | 204.4 (44.7) | 205.3 (49.6) | 209 (44.7) |

n = number, SD = standard deviation, [a] none of the between group treatment comparisons were statistically significant