Lamotrigine for acute bipolar depression: An exploratory item-level analysis

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Abstract
Objectives: Lamotrigine is used to treat bipolar depression despite inconsistent evidence. Here we present the results of an exploratory item-level analysis of pooled data from five randomized placebo-controlled trials of lamotrigine for acute bipolar depression. The goal was to determine if certain depression scale items were more responsive to lamotrigine treatment.

Methods: The pooled sample contained 1072 adult outpatients treated for up to 7–10 weeks. Depressive symptoms were measured with the Hamilton Depression Rating Scale and the Montgomery–Åsberg Depression Rating Scale. Change scores on individual scale items were compared between treatment groups.

Results: There were statistically significant effects on items assessing depressed mood/sadness, lack of interest/anhedonia, pessimism/guilt, and anergia/fatigue, on both scales. However, there was marked variation in the baseline symptom prevalence, and items with higher scores at baseline tended to have larger and statistically significant treatment effects.

Conclusions: The results suggested a significant treatment effect on core symptoms of depression. A floor effect appeared to limit the sensitivity of other scale items. Given the exploratory nature of the analysis, firm conclusions cannot be drawn, although the results were consistent with past research. Relying on total depression scale sum scores over targeted assessments of core depressive symptoms may have impeded signal detection in the original trials.

KEYWORDS
anticonvulsant, clinimetrics, mood disorder, rating scale

1 INTRODUCTION

Lamotrigine is used to treat acute bipolar depression despite inconsistent evidence (Yatham et al., 2018). Five industry-sponsored monotherapy trials initially failed to find a consistent benefit over a placebo (Calabrese et al., 2008), yet two maintenance trials were positive (Goodwin et al., 2004). As a result, lamotrigine was widely approved for maintenance therapy in bipolar disorder but not for acute depression treatment (Weisler et al., 2008). However, a meta-analysis of the five monotherapy trials subsequently detected a modest efficacy signal (Geddes et al., 2009), and more recent adjunct trials were also supportive (Geddes et al., 2016; van der Loos et al., 2008).

A target lamotrigine dose of 200 mg/day is generally recommended for bipolar disorder although higher doses are sometimes required in...
TABLE 1 Clinical trials used in the pooled analysis

|                  | SCAB2001 | SCAA2010 | SCA40910 | SCA100223 | SCA30924 |
|------------------|----------|----------|----------|------------|----------|
| Sample, n        | Bipolar I| Bipolar I| Bipolar II| Bipolar I  | Bipolar I  |
| Lamotrigine      | 63 (35 F)| 61 (36 F)| 42 (30 F)| 133 (76 F)| 111 (71 F)| 131 (73 F) |
| Placebo          | 66 (39 F)| 61 (38 F)| 42 (23 F)| 124 (66 F)| 110 (70 F)| 128 (69 F) |
| Age, M years (SD) |          |          |          |            |          |
| Lamotrigine      | 41.7 (11.5) | 40.5 (11.9) | 39.5 (10.4) | 37.4 (12.5) | 38.8 (11.5) | 40.5 (12.3) |
| Placebo          | 41.9 (12.7) | 39.7 (10.2) | 41.3 (12.5) | 37.2 (11.5) | 36.9 (11.9) | 38.0 (12.0) |
| Current depressive episode > 24 weeksa |          |          |          |            |          |
| Lamotrigine      | 22%      | 28%      | 17%      | 19%        | 30%      | 34% |
| Placebo          | 29%      | 21%      | 26%      | 23%        | 24%      | 43% |
| Lamotrigine dosing, mg/day |          |          |          |            |          |
| Week 1–2: 25     |          |          |          | Week 1–2: 25 |          |          |
| Week 3: 50       |          |          |          | Week 3–4: 50 |          |          |
| Week 4: 100      |          |          |          | Week 5: 100 |          |          |
| Week 5–7: 200    |          |          |          | Week 6–8: 200 |          |          |
|                   |          |          |          | Week 6–8: 200 |          |          |
|                   |          |          |          | Week 8–10: 100–400 |          |          |

Note. Detailed descriptions can be found at https://www.gsk-studyregister.com and in Calabrese et al. (2008). F = female. 

*aBased on the Safety populations for SCA40910, SCA100223, and SCA30924. 
bFlexible dosing based on tolerability.

clinical practice (Yatham et al., 2018). Suboptimal dosing could explain the negative results from the monotherapy trials (Geddes et al., 2016; Yatham et al., 2018). In four of five trials, 200 mg/day was the maximum dose, and it was not achieved until the final 3 weeks (Calabrese et al., 2008). In contrast, doses up to 400 mg/day were used in both maintenance trials (Goodwin et al., 2004).

Another possible explanation for the inconsistent findings is that lamotrigine may be more effective for specific depressive symptoms that were not deliberately assessed in the original trials. This was suggested by an open-label trial that used flexible doses at an average of 250 mg/day (Bowen et al., 2014; Peters & Bowen, 2018), but also trials in which 200 mg/day was the maximum dose (Mitchell et al., 2013; Peters et al., 2018). Therefore, higher doses may not be required to detect these effects.

Here we report the results of an exploratory item-level analysis of data from the five original acute bipolar depression monotherapy trials (Calabrese et al., 2008). The purpose was to further elucidate specific depressive symptoms that might be more responsive to lamotrigine compared to placebo.

2 | METHODS

2.1 | Design

This study used pooled data from five randomized, double-blind, placebo-controlled, parallel-group, monotherapy trials of lamotrigine for acute bipolar depression (Calabrese et al., 2008). Data access was requested from the trial sponsors through clinicalstudydatarequest.com. The analyses reported here were conducted post hoc after another study (Peters et al., 2021) with permission from the sponsor and an independent review panel. The trials are described in Table 1 and in more detail elsewhere (Calabrese et al., 2008). These were conducted in accordance with the Declaration of Helsinki with ethics approval, and all participants provided informed consent (Calabrese et al., 2008). The trials were conducted solely in the United States, except SCAB2001 (15 centers in the United States, 6 in the United Kingdom, Australia, and France). In all trials, lamotrigine was administered with a fixed-dose titration up to 200 mg/day (except in trial SCAA2010 in which it was dosed flexibly at 100–400 mg/day) for up to 7–10 weeks (see Table 1). We did not include data from one fixed-dose 50 mg/day arm in trial SCAB2001 as this dose is considered subtherapeutic (Geddes et al., 2009; Yatham et al., 2018).

2.2 | Sample

The pooled sample consisted of 1072 adult outpatients (age ≥ 18 years, M = 39.0, SD = 11.9; 58.4% female) currently in an acute major depressive episode (duration ≥ 2 or 8 weeks, depending on the trial) with a diagnosis of bipolar disorder type I or II (see Table 1). Diagnoses were confirmed with the Structured Clinical Interview for DSM-IV (First et al., 1994). A 17-item Hamilton Depression Rating Scale (HAMD-17) (Hamilton, 1960) score ≥ 18 was also required. Additional inclusion criteria varied between trials (see Calabrese et al., 2008). Common exclusion criteria were previous lamotrigine treatment; concurrent/current psychotropic medication or psychotherapy; abnormal thyroid tests; epilepsy; active suicidality; panic disorder, bulimia nervosa, obsessive-compulsive disorder, or social phobia in the last 12 months; rapid-cycling; substance abuse/dependence; and
### TABLE 2  HAMD items with baseline prevalence and change scores

| Item                  | Baseline | Change scores, M (SD) | \( z \) |
|-----------------------|----------|----------------------|--------|
|                       | M (SD)   | LTG                  | PBO    |        |
| 1. Depressed mood     | 2.9 (.50)| 1.23 (.12)           | 1.05 (.12) | 2.51* |
| 2. Guilt              | 2.0 (.80)| 0.94 (.11)           | 0.78 (.11) | 2.21* |
| 3. Suicide            | 1.0 (.80)| 0.52 (.86)           | 0.47 (.87) | 0.89  |
| 4. Insomnia, early    | 1.5 (.79)| 0.49 (.98)           | 0.50 (.10) | −0.23 |
| 5. Insomnia, middle   | 1.4 (.77)| 0.43 (.97)           | 0.47 (.98) | −0.64 |
| 6. Insomnia, late     | 1.2 (.85)| 0.45 (.10)           | 0.46 (.97) | −0.02 |
| 7. Work and interests | 2.9 (.58)| 1.37 (.13)           | 1.06 (.12) | 3.84***|
| 8. Retardation        | 1.3 (.82)| 0.66 (.92)           | 0.55 (.93) | 1.89†  |
| 9. Agitation          | 1.1 (.84)| 0.33 (.93)           | 0.37 (.87) | −0.06 |
| 10. Anxiety, psychic  | 2.3 (.71)| 0.79 (.12)           | 0.68 (.11) | 1.59  |
| 11. Anxiety, somatic  | 1.7 (.94)| 0.67 (.11)           | 0.61 (.11) | 0.67  |
| 12. Somatic, GI       | 0.8 (.76)| 0.31 (.88)           | 0.36 (.82) | −0.55 |
| 13. Somatic, general  | 1.7 (.52)| 0.76 (.91)           | 0.62 (.90) | 2.47*  |
| 14. Genital           | 1.3 (.81)| 0.45 (.92)           | 0.45 (.89) | −0.09 |
| 15. Hypochondriasis   | 0.7 (.76)| 0.29 (.82)           | 0.19 (.80) | 1.80†  |
| 16. Weight loss       | 0.3 (.59)| 0.07 (.67)           | 0.13 (.71) | −1.29 |
| 17. Insight           | 0.2 (.41)| 0.03 (.50)           | 0.04 (.40) | −0.05 |
| 18. Diurnal variation | 0.9 (.83)| 0.46 (.87)           | 0.38 (.93) | 1.33  |
| 19. Depersonalization | 0.4 (.72)| 0.20 (.75)           | 0.24 (.71) | −0.74 |
| 20. Paranoid          | 0.4 (.59)| 0.09 (.60)           | 0.17 (.63) | −1.82† |
| 21. Obsessional/compulsive | 0.4 (.59)| 0.09 (.54)           | 0.11 (.54) | −0.34 |
| 22. Hypersomnia, early| 0.5 (.80)| 0.23 (.81)           | 0.18 (.83) | 0.72  |
| 23. Hypersomnia, oversleep | 0.4 (.72)| 0.16 (.73)           | 0.14 (.77) | 0.34  |
| 24. Hypersomnia, napping | 0.6 (.81)| 0.18 (.89)           | 0.20 (.91) | −0.03 |
| 25. Increased appetite | 0.3 (.65)| 0.14 (.67)           | 0.13 (.71) | 0.07  |
| 26. Weight gain       | 0.3 (.60)| 0.11 (.67)           | 0.10 (.64) | 0.01  |
| 27. Psychic retardation | 1.1 (.84)| 0.55 (.90)           | 0.49 (.91) | 0.86  |
| 28. Motor retardation | 1.0 (.84)| 0.54 (.86)           | 0.46 (.91) | 1.73†  |
| 29. Helplessness      | 1.4 (.88)| 0.63 (1.1)           | 0.54 (1.1) | 1.41  |
| 30. Hopelessness      | 1.6 (.90)| 0.70 (1.1)           | 0.65 (1.1) | 0.66  |
| 31. Worthlessness     | 1.7 (.86)| 0.72 (1.0)           | 0.65 (1.0) | 1.31  |

Note. Change scores were compared between treatment conditions with Wilcoxon rank-sum tests. A negative \( z \) score indicates the change score was larger in the placebo group. HAMD = Hamilton Depression Rating Scale; LTG = lamotrigine; PBO = placebo. \( * p < .05; \quad ** p < .01; \quad *** p < .001; \quad † p < .10. \)

medical conditions that could interfere with treatment (Calabrese et al., 2008).

#### 2.3 Instruments

Depressive symptoms were measured with the 17- and 31-item versions of the Hamilton Depression Rating Scale (HAMD-17 and HAMD-31) (Hamilton, 1960; Williams et al., 1988) and the 10-item Montgomery–Åsberg Depression Rating Scale (MADRS) (Montgomery & Åsberg, 1979). The HAMD-17 and MADRS are commonly used and accepted in regulatory trials in the United States and Europe. We included all HAMD-31 items because these cover additional symptoms not assessed by the HAMD-17. The rationale for also including the MADRS was that this allowed us to look for consistency across scales. Scales were administered at baseline and weekly until study completion.

#### 2.4 Analysis

Change scores (baseline – final score) were calculated for each depression scale item. Missing scores were filled by carrying forward the last observation, consistent with the original trials
(Calabrese et al., 2008). Change scores were then compared between treatment groups with Wilcoxon rank-sum tests. A nonparametric test was chosen in case some items (particularly those with restricted ranges) were not normally distributed. For each item, we also calculated mean baseline scores and the proportion of patients scoring zero at baseline to gauge the extent that treatment effects were related to baseline prevalence (Hieronymus et al., 2019).

3 | RESULTS

HAMD-17 item-level baseline and change scores are presented in Table 2. Significant treatment effects were detected on items 1 (depressed mood), 2 (guilt), 7 (work and interest), and 13 (general somatic/fatigue). The respective Cohen’s d effect sizes were 0.15, 0.14, 0.24, and 0.15. Among the additional HAMD-31 items (also in Table 2), the only marginally significant effect in favor of lamotrigine was on item 28 (motor retardation; p = .08, d = .09). MADRS item-level scores (see Table 3) were generally consistent, with significant effects on items 1 (apparent sadness; d = 0.15), 2 (reported sadness; d = 0.14), 7 (lassitude; d = 0.17), 8 (inability to feel; d = 0.20), and 9 (pessimistic thoughts; d = 0.15). In general, items with significant or marginally significant effects tended to have higher baseline scores, with some exceptions (e.g., HAMD items 10 and 11 vs. 8 and 15; MADRS item 6 vs. 7 and 8; see Tables 2 and 3). It was noted that the items with significant or marginally significant effects also roughly matched the items from the HAMD-6 subscale (i.e., 1, 2, 7, 8, 10, and 13), which has established psychometric and clinimetric advantages over the HAMD-17 (Carrozzino et al., 2020; Timmerby et al., 2017). Therefore, we made the post-hoc decision to also calculate treatment effects with analysis of variance tests on the MADRS, in addition to also calculate treatment effects with analysis of variance tests on the HAMD-6 (F = 11.7, p < .001, d = .21) and a subscale of the six corresponding MADRS items (i.e., 1, 2, 3, 7, 8, and 9; F = 9.69, p = .002, d = .19), which were larger and more strongly significant compared to their parent scales (HAMD-17, F = 3.82, p = .051, d = .12; MADRS, F = 4.42, p = .04, d = .13).

4 | DISCUSSION

The goal of the analysis was to identify specific depressive symptoms that were more responsive to lamotrigine treatment. We found that treatment effects on HAMD-6 subscale items (in particular, anhedonia/interest, mood, energy, and guilt) were larger, with consistency across scales. This finding is important not because it is novel but because it has already been demonstrated with striking consistency for numerous second-generation antidepressants, albeit mostly in unipolar depression (Bech et al., 2002, 2004, 2010; Carrozzino et al., 2020; Entsuah et al., 2002; Faries et al., 2000; Lisinski et al., 2020; Østergaard et al., 2014; Schneider et al., 2003; Timmerby et al., 2017). We did not plan to focus on the HAMD-6 specifically, and although the analysis was exploratory, convergence with past research is reassuring. Previously it has been suggested that the lamotrigine monotherapy program failed, at least in part, due to the short trial durations combined with slow dose titrations, and suboptimal end-trial doses (Yatham et al., 2018). The current results suggest that relying on HAMD-17 and MADRS sum scores over targeted assessments of core depressive symptoms also impeded signal detection in the original trials. The results derived from item-level change scores are also consistent with a prior reanalysis of two placebo-controlled lamotrigine trials (unipolar and bipolar depression) that found significant effects on factors assessing depressive cognitions and psychomotor retardation (Mitchell et al., 2013). However, in contrast to the current results, the anergia factor (containing the work/interest and general somatic items) did not clearly improve, possibly because it also contained the insight and libido items (Mitchell et al., 2013). Past research has suggested that lamotrigine may dampen affective instability and related symptoms such as irritability in patients with mood disorders.

### TABLE 3  MADRS items with baseline prevalence and change scores

| Item                          | Baseline M (SD) | %Zero | Change scores, M (SD) | LTG | PBO | z  |
|-------------------------------|----------------|-------|-----------------------|-----|-----|----|
| 1. Apparent sadness           | 3.5 (.90)      | 0.4   | 1.58 (1.6)            | 1.35 (1.6) | 2.37** |
| 2. Reported sadness           | 3.8 (.80)      | 0.3   | 1.68 (1.7)            | 1.44 (1.6) | 2.46*  |
| 3. Inner tension              | 3.1 (.95)      | 1.8   | 1.04 (1.5)            | 0.87 (1.4) | 1.84  |
| 4. Reduced sleep              | 3.2 (1.5)      | 10.1  | 0.96 (1.8)            | 1.07 (1.8) | −0.81 |
| 5. Reduced appetite           | 1.6 (1.5)      | 40.8  | 0.63 (1.7)            | 0.71 (1.6) | −0.61 |
| 6. Concentration              | 3.3 (1.0)      | 2.2   | 1.31 (1.7)            | 1.18 (1.5) | 1.29  |
| 7. Lassitude                  | 3.4 (1.1)      | 1.9   | 1.53 (1.6)            | 1.24 (1.7) | 2.72** |
| 8. Inability to feel          | 3.4 (1.1)      | 1.8   | 1.64 (1.6)            | 1.31 (1.7) | 3.16** |
| 9. Pessimistic thoughts       | 2.7 (1.1)      | 3.0   | 1.22 (1.5)            | 0.99 (1.5) | 2.44* |
| 10. Suicidal thoughts         | 1.4 (1.1)      | 27.2  | 0.68 (1.2)            | 0.66 (1.3) | 0.40  |

Note. Change scores were compared between treatment conditions with Wilcoxon rank-sum tests. A negative z score indicates the change score was larger in the placebo group. MADRS = Montgomery–Åsberg Depression Rating Scale; LTG = lamotrigine; PBO = placebo. *p < .05; †p < .01; ‡p < .001; ††p < .10.
(Bowen et al., 2014; Peters & Bowen, 2018). Although these were not assessed in the current study, the positive effect on MADRS item 8 (inability to feel) argues against emotional blunting in this sample.

The items with the largest effects also tended to be more prevalent in the sample at baseline, although not invariably. This suggests a floor effect, to some extent, may have limited the sensitivity of other items. Alternatively, the lack of prominent effects on the items assessing sleep and appetite/weight would also be in keeping with lamotrigine being weight-neutral and not overly sedating (Bowden et al., 2004; Calabrese et al., 2008). The marked variation of baseline prevalence across depressive symptoms was similar to that reported in a recent pooled analysis of trial data from patients with unipolar depression being treated with selective serotonin reuptake inhibitors (Hieronymus et al., 2019). This should be noted for future clinical trials, particularly if symptom-level effects are being examined, as it would be difficult to detect a significant effect if the majority of the sample is without the symptom in question.

Given the exploratory nature of the analysis, the results need to be considered hypothesis-generating until replicated with additional data. Furthermore, the results may not generalize to broader clinical populations, and only clinician-rated symptom scales were used to measure efficacy. We also did not test for interactions with other variables (e.g., age, sex). The use of single items to assess symptoms is another limitation, although it does permit comparison with a substantial number of industry-sponsored trials.

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CONFLICTS OF INTEREST
YZ has received research grants from ZYUS Life Sciences Inc., Aurora Cannabis Inc., and the Saskatchewan Health Research Foundation. RL has received research funding from AA Pharma and has attended an advisory board meeting with Pfizer. LB has received research computing credits from Google. EP and HL have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study were provided by GlaxoSmithKline via ClinicalStudyDataRequest.com. Restrictions apply to the availability of these data, which were used under license for this study.

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REFERENCES
Bech, P., Boyer, P., Germain, J.-M., Padmanabhan, K., Hautdiquet, V., Pitrosky, B., & Tourian, K. (2010). HAM-D17 and HAM-D6 sensitivity to change in relation to desvenlafaxine dose and baseline depression severity in major depressive disorder. Pharmacopsychiatry, 43, 271–276. https://doi.org/10.1055/s-0030-1263173
Bech, P., Tanghøj, P., Andersen, H., & Overe, K. (2002). Citalopram dose-response revisited using an alternative psychometric approach to evaluate clinical effects of four fixed citalopram doses compared to placebo in patients with major depression. Psychopharmacology, 163, 20–25. https://doi.org/10.1007/s00213-002-1147-6
Bech, P., Tanghøj, P., Cialdella, P., Andersen, H. F., & Pedersen, A. G. (2004). Escitalopram dose–response revisited: An alternative psychometric approach to evaluate clinical effects of escitalopram compared to citalopram and placebo in patients with major depression. International Journal of Neuropsychopharmacology, 7, 283–290. https://doi.org/10.1017/S1461145704004365
Bowden, C. L., Asnis, G. M., Ginsberg, L. D., Bentley, B., Leadbetter, R., & White, R. (2004). Safety and tolerability of lamotrigine for bipolar disorder. Drug Safety, 27, 173–184. https://doi.org/10.2165/00002018-200427030-00002
Bowden, R. C., Balbuena, L., & Baetz, M. (2014). Lamotrigine reduces affective instability in depressed patients with mixed mood and anxiety disorders. Journal of Clinical Psychopharmacology, 34, 747–749. https://doi.org/10.1097/JCP.0000000000001164
Calabrese, J. R., Huffman, R. F., White, R. L., Edwards, S., Thompson, T. R., Ascher, J. A., Monaghan, E. T., & Leadbetter, R. A. (2008). Lamotrigine in the acute treatment of bipolar depression: Results of five double-blind, placebo-controlled clinical trials. Bipolar Disorders, 10, 323–333. https://doi.org/10.1111/j.1399-5618.2007.00500.x
Carrozzino, D., Patierno, C., Fava, G. A., & Guidi, J. (2020). The Hamilton Rating Scales for depression: A critical review of clinimetric properties of different versions. Psychotherapy and Psychosomatics, 89, 133–150. https://doi.org/10.1159/000506879
Entsuah, R., Shaffer, M., & Zhang, J. (2002). A critical examination of the sensitivity of unidimensional subscales derived from the Hamilton Depression Rating Scale to antidepressant drug effects. Journal of Psychiatric Research, 36, 437–448. https://doi.org/10.1016/S0022-3956(02)00024-9
Faries, D., Herrera, J., Rayamajhi, J., DeBrotta, D., Demitrack, M., & Potter, W. Z. (2000). The responsiveness of the Hamilton Depression Rating Scale. Journal of Psychiatric Research, 34, 3–10. https://doi.org/10.1016/S0022-3956(99)00037-0
First, M., Spitzer, R., Gibbon, M., & Williams, J. (1994). Structured clinical interview for axis DSM-IV disorders. Biometrics Research.
Geddes, J. R., Calabrese, J. R., & Goodwin, G. M. (2009). Lamotrigine for treatment of bipolar depression: Independent meta-analysis and meta-regression of individual patient data from five randomised trials. The British Journal of Psychiatry, 194, 4–9. https://doi.org/10.1192/bjp.bp.107.048504
Geddes, J. R., Gardiner, A., Rendell, J., Voysey, M., Tunbridge, E., Hinds, C., Yu, L.-M., Hainsworth, J., Attenburrow, M.-J., Simon, J., Goodwin, G. M., & Harrison, P. J. & CEQUEL Investigators and Collaborators (2016). Comparative evaluation of quetiapine plus lamotrigine combination versus quetiapine mono-therapy (and folic acid versus placebo) in bipolar depression (CEQUEL): A 2x2 factorial randomised trial. Lancet Psychiatry, 3, 31–39. https://doi.org/10.1016/S2215-0366(15)00450-2
Goodwin, G. M., Bowden, C. L., Calabrese, J. R., Grune, H., Kasper, S., White, R., Greene, P., & Leadbetter, R. (2004). A pooled analysis of 2 placebo-controlled 18-month trials of lamotrigine and lithium maintenance in bipolar I disorder. The Journal of Clinical Psychiatry, 65, 432–441. https://doi.org/10.4088/jcp.v65n0321
Hamilton, M. (1960). A rating scale for depression. Journal of Neurology, Neurosurgery, and Psychiatry, 23, 56–62. https://doi.org/10.1136/jnnp.23.1.56
Hieronymus, F., Lisinski, A., Nilsson, S., & Eriksson, E. (2019). Influence of baseline severity on the effects of SSRIs in depression: An item-based, patient-level post-hoc analysis. Lancet Psychiatry, 6, 745–752. https://doi.org/10.1016/S2215-0366(19)30216-0

Lisinski, A., Hieronymus, F., Näslund, J., Nilsson, S., & Eriksson, E. (2020). Item-based analysis of the effects of duloxetine in depression: A patient-level post hoc study. Neuropsychopharmacology, 45, 553–560. https://doi.org/10.1038/s41386-019-0523-4

Mitchell, P. B., Hadzi-Pavlovic, D., Evoniuk, G., Calabrese, J. R., & Bowden, C. L. (2013). A factor analytic study in bipolar depression, and response to lamotrigine. CNS Spectrums, 18, 214–224. https://doi.org/10.1017/S1092852913000291

Montgomery, S. A., & Åsberg, M. (1979). A new depression scale designed to be sensitive to change. The British Journal of Psychiatry, 134, 382–389. https://doi.org/10.1192/bjp.134.4.382

Østergaard, S. D., Bech, P., Trivedi, M. H., Wisniewski, S. R., Rush, A. J., & Fava, M. (2014). Brief, unidimensional melancholia rating scales are highly sensitive to the effect of citalopram and may have biological validity: Implications for the research domain criteria (RDoC). Journal of Affective Disorders, 163, 18–24. https://doi.org/10.1016/j.jad.2014.03.049

Peters, E. M., & Bowen, R. (2018). Irritability in a mixed sample of patients with unipolar and bipolar II depression predicts responsiveness to lamotrigine. Personalized Medicine in Psychiatry, 7-8, 27–30. https://doi.org/10.1016/j.pmp.2018.01.001

Peters, E. M., Bowen, R., & Balbuena, L. (2018). Melancholic symptoms in bipolar II depression and responsiveness to lamotrigine in an exploratory pilot study. Journal of Clinical Psychopharmacology, 38, 509–512. https://doi.org/10.1097/JCP.0000000000000947

Peters, E. M., Zhang, Y., Lodhi, R., Li, H., & Balbuena, L. (2021). Melancholic features in bipolar depression and response to lamotrigine: A pooled analysis of five randomized placebo-controlled trials. Journal of Clinical Psychopharmacology, 41, 315–319. https://doi.org/10.1097/JCP.0000000000001393

Schneider, L. S., Nelson, J. C., Clary, C. M., Newhouse, P., Krishnan, K. R. R., Shiovitz, T., & Weins, K. (2003). An 8-week multicenter, parallel-group, double-blind, placebo-controlled study of sertraline in elderly outpatients with major depression. American Journal of Psychiatry, 160, 1277–1285. https://doi.org/10.1176/appi.ajp.160.7.1277

Timmerby, N., Andersen, J. H., Østergaard, S. D., & Bech, P. (2017). A systematic review of the clinimetric properties of the 6-item version of the Hamilton Depression Rating Scale (HAM-D6). Psychotherapy and Psychosomatics, 86, 141–149. https://doi.org/10.1159/000457131

van der Loos, M. L., Mulder, P. G., Erwin, G. T. M., Blom, M. B., Vergouwen, A. C., de Keyzer, H. J., Notten, P. J. H., Luteijn, M. L., Timmermans, M. A., Vieta, E., & Nolen, W. A. (2008). Efficacy and safety of lamotrigine as add-on treatment to lithium in bipolar depression: A multicenter, double-blind, placebo-controlled trial. The Journal of Clinical Psychiatry, 70, 223–231. https://doi.org/10.4088/jcp.08m04152https://doi.org/10.4088/JCP08m04152

Weisler, R. H., Calabrese, J. R., Bowden, C. L., Ascher, J. A., DeVeau-Geiss, J., & Evoniuk, G. (2008). Discovery and development of lamotrigine for bipolar disorder: A story of serendipity, clinical observations, risk taking, and persistence. Journal of Affective Disorders, 108, 1–9. https://doi.org/10.1016/j.jad.2007.09.012

Williams, J., Link, M., Rosenthal, N., & Terman, M. (1988). Structured interview guide for the Hamilton Depression Rating Scale-Seasonal Affective Disorder Version (SIGH-SAD). New York State Psychiatric Institute.

Yatham, L. N., Kennedy, S. H., Parikh, S. V., Schaffer, A., Bond, D. J., Frey, B. N., Sharma, V., Goldstein, B. I., Rej, S., Beaulieu, S., Alda, M., MacQueen, G., Milev, R. V., Ravindran, A., O’Donovan, C., McIntosh, D., Lam, R. W., Vazquez, G., Kapczinski, F., … Beaulieu, S. (2018). Canadian Network for Mood and Anxiety Treatments (CANNAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. Bipolar Disorders, 20, 97–170. https://doi.org/10.1111/bdi.12609