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A Double-Blind, Placebo-Controlled Trial of Lamotrigine for Pathologic Skin Picking: Treatment Efficacy and Neurocognitive Predictors of Response

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INTRODUCTION

Pathologic skin picking (PSP) is characterized by repetitive and compulsive picking of skin which causes tissue damage. Although there have been no population-wide epidemiological studies of PSP, it has an estimated prevalence rates of 2.0%–5.4% in the general population (1–2). Individuals with PSP report that picking behavior causes scarring and infections, impairment in daily functioning, and significant distress stemming from their inability to control the behavior (3–6).

Treatment research for PSP is sparse. There has been only one randomized controlled study of psychotherapy for PSP (habit reversal compared to wait list) (7), and only two placebo-controlled, double-blind pharmacotherapy studies published to date (8–9). In the first pharmacotherapy study, 20 subjects were randomized to either fluoxetine or placebo for 10 weeks (n=10 per treatment arm). Fluoxetine demonstrated significant reduction in PSP symptoms on only one of three measures used to rate improvement (a self-report visual analog scale assessing change in skin-picking behavior with a Cohen's d effect size of 1.31) (8). The lack of significant active treatment benefits across other outcome measures may have been due to actual non-significance from the medication or possible due to type II error and limited statistical power. The other study consisted of 45 subjects treated with citalopram 20mg/day for 4 weeks (n=23 in citalopram group; n=22 in placebo group). In that study, citalopram failed to produce a greater benefit than placebo on the primary outcome measure although a secondary measure of quality of life found some additional improvement for medication (9).

Because data on the treatment response of PSP to pharmacotherapy are limited, the primary aim of the proposed study was to evaluate the efficacy and safety of lamotrigine in PSP. The rationale for the use of lamotrigine was twofold: first, glutamatergic dysfunction has been implicated in the pathophysiology of obsessive compulsive disorder (OCD) (10–11), a disorder with some phenomenological and possible neurobiological links to PSP (for

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example, both PSP and OCD have similar ages of onset, individuals with both disorders spend excessive amount of time engaged in behaviors that are intended to reduce tension or anxiety, rates of co-occurring OCD are elevated in PSP samples and vice versa, and PSP is more common in first-degree relatives on OCD patients compared to controls (12–13)); and second, clinical reports supported possible efficacy of glutamatergic modulators in the treatment of both impulse control and obsessive compulsive disorders (14–16). Lamotrigine is thought to act via inactivation of voltage-sensitive Na^+ and possibly Ca^{2+} channels, leading to suppression of abnormally increased neuronal firing and thus inhibiting excessive release of glutamate (17–18).

Because lamotrigine may target medial prefrontal glutamatergic drive to the nucleus accumbens (19), it may correct the underlying pathophysiology and symptoms of PSP. In fact, an earlier open-label study of lamotrigine in 24 subjects with PSP found that 67% had significant improvement in picking symptoms after 12 weeks of treatment (20). Therefore, our hypothesis was that lamotrigine would be more effective than placebo in treating individuals with PSP. The secondary aim of this study was to evaluate whether treatment responders and non-responders differed in terms of baseline cognitive flexibility and inhibitory control. Because cognitive flexibility appears dependent upon prefrontal cortical integrity (21), and because lamotrigine should modulate prefrontal glutamate functioning, we hypothesized that PSP subjects with impaired cognitive flexibility at baseline would respond preferentially to treatment in this study.

METHODS AND MATERIALS

Subjects

Men and women aged 18 to 65 with a primary diagnosis of PSP were recruited by newspaper advertisements for medication treatment. The diagnostic criteria for PSP, based on DSM-IV criteria for other impulse control disorders, has been previously reported (20, 22) and include the following: 1) Recurrent picking at or otherwise manipulating the skin that results in noticeable damage to the skin; 2) an increasing sense of tension, or an unpleasant emotional or physical state, immediately before picking the skin, or when trying to resist picking; 3) pleasure, gratification or relief at the time of picking; 4) the disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of function; 5) the skin picking is not due to a general medical condition; and 6) the skin picking is not better accounted for by another mental disorder (e.g., body dysmorphic disorder, obsessive compulsive disorder, delusion disorder, substance use disorder). Although several studies have not included criteria 3 and 4 into their definition of PSP (7, 9), we have done so to keep it consistent with the current DSM-IV-TR diagnostic criteria for trichotillomania with which it shares phenomenological features (6, 10).

All subjects were required to have picked their skin during the week prior to enrollment and to have picked on average at least once per week for the past 3 months. Women's participation required negative results on a beta-human chorionic gonadotropin pregnancy test and stable use of a medically accepted form of contraception.

Exclusion criteria included: 1) unstable medical illness or clinically significant abnormalities on laboratory tests, or physical examination; 2) myocardial infarction within 6 months; 3) current pregnancy or lactation, or inadequate contraception in women of childbearing potential; 4) use of psychotropic medication; 5) any thoughts of suicide; 6) current Axis I disorder determined by the Structured Clinical Interview of DSM-IV (SCID) (23) and by SCID-compatible modules for impulse control disorders (24); 7) lifetime history of bipolar disorder type I or II, dementia, schizophrenia, or any psychotic disorder determined by SCID; 8) positive urine drug screen at screening; 9) initiation of psychotherapy or behavior

therapy specifically for PSP within 3 months prior to study baseline; or 10) previous treatment with lamotrigine.

The institutional review board for the University of Minnesota approved the study and the informed consent. One investigator discussed potential risks of the study, as well as alternative treatments, with subjects. After complete description of the study, subjects provided written informed consent. This study was carried out in accordance with the Declaration of Helsinki. Data were collected from August, 2007 to September, 2009.

Study Design

After screening, eligible subjects were randomized to either lamotrigine or matching placebo (in block sizes of eight, using computer-generated randomization with no clinical information). Randomization was done by the investigational drug pharmacy at the University of Minnesota and random numbers were assigned to each pill bottle dispensed to subjects. Consequently, the investigators, subjects, and research staff were blind to which arm of the study subjects were assigned.

Dose range selection was based on lamotrigine's clinical data in PSP. The previous open-label study of lamotrigine in individuals with PSP suggested efficacy with daily doses up to 300mg (20). Subjects began lamotrigine at 25mg/day every other day for 1 week. At week 1, the dose was raised to 25mg/day. At week 2, the dose was raised to 50mg/day for two weeks. Thereafter, all visits were scheduled every two weeks at which times the dose could be increased to 100mg/day, then 200mg/day, and finally 300mg/day unless clinical improvement was attained at a lower dose (clinical improvement was assessed by the investigator with respect to skin picking behavior, thoughts, and urges). If clinically necessary (e.g., because of side effects or an adequate response to a lower dose), the dose was raised more slowly or the target dose of 300mg/day was not reached. Subjects could not take other psychotropic medications during the study, and psychotherapy of any form (including cognitive-behavioral therapy) was not allowed during the study. Subjects who were not compliant with their use of study medication (i.e. failing to take medication for three or more consecutive days) were discontinued from the study.

Screening Assessments—Subjects were evaluated at entry into the study by the Structured Clinical Interview for DSM-IV (SCID) (23) and SCID-compatible modules for impulse control disorders (24). Medical history, physical examination, and routine laboratory testing were performed. Skin picking symptoms were assessed using the clinician-administered Yale Brown Obsessive Compulsive Scale Modified for Neurotic Excoriation (NE-YBOCS) (25). Subjects reported severity of skin picking using the self-rated Skin Picking Scale (26) and the Skin Picking Symptom Assessment Scale (SP-SAS) (20). Anxiety symptoms were rated with the Hamilton Anxiety Rating Scale (HAM-A) (27). Depressive symptoms were assessed using the Hamilton Depression Rating Scale (HAM-D) (28). Psychosocial functioning was evaluated using the self-report version of the Sheehan Disability Scale (SDS) (29).

Efficacy and Safety Assessments—Subjects were seen weekly for two weeks, every two weeks for the next 6 weeks, and then one final visit after the last 4 weeks of the 12-week study. The primary outcome measure was the change from baseline using the Yale Brown Obsessive Compulsive Scale Modified for Neurotic Excoriation (NE-YBOCS) (25). The NE-YBOCS is a modification of the Yale Brown Obsessive Compulsive Scale, a reliable and valid, clinician-administered scale for OCD. This modified measure is a 10-item scale that rates picking symptoms during the last seven days on a severity scale from 0 to 4 for each item (total scores range from 0 to 40 with higher scores reflecting greater illness

severity). The first five items of the NE-YBOCS comprise the picking urge/thought subscale (time occupied with urges/thoughts; interference and distress due to urges/thoughts; resistance against and control over urges/thoughts), and items 6–10 comprise the picking behavior subscale (time spent picking; interference and distress due to picking; ability to resist and control picking behavior). This modification of the Y-BOCS has previously been used in treatment studies of PSP (20, 25, 30) and demonstrated good psychometric properties in the current study (test–retest reliability showed a good correlation (n = 32; r = .747; p<.001) and the NE-YBOCS showed a good convergent validity when compared with the CGI Severity at visits 1 through 7 (n = 32, r = .698–.851; p<.001)).

Both NE-YBOCS subscales were evaluated as secondary efficacy measures. Other secondary outcome measures consisted of:

Skin Picking Scale: The Skin Picking Scale is a 6-item, self-report measure for the assessment of skin picking. Individual scale items range from 0 to 4 with a total score range of 0 to 24. The scale has demonstrated moderate internal consistency and good construct validity when correlated with self-reported average duration of skin picking episodes. Sensitivity and specificity analyses suggest that a cut-off score of 7 differentiates severe self-injurious and non-self-injurious skin pickers (26).

Skin Picking Symptom Assessment Scale (SP-SAS): The SP-SAS is a modification of a reliable and valid self-report scale used for other impulse control disorders such as pathological gambling (31) and kleptomania (32). Subjects completed the SP-SAS at each study visit. The SP-SAS is a 12-item, reliable and valid, self-rated scale assessing picking urges, thoughts, and behaviors during the previous seven days (20). Each item is rated 0 to 4 with a possible total score of 48.

Clinical Global Impression-Improvement and Severity scales (CGI) (33): The CGI consists of two reliable and valid 7-item Likert scales used to assess severity and change in clinical symptoms. The improvement scale was used every visit after the screening visit. The scale ranges from 1 = “very much improved” to 7 = “very much worse.” CGI-Improvement was rated by the clinician at each visit. The CGI severity scale was used at each visit and ranges from 1 = “not ill at all” to 7 = “among the most extremely ill.” The CGI improvement was used to rate only changes in symptoms of skin picking.

Sheehan Disability Scale (SDS) (29): The SDS is a three-item, reliable and valid self-report scale that assesses functioning in three areas of life: work, social or leisure activities, and home and family life.

Hamilton Anxiety Rating Scale (HAM-A) (27): The HAM-A is a reliable and valid, clinician-administered, 14-item scale that provides an overall measure of global anxiety.

Hamilton Depression Rating Scale (HAM-D) (28): The HAM-D is a valid and reliable, 17-item, clinician-administered rating scale assessing severity of depressive symptoms.

Safety assessments at each visit included evaluations of sitting blood pressure, heart rate, and weight. Adverse effects were documented and included time of onset and resolution, severity, action taken and outcome. Subjects reporting a rash of any kind were discontinued from the study immediately for safety reasons. The investigator recorded use of concomitant medications in terms of daily dosage, start and stop dates, and reason for use. Laboratory assessments (e.g., clinical chemistry, hematology, and urine toxicology) and urine pregnancy tests were performed only at screening. Compliance was monitored by pill count.

Cognitive Testing—Cognitive testing was conducted using two previously validated tests taken from CANTABeclipse software (34). The choice of cognitive challenges was based on the clinical features of PSP. The compulsive and repetitive behaviors seen in PSP resemble those seen in trichotillomania (TTM) and possibly obsessive compulsive disorder (OCD). The overwhelming urges to pick coupled with a sense of relief or calm after engaging in the behavior reported by those with PSP are very similar to the urges to engage in compulsive acts reported by those with TTM or OCD. Tests of neurocognitive functioning have been examined in TTM and OCD (35). Significant deficits of motor inhibition (Stop-signal task) were noted in both the TTM and OCD groups but only the OCD group showed deficits in extra-dimensional set-shifting (35). Due to the clinical similarities of PSP to TTM, we chose cognitive tasks that would best reflect the underlying impulsivity and cognitive flexibility of PSP. All testing was conducted in the same controlled environment to minimize confounding variables across subjects. The order of the tasks was fixed.

The stop-signal task was used to assess motor inhibition (36–37). On this test, subjects were instructed to respond to a left- or right-facing arrow which appeared on a computer screen in a rapid fashion. Corresponding motor responses were measured as were the subjects' ability to inhibit responses when an auditory "beep" (stop-signal) sound occurred on a subset of trials. Through an algorithm, the time taken to internally suppress prepotent motor responses was measured, i.e. Stop-Signal Reaction Times (SSRT). Key outcome variables were SSRT, mean reaction time on 'go' trials, and the total number of directional errors made. Inhibitory control on this task, as indexed by SSRT, has been shown to be dependent on distributed neural circuitry including the right inferior frontal gyrus (38).

Cognitive flexibility, i.e. set-shifting, was measured using the using the Intra-dimensional/ Extra-dimensional Shift Task (ID/ED task), developed from the Wisconsin Card Sorting Test assessing frontal lobe integrity (39). This test involved nine stages using multidimensional stimuli presented as a visual discrimination task. On the task, subjects were presented with two stimuli on-screen for each trial, and attempted to learn an underlying 'rule' about which stimulus was correct. After each choice, the task provided the subject with feedback (right/wrong). After meeting learning criterion (6 consecutive correct choices), the rule was changed by the computer. Where learning criterion was not obtained within 50 trials, the task terminated. Key outcome variables were the number of errors made on the task overall (total errors, and total corrected errors) along with total errors for the Intra-dimensional (ID) and Extra-dimensional (ED) stages of the task. The 'total corrected errors' measure accounted for errors that would have been made had the subject completed all stages of the task. Cognitive flexibility, as measured by this task, has been found to be dependent on prefrontal cortex integrity (e.g. 21).

Data Analysis—Sample size calculation, using baseline NE-YBOCS total scores reported in a previous study (mean score of 19.5 (SD 6.2)), was based on a simple test of mean differences. For this study, we assumed 15% and 40% decreases for placebo and for lamotrigine groups, respectively, by week 12, leading to mean scores of 17.8 and 11.7. Normal distribution was assumed. To detect a mean difference of 6.1 with 80% power and 5% significance level in a two-sided test, 36 subjects would be needed.

All randomized subjects were included in the analyses of baseline demographics and safety according to an intent-to-treat principle. In all efficacy analyses, only subjects who returned for one visit after starting medication were included. All tests of hypotheses were performed using a two-sided significance level of .05.

Primary analysis used the last observation carried forward (LOCF). Baseline and subsequent scores were compared with paired t-tests, two-tailed, Fisher's exact test, and Mann-Whitney.

General linear models were used to explore the relationship of treatment assignment, time, and interaction between scores at baseline and endpoint.

Cognitive testing was examined as a possible predictor of treatment response. Subjects were grouped into "responders" (i.e. ≥35% reduction on the NE-YBOCS at last visit compared to baseline) or non-responders at study endpoint. Although there is no agreed upon definition of "response" in the treatment of PSP, we used a reduction of 35% on the NE-YBOCS to define "response in this study for several reasons: our previous open-label study of lamotrigine in PSP found that subjects overall demonstrated a 42% reduction on the NE-YBOCS (20) and to reduce possible placebo response, we wanted a more stringent definition of response than found in treatment studies of OCD where 25% reduction is the standard (40). Scores on baseline cognitive tasks were examined with the rater (SRC) blind to group assignment. Responders were compared to non-responders using one-tailed unpaired t-tests, assuming equal variance.

RESULTS

Subject Characteristics

Of 41 subjects screened, 35 subjects with a current diagnosis of PSP met inclusion/exclusion criteria and were enrolled. Thirty-two subjects (mean age = 32.8 ± 13.3 years [range 18–65]; 29 females [90.6%]) returned for at least one post-baseline assessment. Sixteen subjects were randomly assigned to lamotrigine and 16 were assigned to placebo. Demographics characteristics at baseline are presented (Table 1). There were no statistically significant imbalances regarding age, gender, employment, living status, or measures of symptom severity between treatment groups at baseline.

PSP symptoms at baseline were generally moderate for the entire group. The mean score on the NE-YBOCS was 19.5 ± 4.1 [range 11 – 28]. Mean baseline score for the CGI-Severity scale was 4.2 ± 0.5, corresponding to moderate severity. Mean Sheehan Disability scale score at baseline was 13.3 ± 6.9 which corresponds to moderate social and occupational disability.

Mean age at onset of skin picking was 13 ± 9.18 years (range 4–58). Twenty-four subjects (75%) reported picking at more than one body part, and 17 (53.1%) picked at more than two. Fifteen subjects (46.9%) reported picking primarily at the face or head, 13 (40.6%) at the feet or hands, 3 (9.4%) at the arms or legs, and 1 (3.1%) at their torso. 30 (93.8%) were aware of beginning their picking behavior at least 50% of the time, whereas 2 (6.3%) were aware of picking less than 50% of the time and therefore were picking "automatically" most of the time.

Premature Discontinuation

Premature discontinuation (defined by categories in the study protocol and assigned by investigators to explain a subject's termination from the study – Adverse Events, Lack of Efficacy, Loss to Follow-up, Subject Withdrawal, or Other) was fairly common in both groups, with 7 (21.9%) of the 32 randomized subjects dropping out before week 12. Four (25%) of 16 subjects assigned to lamotrigine and 3 (18.8%) of 16 subjects assigned to placebo discontinued the study prior to 12 weeks. The most common reasons for discontinuation in subjects taking lamotrigine were an inability to meet the study schedule (n=3 [18.8%)]) and an adverse event of feeling disoriented (n=1 [6.3%]). Although no subjects on lamotrigine experienced a rash, two subjects in the placebo group reported a rash and were discontinued from the study for safety reasons.

Efficacy Results

Treatment with lamotrigine did not yield significantly greater efficacy than placebo at study end-point as assessed by the NE-YBOCS total score (Table 2 and 3).

Secondary outcome measures were consistent with the NE-YBOCS total score. In fact, there were no significant differences between treatment groups on any secondary measure (Table 2 and 3). The numerical improvement on all secondary measures for those on lamotrigine was greater than for those on placebo, but this difference never reached statistical significance (Table 2). In addition, of the 32 subjects, 7 of the 16 subjects (43.8%) of those assigned to lamotrigine were responders (defined as ≥35% reduction on the NE-YBOCS) at study endpoint compared to 5 of the 16 (31.3%) assigned to placebo.

Table 3 shows that there was significant improvement over time independent of treatment on several PSP scales. Total scores on the NE-YBOCS (p=.014), the behavior subscale of the NE-YBOCS (p=.005), the Skin Picking Scale (p=.001), and the SP-SAS (p=.001) all demonstrated significant improvement over time. Additionally, the SDS demonstrated significant functional improvement over time (<.001).

Cognitive Predictors of Treatment Response

For those subjects assigned to lamotrigine, responders were compared to non-responders on cognitive tasks and significant baseline between-group differences were found (Table 4). Those who responded to lamotrigine exhibited significantly more ID/ED total errors at baseline (23 vs 11, > p=0.017) and more ID/ED total errors corrected (34 vs 11, p=0.017). This finding was driven by responders exhibiting worse ED-shifting (15 vs 5 errors, p=0.023).

In addition, lamotrigine responders showed longer (impaired) stop-signal reaction times at baseline (212 vs 164ms, p=0.008). For those who were assigned to placebo, placebo responders also demonstrated significantly longer (impaired) stop-signal reaction times at baseline compared to non-responders (294ms vs 167ms, p=0.022)

Safety and Tolerability

The incidence and severity of adverse experiences in lamotrigine-treated subjects were consistent with prior studies (20), and no unusual experiences were reported. Most adverse experiences were of mild to moderate intensity and most commonly occurred during the first week of drug treatment. Mean values in HAM-D and HAM-A scores remained at low levels throughout the study in all treatment groups, with no statistically significant differences between groups.

DISCUSSION

This randomized, double-blind, clinical trial failed to find lamotrigine superior to placebo in the treatment of PSP based on either the primary outcome measure or any secondary outcome measure. This study, the first to examine the efficacy of a possible glutamatergic agent (41–42) in individuals with PSP, found that skin picking symptoms failed to improve more in those assigned to active treatment than placebo. This finding appears to be inconsistent with an earlier open-label study which found a robust lamotrigine treatment response (20). One possible interpretation of these apparent “inconsistent” results with the earlier open-label study is that the earlier study did not include a placebo comparison. The results of this study demonstrate significant improvement over time in subjects independent of treatment. Future studies may need to use longer studies to see if time alone is associated with sustained improvement.

Another possible explanation for the overall negative results of this study could be that PSP is more heterogeneous than initially thought. That is, although many individuals will meet PSP criteria, there could be distinct pathophysiologies in any group of individuals with PSP with each giving rise to the same symptoms. Support for this explanation can be found in the analyses of the baseline cognitive tasks. Impaired flexibility (ED shifting) seems to be a marker of subsequent treatment response for those assigned to lamotrigine but not to placebo. Because impairments on this task are likely associated with deficiencies in the prefrontal cortex, this may suggest that only certain individuals with PSP prefrontal cortical dysfunction will respond to lamotrigine. Because lamotrigine appears to modulate glutamate from the medial prefrontal cortex to the nucleus accumbens, it would make sense that only PSP individuals with dysfunction of the medial prefrontal cortex would respond to this medication. The cognitive task therefore suggests that a certain sub-group of PSP subjects may have a particular pathophysiology and that knowing that pathology can improve treatment approaches. Future trials with lamotrigine and other glutamatergic agents could selectively enroll patients with impaired cognitive flexibility, since such impairment appears to be predictive of beneficial treatment response.

This study demonstrated that both lamotrigine-treated and placebo-treated subjects improved over a 12-week period, but unlike the open-label study of lamotrigine, the improvement seen here was much less. The primary outcome measure, the NE-YBOCS, saw a decrease of approximately of three or four points when compared to baseline. This is markedly less than the mean decrease of eight to nine points seen in the open-label study (20). Similarly the SP-SAS demonstrated a mean decrease of approximately 5 to 7 points in this study whereas the same scale witnessed a mean decrease of 10 points in the open-label study (20). The overall baseline measures for subjects in this study did not differ from those enrolled in the previous study and so baseline severity does not seem to explain these differences in treatment response. One explanation might be that expectancy dampens the results for both groups. In an open-label study, everyone knows they are receiving actual medication, but in a double-blind design, both groups may be less convinced that they are receiving medication and this may result in a more attenuated response. Support for this explanation can be found in alcohol research where those who believed they had been taking active medication consumed fewer alcoholic drinks and reported less alcohol dependence and cravings, independent of actual treatment assignment (43).

This pilot study represents only the third double-blind, placebo-controlled pharmacological study for PSP, and the only one to examine a non-serotonergic medication and to use cognitive tasks as predictors of treatment response. There exist, however, several limitations. First, the sample size for this study was small and may have precluded the identification of treatment outcomes between groups. The question of whether a larger sample would have detected differences between lamotrigine and placebo deserves further examination. In addition, the small sample sizes in each arm of the neurocognitive assessments suggest a need for larger replication studies to determine if one or more outliers may be responsible for these findings. Second, the study enrolled subjects seeking pharmacological treatment, not psychotherapy. These results, therefore, may not generalize completely to the larger population of people with PSP. Third, this study did not include behavioral therapy. Effective behavioral treatments (e.g., habit reversal and acceptance and commitment therapy) for PSP have been published (7, 44) and should be considered in conjunction with pharmacotherapies. It is possible that pharmacotherapy may have greater benefit when used in conjunction with psychotherapy and not when used as monotherapy. Finally, the study was only 12 weeks in duration. It is possible that more time was needed for response and that a longer trial might have demonstrated benefit from lamotrigine.

There are currently no Food and Drug Administration approved treatments for PSP. In this study, lamotrigine- and placebo-treated groups demonstrated comparable overall improvement. Further studies are needed to determine effective pharmacotherapies for this problem. Given that PSP, however, may be heterogeneous, future research should incorporate cognitive measures that reflect distinct pathophysiologies to determine differences in people who meet diagnostic criteria for PSP and thereby lead to more targeted pharmacotherapies.

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Table 1

Demographic Comparison between Pathologic Skin Picking Subjects Assigned to Lamotrigine or Placebo at Baseline

	Placebo (n=16)	Lamotrigine (n=16)	Statistic *	Df	p-value
Gender, n (%)					
Female	14 (87.5)	15 (93.8)	f	n/a	1.00
Male	2 (12.5)	1 (6.3)			
Race, n (%)					
Caucasian	15 (93.8)	15 (93.8)	f	n/a	1.00
Other	1 (6.3)	1 (6.3)			
Age					
Mean (± SD), [range], years	31.63 (13.3) [18–60]	33.2 (14.1) [18–65]	−.303z	n/a	.804
Marital, n (%)					
Single/Living Together/Gay	11 (68.8)	7 (43.8)	f	n/a	.285
Married	5 (31.3)	8(50.0)			
Divorced/Separated/Widowed	0 (0.0)	1 (6.3)			
Education, n (%)					
High School or less	1 (6.3)	1 (6.3)	f	n/a	1.00
Any college	15 (93.8)	15 (93.8)			
Employment, n (%)					
Employed	14 (87.5)	10 (62.5)	f	n/a	.220
Unemployed	2 (12.5)	6 (37.5)			

*Statistic: f = Fisher's Exact test z = Mann-Whitney c= Chi-Square

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Table 2

Change in Primary and Secondary Efficacy Measures

Change in scores from Baseline to Study Endpoint (LOCF)	Placebo (n=16)	Lamotrigine (n=16)	Statistic *	Df	p-value
NE-YBOCS Total - change					
Mean (± SD), Median [range]	−3.37 (10.50) −2.50 [−23, 20]	−4.25 (5.50) −5.15 [−10, 6]	−.299t	30	.767
NE-YBOCS Thoughts/Urge - change					
Mean (± SD), Median [range]	−1.00 (6.47) −1.00 [−11, 16]	−1.625 (3.24) −1.00 [−7, 4]	−.345t	30	.732
NE-YBOCS Behavior - change					
Mean (± SD), Median [range]	−2.37 (4.95) −1.50 [−13, 4]	−2.62 (4.45) −3.00 [−11, 7]	−.150t	30	.882
Skin Pick Scale -change					
Mean (± SD), Median [range]	−2.18 (4.86) −1.50 [−11, 6]	−3.62 (3.98) −3.00 [−12, 3]	−.915t	30	.367
SP-SAS -change					
Mean (± SD), Median [range]	−5.43 (10.26) −4.00 [−28, 13]	−7.59 (9.29) −8.00 [−30, 8]	−.623t	30	.538
CGI Severity - change					
Mean (± SD), Median [range]	−.250 (1.29) .00 [−4, 2]	−.500 (.81) .00 [−2, 1]	−.655t	30	.518
SDS -change					
Mean (± SD), Median [range]	−7.37 (6.70) −4.00 [−19, 0]	−7.62 (5.57) −7.50 [−17, 0]	−.132z	n/a	.895
HAM-D - change					
Mean (± SD), Median [range]	−.125 (1.14) .00 [−2, 2]	−1.31 (2.91) −1.50 [−6, 4]	−1.516t	30	.140
HAM-A - change					
Mean (± SD), Median [range]	−.312 (1.81) .00 [−4, 3]	−1.06 (2.81) −1.00 [−7, 5]	−.750t	30	.353

* Statistic: t = t-test z = Mann-Whitney

Intent-to-treat with last observation carried forward

Abbreviations: NE-YBOCS = Yale Brown Obsessive Compulsive Scale Modified for Neurotic Excoriation; SP-SAS = Skin Picking Symptom Assessment Scale; CGI = Clinical Global Impression severity scale; SDS= Sheehan Disability Scale; HAM-D= Hamilton Depression Scale; HAM-A= Hamilton Anxiety Scale; n/a = not applicable

Table 3

General Linear Model of Primary and Secondary Measures

	Variable	Degrees Freedom	F-Statistic	P-Value	Effect Size Partial-Eta Squared	Observed Power
NE-YBOCS Total	NE-YBOCS Total - Trend	(1,30)	6.791	.014	NS	.713
	Interaction	(1,30)	.089	.767	NS	.060
	Arm of Study	(1,30)	2.891	.099	.132	.377
NE-YBOCS Thoughts/Urge	NE-YBOCS Thoughts/Urge - Trend	(1,30)	2.105	.157	.231	.290
	Interaction	(1,30)	.119	.732	NS	.063
	Arm of Study	(1,30)	4.555	.041	NS	.542
NE-YBOCS Behavior	NE-YBOCS Behavior - Trend	(1,30)	9.016	.005	.185	.828
	Interaction	(1,30)	.023	.882	NS	.052
	Arm of Study	(1,30)	.609	.441	NS	.118
Skin Picking Scale	Skin Picking Scale - Trend	(1,30)	13.692	.001	NS	.947
	Interaction	(1,30)	.837	.367	NS	.144
	Arm of Study	(1,30)	.124	.727	NS	.063
SP-SAS	SP-SAS - Trend	(1,30)	14.168	.001	NS	.954
	Interaction	(1,30)	.388	.538	NS	.093
	Arm of Study	(1,30)	.033	.858	NS	.054
CGI Severity	CGI Severity -Trend	(1,30)	3.857	.059	.612	.477
	Interaction	(1,30)	.429	.518	NS	.097
	Arm of Study	(1,30)	1.098	.303	NS	.174
SDS	SDS - Trend	(1,30)	47.389	<.001	.313	1.00
	Interaction	(1,30)	.013	.909	NS	.051
	Arm of Study	(1,30)	.243	.625	NS	.077
HAM-D	HAM-D - Trend	(1,30)	3.369	.076	.321	.427
	Interaction	(1,30)	2.299	.140	NS	.312
	Arm of Study	(1,30)	2.698	.111	NS	.356
HAM-A	HAM-A - Trend	(1,30)	2.695	.111	.114	.356
	Interaction	(1,30)	.802	.378	NS	.140
	Arm of Study	(1,30)	2.847	.102	NS	.372

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Trend refers to trend over time across arms; significance indicates that by combining placebo and active scores together scores at one time point were higher than scores at the other time point regardless of arm of the study;

Interaction tests whether there is an interaction between scores at baseline versus endpoint (i.e. slope of line) and the arm of the study;

Arm of the study tests whether one group's average scores are higher than the other group across time points.

Abbreviations: NE-YBOCS = Yale Brown Obsessive Compulsive Scale Modified for Neurotic Excoriation; SP-SAS = Skin Picking Symptom Assessment Scale; CGI = Clinical Global Impression severity scale; SDS= Sheehan Disability Scale; HAM-D= Hamilton Depression Scale; HAM-A= Hamilton Anxiety Scale

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Table 4

Performance on Key Cognitive Indices (mean ± SD), for Responders (Resp) and Non-responders (Non-resp), for each Treatment Arm

	Lamotrigine treatment				Placebo treatment			
	Resp (n=7)	**Non-resp (n=9)**	**Sig.**	**E**	**Resp (n=5)**	**Non-resp (n=11)**	**Sig.**	**E**
IED Total errors	22.86 ± 12.46	11.22 ± 7.28	*	1.18	14.6 ± 9.4	15.44 ± 10.51		−0.08
IED Total errors (adjusted)	33.57 ± 24.58	14 ± 15.48	*	0.98	14.6 ± 9.4	15.44 ± 10.51		−0.08
IED Total errors, ID shift	0.43 ± 0.79	0.22 ± 0.44		0.34	3.2 ± 7.16	0.33 ±0.71		0.69
IED Total errors, ED shift	15.14 ± 11.33	4.89 ± 7.3	*	1.11	4.8 ± 5.81	6.11 ± 6.77		−0.20
SST Median correct RT on GO trials	551 ± 196.74	438.78 ± 128.1		0.70	508.4 ± 218.93	486.72 ± 125.61		0.13
SST SSRT	211.55 ± 44.83	164.38 ± 23.83	**	1.37	294.43 ± 158.18	167.7 ± 51.23	*	1.26
SST Proportion of successful stops	0.54 ± 0.1	0.51 ± 0.04		0.42	0.51 ± 0.21	0.52 ± 0.09		−0.07
SST Direction errors on stop and go trials	3.57 ± 3.69	4 ± 4.9		−0.10	6.6 ± 11.13	3 ± 5.94		0.45

Sig.: Significant difference between responders and non-responders within group,

* $p<0.05$,

** $p<0.01$ E: Effect size, Cohen's D, using pooled standard deviation