**Supplementary**

**Table S1.** Sociodemographic and clinical characteristics of the groups treated or not with lithium.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Variable** |  | **Without lithium intake**  **Mean (sd)/**  **Number (%)** | **With lithium intake**  **Mean (sd)/**  **Number (%)** | **Statistical analysis** | ***p*-Value \*** |
| **Sociodemographic** |  |  |  |  |  |
| n |  | 584 | 176 |  |  |
| Age (years) |  | 40.09 (12.78) | 40.56 (12.11) | F = 0.186 | 0.67 |
| Sex | Men | 216 (37) | 81 (46) | χ2 = 4.27 | 0.04 |
|  | Women | 368 (63) | 95 (54) |  |  |
| Single | No | 271 (50.9) | 81 (52.3) | χ2 = 0.04 | 0.84 |
|  | Yes | 261 (49.1) | 74 (47.7) |  |  |
| Education | No | 207 (39.3) | 48 (30.8) | χ2 = 3.37 | 0.07 |
| (High school diploma) | Yes | 320 (60.7) | 108 (69.2) |  |  |
| **Clinical** |  |  |  |  |  |
| BD subtype | I | 231 (39.6) | 108 (61.4) | χ2 = 28.0 | > 0.0001 |
|  | II | 276 (47.3) | 59 (33.5) |  |  |
|  | NOS | 77 (13.2) | 9 (5.1) |  |  |
| Age at BD onset (years) |  | 23.36 (9.55) | 23.85 (8.37) | F =0.37 | 0.55 |
| Number of depressive episodes |  | 5.23 (4.93) | 5.59 (4.71) | F =0.62 | 0.43 |
| Number of manic episodes |  | 0.9 (2.09) | 1.38 (2.04) | F =6.7 | 0.01 |
| Number of hypomanic episodes |  | 3.39 (5.06) | 3.41 (4.57) | F =0.002 | 0.96 |
| Number of  hospitalizations | 0 | 158 (29.7) | 29 (17.6) | χ2 =21.15 | 0.0001 |
|  | 1 | 119 (22.4) | 26 (15.8) |  |  |
|  | 2-3 | 149 (28) | 54 (32.7) |  |  |
|  | > 3 | 106 (19.9) | 56 (33.9) |  |  |
| Lifetime history of suicide attempt | No | 387 (66.3) | 115 (65.3) | χ2 = 0.019 | 0.89 |
|  | Yes | 197 (33.7) | 61 (34.7) |  |  |
| Lifetime substance use disorder (abuse/dependence) | No | 369 (63.2) | 128 (72.7) | χ2 =5.028 | 0.02 |
|  | Yes | 215 (36.8) | 48 (27.3) |  |  |
| Lifetime anxiety disorder | No | 328 (56.2) | 114 (64.8) | χ2 = 3.772 | 0.05 |
|  | Yes | 256 (43.8) | 62 (35.2) |  |  |
| Lifetime eating disorder | No | 462 (79.1) | 147 (83.5) | χ2 = 1.389 | 0.24 |
|  | Yes | 122 (20.9) | 29 (16.5) |  |  |
| Multiple sclerosis | No | 560 (99.3) | 174 (100) |  | 0.58 |
|  | Yes | 4 (0.7) | 0 (0) |  |  |
| Cancer | No | 524 (96.9) | 165 (98.2) |  | 0.44 |
|  | Yes | 17 (3.1) | 3 (1.8) |  |  |
| Inflammatory bowel disease | No | 557 (99.3) | 168 (98.8) |  | 0.63 |
|  | Yes | 4(0.7) | 2 (1.2) |  |  |
| Rheumatoid arthritis | No | 570 (99.8) | 174 (100) |  | 1 |
|  | Yes | 1 (0.2) | 0 (0) |  |  |
| Peptic ulcer disease | No | 534 (95.5) | 167 (98.2) | χ2 =1.91 | 0.17 |
|  | Yes | 25 (4.5) | 3 (1.8) |  |  |
| QIDS-SR |  | 9.79 (5.84) | 8.9 (5.38) | F = 3.21 | 0.07 |
| YMRS | 0 | 297 (51.1) | 106 (60.2) | χ2 = 4.65 | 0.1 |
|  | (1–7) | 225 (38.7) | 57 (32.4) |  |  |
|  | >7 | 59 (10.2) | 13 (7.4) |  |  |
| PSQI (0–21) |  | 7.32 (3.94) | 6.47(3.7) | F = 6.59 | 0.01 |
| STAI Y-A (state) (0–60) |  | 42.7 (14.29) | 40.9(14.0) | F = 2.21 | 0.14 |
| MAThyS Emotional (0–40) |  | 21.87 (6.69) | 20.94 (5.96) | F =2.76 | 0.1 |
| MAThyS Motivation (0–40) |  | 17.61 (7.04) | 16.5 (6.17) | F = 2.38 | 0.12 |
| MAThyS Cognition (0–40) |  | 20.76 (6.15) | 19.75(5.5) | F =3.84 | 0.05 |
| MAThyS Sensory perception (0–50) |  | 26.09(5.05) | 25.74 (4.95) | F = 0.67 | 0.41 |
| MAThyS Psychomotor  (0–30) |  | 12.96 (5.58) | 12.06(5.04) | F =3.66 | 0.06 |
| AIM |  | 3.754(0.669) | 3.589(0.69) | F =8.10 | 0.004 |
| ALS |  | 1.32 (0.69) | 1.09 (0.64) | F =15.6 | 0.0001 |
| BDHI  Expressive Component |  | 21.44 (7.99) | 19.02 (7.64) | F =12.7 | 0.0004 |
| BDHI  Attitudinal Component |  | 7.67 (4.37) | 6.77 (4.31) | F =5.82 | 0.02 |
| BIS-10 |  | 67.95 (11.33) | 66.01 (11.65) | F = 3.95 | 0.047 |
| **Drugs** |  |  |  |  |  |
| Anticonvulsants | No | 265(45.4) | 109(61.9) | χ2 = 14.18 | |  |  | | --- | --- | |  | 0.0002 | |
|  | Yes | 319(54.6) | 67(38.1) |  |  |
| Antipsychotics | No | 337(57.7) | 100(56.8) | χ2 =0.02 | 0.9 |
|  | Yes | 247(42.3) | 76 (43.2) |  |  |
| Anxiolytics | No | 450(77.1) | 135 (76.7) | χ2 = 0 | 1 |
|  | Yes | 134(22.9) | 41(23.3) |  |  |
| Hypnotics | No | 508(87) | 148(84.1) | χ2 =0.73 | 0.39 |
|  | Yes | 76 (13) | 28(15.9) |  |  |
| Antidepressants | No | 340 (58.2) | 115(65.3) | χ2 = 2.57 | 0.11 |
|  | Yes | 244(41.8) | 61(34.7) |  |  |

BD: bipolar disorder; NOS not otherwise specified; QIDS-SR: Quick Inventory of Depressive Self-report; YMRS: Young Mania Rating Scale; PSQI: Pittsburgh Sleep Quality Index; STAI-Y: State–Trait Anxiety Inventory; MAThyS: Multidimensional Assessment of Thymic States; AIM: Affect Intensity Measure; ALS: Affective Lability Scale; BDHI: Buss–Durkee Hostility Inventory; BIS-10: Barratt Impulsiveness Scale; \*p-values are not corrected for multiple comparison, nor adjusted for other variables.

**Table S2**: Odds ratios for the model 1 with all confounding variables

|  |  |  |  |
| --- | --- | --- | --- |
|  | **OR [CI]** | **Statistic**  **(z-value)** | **p-value** |
| Lithium salts [yes] | 0.58 [0.34-0.95] | -2.11 | **0.035** |
| Age | 1.02 [1.01-1.04] | 2.71 | **0.007** |
| Sex [F] | 1.26 [0.83-1.93] | 1.09 | 0.276 |
| BD type II | 0.90 [0.59-1.37] | -0.49 | 0.627 |
| BD type NOS | 0.69 [0.36-1.30] | -1.13 | 0.259 |
| Lifetime anxiety disorder | 1.14 [0.76-1.71] | 0.63 | 0.527 |
| Lifetime substance use disorder | 1.01 [0.73-1.65] | 0.45 | 0.652 |
| Lifetime eating disorder | 0.95 [0.59-1.52] | -0.20 | 0.842 |
| History of suicide attempt | 1.02 [0.68-1.51] | 0.073 | 0.942 |
| AIM | 0.95 [0.65-1.38] | -0.30 | 0.768 |
| ALS | 1.22 [0.78-1.92] | 0.87 | 0.386 |
| BIS -10 | 0.99 [0.97-1.01] | -0.56 | 0.577 |
| BDHI  Expressive Component | 1.02 [0.99-1.05] | 1.24 | 0.215 |
| BDHI  Attitudinal Component | 0.99 [0.93-1.05] | -0.28 | 0.781 |
| QIDS-SR (Box–Cox) | 1.21 [1.07-1.38] | 2.96 | **0.003** |
| PSQI | 1.13 [1.07-1.20] | 4.17 | **> 0.0001** |
| MAThyS Emotional ✧  [20–23] | 1.44 [0.85-2.46] | 1.34 | 0.180 |
| MAThyS Emotional ✧  [24–40] | 1.34 [0.80-2.25] | 1.10 | 0.271 |
| MAThyS Motivation ✦  [16–20] | 1.57 [0.91-2.73] | 1.61 | 0.109 |
| MAThyS Motivation ✦  [21–40] | 1.95 [0.99-3.83] | 1.93 | 0.053 |
| MAThyS Psychomotor \*  [11 – 15] | 0.74 [0.43-1.24] | -1.14 | 0.253 |
| MAThyS Psychomotor \*  [16 – 30] | 0.68 [0.36-1.28] | -1.20 | 0.231 |
| MAThyS Sensory perception [26 – 27] ✤ | 1.40 [0.80-2.37] | 1.19 | 0.232 |
| MAThyS Sensory perception [28 – 50] ✤ | 1.12 [0.71-1.77] | 0.48 | 0.628 |
| MAThyS Cognition ✵  [20 – 22] | 1.04 [0.61-1.79] | 0.15 | 0.881 |
| MAThyS Cognition ✵  [23 – 40] | 1.07 [0.62-1.85] | 0.23 | 0.819 |

BD: bipolar disorder. NOS: not otherwise specified. QIDS-SR: Quick Inventory of Depressive Self-report. PSQI: Pittsburgh Sleep Quality Index. MAThyS: Multidimensional Assessment of Thymic States. AIM: Affect Intensity Measure. ALS Affective Lability Scale. BDHI: Buss–Durkee Hostility Inventory. BIS-10: Barratt Impulsiveness Scale. ✧The reference for comparison is the score [0-19] of the MAThyS Emotional subscale. ✦ The reference for comparison is the score [0-15] of the MAThyS Motivation. \* The reference for comparison is the score [0-10] of the MAThyS Psychomotor subscale. ✤ The reference for comparison is the score [0-25] of the MAThyS Sensory perception subscale. ✵ The reference for comparison is the score [0-19] of the MAThyS Cognition subscale.

**Table S3**: Odds ratios of lithium association with pain after sequential addition of variables in the model.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Variables added to the model** | **N** | **OR [CI] for lithium salt** | ***z*-value for lithium salt** | ***p*-value for lithium salt** |
| Education  (high school diploma) | 683 | 0.57 [0.33-0.96] | -2.07 | 0.04 |
| Single | 687 | 0.57 [0.33-0.95] | -2.09 | 0.04 |
| Age at first episode | 724 | 0.58 [0.35-0.95] | -2.12 | 0.03 |
| Number of depressive episodes | 620 | 0.49 [0.27-0.85] | -2.47 | 0.01 |
| STAI Y-A score | 758 | 0.6 [0.36-0.97] | -2.05 | 0.04 |
| Cancer | 709 | 0.53 [0.3-;0.88] | -2.4 | 0.02 |
| Peptic ulcer disease | 729 | 0.56 [0.33-0.93] | -2.18 | 0.03 |
| Anticonvulsants | 760 | 0.59 [0.35-0.96] | -2.07 | 0.04 |
| Antipsychotics | 760 | 0.59 [0.36-0.96] | -2.07 | 0.04 |
| Anxiolytics | 760 | 0.59 [0.35-0.95] | -2.1 | 0.04 |
| Hypnotics | 760 | 0.59 [0.36-0.96] | -2.06 | 0.04 |
| Antidepressants | 760 | 0.59 [0.35-0.96] | -2.08 | 0.04 |

**N**: number of patients for whom all variables were available without any missing data; STAI Y-A: State–Trait Anxiety Inventory

**Table S4**: Odds ratios of the association between blood lithium concentration ≥0.5 mmol/l and pain after sequential addition of variables into the model

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Variables added to the model** | **N** | **OR [CI] for lithium salt**  **[≥ 0.5mmol/l]** | ***z*-value for lithium salt**  **[≥ 0.5mmol/l]** | ***p*-value for lithium salt**  **[≥ 0.5mmol/l]** |
| Education  (high school diploma) | 683 | 0.51 [0.27-0.92] | -2.14 | 0.03 |
| Single | 687 | 0.51 [0.27-0.92] | -2.16 | 0.03 |
| Age of first episode | 724 | 0.44 [0.23-0.78] | -2.67 | 0.008 |
| Number of depressive episodes | 620 | 0.44 [0.23-0.78] | -2.86 | 0.004 |
| STAI Y-A score | 758 | 0.44 [0.24-0.79] | -2.65 | 0.008 |
| Cancer | 709 | 0.39 [0.2-0.71] | -2.9 | 0.004 |
| Peptic ulcer disease | 729 | 0.4 [0.2-0.73] | -2.81 | 0.005 |
| Anticonvulsants | 760 | 0.45 [0.24-0.8] | -2.62 | 0.009 |
| Antipsychotics | 760 | 0.45 [0.24-0.8] | -2.62 | 0.009 |
| Anxiolytics | 760 | 0.44 [0.23-0.79] | -2.66 | 0.008 |
| Hypnotics | 760 | 0.45 [0.24-0.8] | -2.6 | 0.009 |
| Antidepressants | 760 | 0.45 [0.24-0.79] | -2.64 | 0.008 |

**N**: number of patients for whom all variables were available without missing data; STAI: State–Trait Anxiety Inventory