A Pilot Open Series of Lamotrigine in Eating Disorders Characterized by Significant Affect Dysregulation and Poor Impulse Control

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INTRODUCTION

- First-line interventions (behavioral therapies and selective serotonin reuptake inhibitors - SSRIs), are often ineffective for a large proportion of BN patients who have been described as multi-impulsive, and who struggle with affective instability and dysregulated behaviors (Halmi, 2013; Mitchell, 2007; Rossiter,1993; Wilson, 2007).
- Patients with the binge-eating/purging subtype of anorexia nervosa (AN-B/P) have been less studied, but authors link significant emotion regulation difficulties and impulsive behaviors, along with poor treatment response, to this group as well (Racine, 2013).
- Consistent with the literature, our clinical experience is that severely dysregulated eating disorder patients often have little or no response to antidepressant monotherapy, and in some cases, appear to become more agitated with this treatment. This led to speculation that medications with mood-stabilizing properties (Crawford, 2015; Reich, 2009; Tritt, 2005) may be a better alternative.
- We previously reported a positive response to lamotrigine, an antiepileptic drug, in five patients with BN and AN who had significant affect dysregulation and impulsivity (Trunko, 2014). Though encouraging, these case reports were based on personal observation and our desire to support potential future controlled trials with lamotrigine led to this current follow up.

OBJECTIVE

This current study aimed to confirm our observations of positive responses to lamotrigine, in a larger series of patients, utilizing standardized instruments (Pgohl, 2009; Zanarini) designed to assess changes in affect and behavioral dysregulation in response to treatment as well as mood and eating disorder symptomology.

METHODS & PROCEDURE

- **Titration and Measures**
- Starting dose lamotrigine = 25 mg/day for two weeks, increased to 50mg/day for the next two weeks, subsequent rate of titration was variable, with a maximum increase of 50 mg/day every two weeks until reaching therapeutic dose (expected range 100mg/day to 300mg/day). Increases and maximum dose were determined by the psychiatrist based on tolerability and therapeutic response.
- Questionnaires completed at intake and approximately ever 2 weeks thereafter (mean time between assessments = 20.5 days, SD = 12.9 days)
  - Borderline Evaluation of Severity Over Time (Pfohl, 2009)
    - Subscales: 1) *Cognitive and affective dysregulation*; 2) *Behavioral dysregulation*; 3) *Skillful behavioral regulation*
  - Zanarini Rating Scale for Borderline Personality Disorder (Zanarini, 2003)
    - Subscales: 1) *Affective dysregulation;* 2) *Impulsive behaviors*; 3) *Unstable interpersonal relationships*

•Secondary outcome measures given at treatment start and at final assessment

- Eating Disorder Examination Questionnaire (Fairburn, 2008)
  - Subscales: 1) *Restraint*; 2) *Shape Concern*; 3) *Weight Concern; 4) Eating Concern*
- State-Trait Anxiety Inventory (Spielberger, 1983)
  - Subscales: 1) *Trait anxiety;* 2) *State anxiety*
- Beck Depression Inventory (Beck, 1996)
  - 21 item self-report questionnaire, rated on a 4-point Likert-type scale ranging from 0-3, with higher scores indicating greater severity of depression.

PARTICIPANTS

ID	Age	Ethnicity	Race	BMI (kg/m2)	Diagnosis at Admission	Days on Lamotrigine at Baseline Assessment	Total Days on Lamotrigine	Final Lamotrigine Dose (mg/day)	Concurrent Medications
1	28	Non-Hispanic	Black	26.3	EDNOS[a]	-2	223	150	quetiapine XR, bupropion XL, levomilnacipran
2	23	Non-Hispanic	White	20.2	EDNOS[b]	-5	246	200	duloxetine, trazodone
3	41	Non-Hispanic	White	21.9	EDNOS[c]	-4	253	100	escitalopram
4	42	Hispanic	Other	28.3	BN	1	190	100	venlafaxine XR, naltrexone
5	18	Non-Hispanic	White	19.7	AN-B/P	1	86	200	sertraline, gabapentin
6	31	Non-Hispanic	White	20.1	AN-B/P	1	85	200	gabapentin, naltrexone
7	25	Non-Hispanic	White	19.1	AN-R	0	102	200	duloxetine, sertraline[d]
8	31	Hispanic	Other	22.3	AN-BP	0	71	100	fluoxetine
9	32	Non-Hispanic	Other	25.7	BN	1	71	200	duloxetine

[a]High-normal to mildly overweight with restrictive eating and purging; [b]Mildly underweight AN with alternating severe restrictive eating, bingeing, and occasional purging; [c]Lifetime history of mostly BN with episodes of AN-B/P. During period of study, most characteristic of low-normal-weight AN-P; [d]Duloxetine was concurrent with lamotrigine for one month and was subsequently replaced with sertraline in the second month. In the third month, lamotrigine was the only medication prescribed. BMI = body mass index; AN-B/P = anorexia nervosa, binge-eating/purging subtype; EDNOS = eating disorder not otherwise specified; BN = bulimia nervosa.

RESULTS

Multilevel Models Examining Change in ZAN-BPD and BEST Scores Over Time

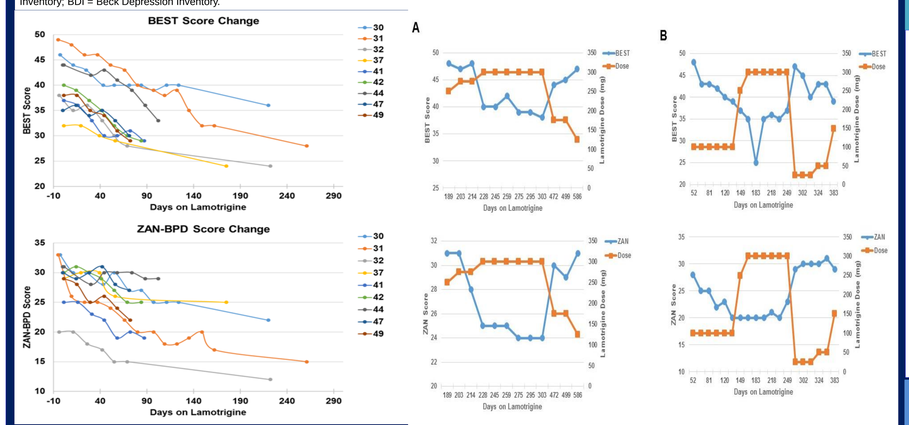
Effect	Estimate	S.E.	df	*F*	*p*
ZAN-BPD Score					
Dose	-0.01963	0.005757	14.5	11.6	0.0041
Days on lamotrigine	-0.02712	0.006105	50.9	19.7	<.0001
BMI	0.6092	0.3819	8.9	2.5	0.1457
Age	-0.2442	0.1637	9.2	2.2	0.1692
BEST Score					
Dose	-0.02644	0.004140	14.9	40.8	<.0001
Days on lamotrigine	-0.04753	0.005945	50.2	63.9	<.0001
BMI	-0.2523	0.5138	9.2	0.2	0.6350
Age	-0.2841	0.2185	9.1	1.7	0.2257

Note: ZAN-BPD = Zanarini Rating Scale for Borderline Personality Disorder; BEST = Borderline Evaluation of Severity Over Time

Scores on Secondary Outcome measures Before and After Lamotrigine Treatment

	Pre	Post		
Measure	***M (SD)***	***M (SD)***	***p***	**Cohen's *d***
EDE-Q Scores				
Restraint	2.8 (1.5)	1.3 (0.9)	0.058	1.21
Eating Concern	2.9 (1.7)	2.2 (1.4)	0.093	0.45
Shape Concern	4.7 (1.2)	3.3 (1.6)	0.093	0.99
Weight Concern	4 (1.8)	3.4 (1.5)	0.406	0.36
Global	3.7 (1.4)	2.7 (1)	0.051	0.82
BDI-II	30.7 (15.4)	24.2 (12.4)	0.314	0.46
STAI State	60.2 (11.4)	60.2 (12.1)	0.799	0
STAI Trait	54 (8.9)	56.1 (10.6)	0.373	-0.21

Note: Presented *p* values represent the results of exploratory related-samples Wilcoxon signed rank tests; EDE-Q = Eating Disorder Examination Questionnaire; STAI = State-Trait Anxiety Inventory; BDI = Beck Depression Inventory.



ANALYSES

- Both ZAN-BPD and BEST scores decreased as dose and time on drug increased
- At 1 month BEST score reduction was very large d=2.41, ZAN-BPD score reduction was moderate to large (d = 0.78) and continue improving several months into lamotrigine titration
- Inclusion of age and BMI in models did not impact findings, and results reported included these covariates.
- 77.8% of patients showed significant treatment response (RCI > 1.96) as measured by ZAN-BPD (mean RCI = 4.46, SD = 3.34)
- 55.6% of patients showed significant treatment response as measured by BEST scores (mean RCI = 2.26, SD = 0.96)

Response to Decrease in Lamotrigine Dose (not included in analyses)

- Patient A – 48 y/o female, AN-B/P, recurrent MDD, GAD, and history of severe affect dysregulation. Tried various psychotropic meds but discontinued them "feeling they were ineffective." Titrated up to 300mg/d (monotherapy), experienced decreases in reactivity, irritability, anger, impulsivity, anxiety, depression, SI, and drives to purge and self harm. Due to side effect concerns, she tapered dose down to 125mg/day, experienced worsening of symptoms. Encouraged by family, she began titrating dose up to 300mg/day.
- Patient B – 21 y/o female, AN-B/P, depressive symptoms, and affect dysregulation. Struggled with utilizing DBT skills in the moment. Titrated up to 300mg/day and experienced reductions in impulsivity, mood lability, suicidal ideation, and stress reactivity. Binge eating, purging, shop lifting, and self- harm also reduced. With successes she tapered off lamotrigine completely. Affect dysregulation became problematic and dangerous behaviors began. With gradual titration up to 300 mg/day, patient achieved life stability.

DISCUSSION

- This is the first study to use standardized measures of affective and behavioral dysregulation to document lamotrigine response in eating-disordered patients over a substantial time period.
- Increasing dose and time on lamotrigine were associated with significant and medium-to-large self-reported reductions in dysregulated emotions and problems with impulse control.
- Data from two additional patients suggested these symptoms worsened with lamotrigine dose reduction and improved after lamotrigine re-titration.
- We found preliminary evidence of reduced eating disorder symptoms and depression, but little change in anxiety symptoms.
- These results are consistent with prior reports of lamotrigine treatment benefit for some patients with BN and AN-B/P-spectrum disorders (Trunko, 2014 ; Rybakowski, 2008; Marilov, 2010) and for some patients with binge-eating behaviors (Guerdjikova, 2009).
- Lamotrigine is a glutamate antagonist, and its effectiveness is believed to be mediated by glutamate reduction.
- Our findings raise the question as to whether glutamatergic abnormalities play a role in affective and behavioral dysregulation in individuals with eating disorders, as they may in bipolar disorder and BPD (Ehrlich, 2015; Krause-Utz, 2014). This could help explain why traditionally used serotonergic antidepressants have limited impact for many of these eating-disordered patients.

CONCLUSION & FUTURE DIRECTIONS

Our preliminary data support further study of lamotrigine for the treatment of dysregulation in eating-disordered patients. A growing body of evidence suggests that dysregulated behaviors may be linked to emotional instability. Pervasive deficits in self-regulatory control may contribute to inadequate response to existing eating disorder treatments, as powerful but only temporary relief of dysregulated and impulsive behaviors may reinforce maladaptive cycles. Data from our small sample must be interpreted with caution as it is premature to propose that lamotrigine is a treatment for dysregulated mood and impulse control in eating disorders. However, our findings preliminarily suggest that directly targeting regulatory deficits may be key to more effective treatment and support the feasibility of studying lamotrigine efficacy in eating-disordered populations. Our pilot findings are perhaps most important in supporting the need for large scale, rigorously controlled investigations of lamotrigine, used with or without concurrent DBT or other therapies, to elucidate how these factors might interact to treat dysregulated behavior in eating disorders.

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