# Supplementary Material

## Supplementary Figure 1: Individual treatment effects

1. Pharmacological



1. Psychological



Forest plots of effect sizes for active treatments (sorted by treatment). ES symbol: circle = mood stabiliser, square = antipsychotic; triangle; NMDA targeting drug; cross = other pharmacological mechanism, star = psychological. Pooled pharmacological treatment effects in blue. Pooled psychological treatment effect in pink.

## Supplementary Figure 2. Placebo effects



Forest plot of effect sizes for control treatments (Hedges’ g ES). Active comparator treatments are indicated in brackets). ES symbol: circle = pill placebo; square = psychological control. Pooled treatment effects in pink (pill placebo) and blue (psychological control).

## Supplementary Table 1: Methodological quality and risk of bias in the included trials.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Potential sources of bias** | | | | | | | | | **Overall  risk of bias judgement** |
| **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** |
| Bauer et al., 2013 | + | + | + | – | + | + | + | + | - | Moderate |
| Baumann et al., 1996 | + | ? | ? | + | + | + | + | + | ? | Moderate |
| Barbee et al., 2011 | + | + | + | + | – | + | + | + | - | Moderate |
| Berman et al., 2007 | + | ? | ? | + | + | + | + | – | - | Moderate |
| Berman et al., 2009 | + | ? | ? | + | + | + | + | – | - | Moderate |
| Dunner et al., 2007 | + | ? | ? | ? | + | + | + | + | + | Moderate |
| Eisendrath et al., 2016 | + | + | + | + | + | + | + | – | + | Low |
| Fang et al., 2017 | + | + | + | + | ? | + | + | + | + | Low |
| McAllister-Williams et al., 2015 | + | + | + | + | + | ? | + | – | + | Low |
| Fonagy et al., 2015 | + | + | ? | + | – | + | + | + | + | Low |
| Girlanda et al., 2014 | + | + | + | – | + | + | + | + | + | Low |
| Hauksson et al., 2017 | + | – | ? | ? | + | + | + | + | + | Moderate |
| Heresco-Levy et al., 2013 | + | + | ? | + | + | + | + | + | – | Low |
| Husain et al., 2017 | + | + | + | + | + | + | + | + | + | Low |
| Maes et al., 1996 | + | ? | ? | + | + | + | + | + | ? | Moderate |
| Marcus et al., 2008 | + | ? | – | + | + | + | + | ? | – | Moderate |
| Moller et al., 2015 | + | + | + | + | + | – | + | + | – | Moderate |
| Nierenberg et al., 2003 | + | ? | ? | + | + | + | + | + | + | Low |
| Nierenberg et al., 2006 | + | ? | – | – | – | – | + | + | + | High |
| Ozaki et al., 2015 | + | ? | ? | + | + | – | + | + | – | Moderate |
| Patkar et al., 2006 | + | ? | ? | ? | ? | – | + | + | – | High |
| Santos et al., 2008 | + | + | + | + | + | + | + | – | + | Low |
| Schindler et al., 2007 | + | + | – | – | – | – | – | + | ? | High |
| Shelton et al., 2001 | + | ? | ? | + | + | + | ? | + | – | Moderate |
| Thase et al., 2015 | + | + | + | + | + | + | + | + | – | Low |
| Thase et al., 2015b | + | + | + | + | + | + | + | + | – | Low |
| Su et al., 2017 | + | ? | ? | + | + | + | + | + | + | Low |
| Yoshimura et al., 2012 | + | ? | ? | – | + | + | + | – | ? | High |
| Evaluations of the 28 included studies for potential sources of bias according to the SIGN tool (Scottish Intercollegiate Guidelines Network, 2012).  1. Question appropriate and clearly focused; 2. Allocation sequence randomly generated; 3. Allocation adequately concealed; 4. Knowledge of allocation adequately prevented (blinding); 5. Group comparability at baseline ensured; 6. Differences among multiple sites adequately addressed; 7. Selective outcome reporting avoided; 8. Intention-to-treat analysis applied; 9. Allegiance effect minimised.  **+**, low risk / **–**, high risk / **?**, unclear risk  Overall risk was judged as follows:  *Low risk = <2 criteria rated high RoB (or <2 if at least one is rated unclear RoB)*  *Moderate risk = 2-4 criteria rated high or unclear RoB*  *High risk = >4 criteria rated high or unclear RoB* | | | | | | | | | | |

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Supplementary Table 2. Characteristics of treatments examined | | | | | | | | | |
|  | **Reference** | **Intervention** | **n** | **Dose** | **Duration (weeks)** | **Outcome measure** | **Baseline severity** | **Reported finding** | **Tolerability** | **Acceptability** |
| **Mood Stabilisers** | | | | | | | | |  |  |
|  | Nierenberg et al., 200320 | Lithium  Placebo | 18  17 | Mean 0.61 mEq/L | 6 | HAMD17 | 21.4  21.7 | 11% responded  18% responded | NR  NR | 11% dropout  12% dropout |
|  | Girlanda et al., 201415 | Lithium  TAU | 29  27 | Mean 0.57 mEq/L | 52 | qIDS | 16.8  20.1 | No group difference (p=.951) | 41% ppts  NR | 7% dropout  11% dropout |
|  | Schindler et al., 200738 d | Lithium  Lamotrigine | 17  17 | Mean 0.71 mmol/L  Mean 153mg | 8 | HAMD17 | 21.5  22.7 | 41% responded  53% responded | AE n=29  AE n=16 | 12% dropout  12% dropout |
|  | Barbee et al., 201127 | Lamotrigine  Placebo | 48  48 | Titrated, max 400mg | 10 | MADRS | 22.19 c  20.73 | Improvement p>.05 active  vs control | 87.5% ppts AE  87.5% ppts AE | 29% dropout  35% dropout |
|  | Santos et al., 200821 | Lamotrigine  Placebo | 17  17 | 200mg | 8 | MADRS | 32.3  28.4 | 27% responded  36% responded | 93% ppts AE  76% ppts AE | 17% dropout  24% dropout |
| **Antipsychotics** | | | | | |  |  |  |  |  |
|  | Berman et al., 200729 | Aripiprazole  Placebo | 182  176 | Titrated, 15mg | 6 | MADRS | 26.0  25.9 | ES 0.39, p < 0.001 for active vs control | AE n=182  AE n=110 | 12% dropout  9% dropout |
|  | Berman et al., 200930 | Aripiprazole  Placebo | 147  149 | Mean 10.7mg | 6 | HAMD17 | 19.8  20.0 | 36.8% vs 18.9%  remission (p<0.001) | AE n=172  AE n=94 | 17% dropout  13% dropout |
|  | Marcus et al., 200832 | Aripiprazole  Placebo | 191  190 | Mean 11mg | 6 | MADRS | 25.2  27.0 | ES 0.35, p < 0.001 for active  vs control | AE n=162  AE n=64 | 15% dropout  15% dropout |
|  | Ozaki et al., 201534 \* | Aripiprazole  Placebo | 75/67  71 | Fixed 3mg / Flexible 3-15mg | 6 | MADRS | 25.2 /25.3  25.5 | MADRS reductions: 10.5 / 9.6 MADRS reduction: 7.4 | NR  NR | NR  NR |
|  | Thase et al., 2015a22 | Brexpiprazole  Placebo | 188  191 | 2mg | 6 | HAMD17 | 21.2  21.6 | 23% responded  16% responded | 59% ppts AE  47% ppts AE | 7% dropout  7% dropout |
|  | Thase et al., 2015b23 | Brexpiprazole  Placebo | 226/230  221 | 1mg/3mg | 6 | HAMD17 | 21.1/21.1  20.7 | 23/22% responded  14% responded | 55/63% ppts AE  47% ppts AE | 4%/9% dropout  6% dropout |
|  | Shelton et al., 200135 | Olanzapine  Placebo | 10  10 | 5mg  - | 8 | HAMD21 | NR  NR | 60% responded  10% responded |  |  |
|  | Dunner et al., 200726 | Ziprasidone | 41 | 80mg / 160mg | 8 | HAMD17 | 19.1/19.7 | ES=0.14 / ES=0.39 (NS) | 100/84% ppts AE | 53% / 50% dropout |
| **NMDA targets** | | | | |  |  |  |  |  |  |
|  | Heresco-Levy et al., 201316 | D-cycloserine  Placebo | 13  13 | Titrated, 1000mg | 6 | HAMD21 | 25.1  27.2 | 54% responded  15% responded | AE n=15  AE n=16 | 23% dropout  11% dropout |
|  | Husain et al., 201717 | Minocycline  Placebo | 21  20 | Titrated, 200mg | 12 | HAMD17 | 34.5  32.6 | 63% responded  22% responded | AE n=21  AE n=20 | 24% dropout  10% dropout |
|  | Su et al., 201711 | Ketamine  Placebo | 24/23  24 | 0.5mg/kg / 0.2mg/kg | 5 days | HAMD17 | 23/23.1  23.3 | 46%/39% responded  13% responded | No unexpected significant AEs | NR |
| **Other pharmacological** | | | | | | | | | | |
|  |  |  |  |  |  |  |  |  |  |  |
|  | Moller et al., 201533 a | Dexmecamylamine  Placebo | 999  335 | 0.1 – 4 mg | 8 | MADRS | 20.9 - 22.2  21.7 | 43 - 53% responded  49% responded | AE n=812  AE n=187 | 13% - 29% dropout  14% dropout |
| **Psychological therapies** | | | | |  |  |  |  |  |  |
|  | Eisendrath et al., 201618 | MBCT  HEP | 67  64 | ~22 hours  ~22 hours | 8 | HAMD17 | 18.3  17.4 | 22.4% vs 13.9%  remission (p=.14) | NR  NR | 13% dropout  16% dropout |
|  | Fonagy et al., 201512 | LTPP  TAU | 67  62 | ~78 hours  - | 78 | HAMD17 | 19.8  20.4 | Partial remission: 32.1% vs 23.9% (p=.37) | NR  NR | 15% dropout  13% dropout |
|  | Hauksson et al., 201725 | CBT – group  - individual  TAU | 59  83  36 | 12 sessions  12 sessions  - | 6 | BDI | 29.96  33.08  30.03 | ES=1.46  ES=2.10  ES=1.16 | NR  NR  NR | 4% dropout  0 dropout  0 dropout |
| **Multiple treatment classes** | | | | |  |  |  |  |  |  |
|  | Bauer et al., 201328 \* | Quetiapine  Lithium | 114  110 | Titrated up to 300mg  Titrated, 0.6–1.2 mmol/L | 6 | MADRS | NR | Quetiapine non-inferior  to lithium | NR  NR | NR  NR |
|  | Fang et al., 201119 | Risperidone  Sodium Valproate  Buspirone  Trazodone  Thyroid hormone | 45  39  46  47  48 | 2mg  600mg  30mg  100mg  80mg | 8 | HAMD17 | NR | 26.7% remitted  48.7% remitted  32.6% remitted  42.6% remitted  37.5% remitted | No significant difference between groups, no SAEs | No significant difference between groups (22% risperidone) |
|  | Nierenberg et al., 200636 d | Lithium  Thyroid hormone | 69  73 | Mean 860mg  Mean 45ug | <12 | HAMD17 | 19.0  17.2 | 16% remitted  25% remitted | Moderate or severe: 64%/58% | 19% <4 weeks  16% <4weeks |
| **Short-term** | | | | |  |  |  |  |  |  |
|  | Baumann et al., 199624 | Lithium  Placebo | 10  14 | 0.5-0.8mmol/L  - | 1 | HAMD21 | 18.7  20.0 | 6/10 responded  2/14 responded | UKU score 5.2  UKU score 6.5 | 0% dropout  0% dropout |
|  | McAllister-Williams et al., 201514 | Metyrapone  Placebo | 69  74 | 1000mg  - | 3 (PO 5 weeks) | MADRS | 27.7 c  28.1 | 20.2% responded  21.6% responded | AE n=134  AE n=95 | 17% dropout  10% dropout |
|  | Yoshimura et al., 201213 d | Aripiprazole | 26 | NR | 4 | HAMD17 | 19.3 | 21% responded | SAS score 2 | 8% dropout |
|  | Patkar et al., 200637 \* | Methylphenidate Placebo | NR  NR | Titrated, < 54mg  - | 4 | HAMD21 | NR  NR | 36/25% responded  20/0% responded b | NR  NR | NR  NR |
|  | Maes et al., 199631 \* | Pindolol  Fluoxetine  Placebo | 8  10  8 | 7.5mg  20mg | 4 | HAMD17 | NR  NR  NR | 5 responded (62.5%)  7 responded (70%)  1 responded (12.5%) | NR  NR  NR | NR  NR  NR |
|  |  |  |  |  |  |  |  |  |  |  |
|  | \* Describes eligible TRD subgroup where full sample did not meet review inclusion criteria.  a Moller et al. (2015) split results by dose and sample recruited within this article. Doses included 0.1mg (n=174, 48% responded, n=80 AEs, 13% dropout), 0.5mg (n=160, 43% responded, n=101 AEs, 21% dropout), 1mg (n=174 51% responded, n=98 AEs, 17% dropout), 2mg (n=116, 53% responded, n=99 AEs, 27% dropout), 4mg (n=334, 39% responded, n=434, 29% dropout). For baseline severity, response and acceptability columns, the range of averages per group is noted in the table.  b % given for patients with stage 2 and stage 3 treatment resistance (Thase and Rush criteria) respectively; n’s not provided. In other instances where multiple values are entered for a single intervention, it is due to values reported for patients taking different doses of medication (i.e. Dunner et al., 2007; Su et al., 2017; Thase et al., 2015a and 2015b; Ozaki et al., 2015).  c  HAMD score for baseline severity but MADRS utilised for outcome assessment  d High risk of bias  UKU = UKU side effects scale; MBCT = mindfulness-based cognitive therapy; HEP = health education program; NR = not reported; mmol/L = millimoles per litre; mEql/L = milliequivalent per litre; PO = primary outcome; HAMD = Hamilton depression rating scale; MADRS = Montgomery–Åsberg depression rating scale; qIDS = quick inventory of depressive symptoms; SR = self-report; BDI = Beck depression inventory; ES = effect size; AE = adverse event; ppts = participants; SAE = serious adverse event; OLA = olanzapine; SAS = Simpson Angus Scale. | | | | | | | | | |

## Supplementary Table 3: initial meta-analytic results

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| *Outcome* | *Spec intervention* | *k* | *N* | *ES (g)* | *SE* | *95% CI* | *Heterogeneity*  *(I2)* |
| **All** | | **26** | **5236** | **1.03** | **0.05** | **0.92 – 1.36** | **83.9** |
| **Pharmacological** | | **23** | **3246** | **1.15** | **0.07** | **1.01 – 1.29** | **82.8** |
| *Mood Stabilisers* | **All** | **10** | **373** | **1.12** | **0.17** | **0.78 – 1.45** | **82.1** |
| Lithium | 6 | 253 | 0.87 | 0.18 | 0.50 – 1.23 | 79.2 |
| Lamotrigine | 3 | 81 | 1.52 | 0.38 | 0.76 - 2.27 | 75.6 |
| Na Valproate | 1 | 39 | 1.64 | 0.25 | 1.16 - 2.12 | n/a |
| Antipsychotics | **All** | **11** | **1529** | **1.17** | **0.09** | **1.00 – 1.34** | **81.4** |
| Aripiprazole | 5 | 681 | 1.41 | 0.11 | 1.19 – 1.63 | 72.7 |
| Brexpiprazole | 2 | 638 | 0.96 | 0.06 | 0.85 – 1.06 | 17.3 |
| Ziprasidone | 1 | 41 | 0.65 | 0.17 | 0.31 - 0.99 | n/a |
| Risperidone | 1 | 45 | 1.15 | 0.19 | 0.77 - 1.53 | n/a |
| Quetiapine | 1 | 114 | 1.05 | 0.12 | 0.82 – 1.28 | n/a |
| Olanzapine | 1 | 10 | 0.98 | 0.38 | 0.22 – 1.73 | n/a |
| NMDA targets | **All** | **3** | **81** | **1.48** | **0.12** | **1.25 – 1.71** | **0.0** |
| Ketamine | 1 | 47 | 1.47 | 0.13 | 1.22 – 1.72 | n/a |
| D-cycloserine | 1 | 13 | 1.47 | 0.46 | 0.57 – 2.36 | n/a |
| Minocycline | 1 | 21 | 1.54 | 0.29 | 0.97 – 2.11 | n/a |
| Other mechanisms | **All** | **6** | **1263** | **1.08** | **0.19** | **0.70 – 1.46** | **87.2** |
| SARI | Trazodone | 1 | 47 | 1.67 | 0.23 | 1.23 - 2.12 | n/a |
| Anxiolytic | Buspirone | 1 | 46 | 1.57 | 0.22 | 1.14 – 2.00 | n/a |
| Thyroid | Thyroid hormone | 2 | 121 | 0.81 | 0.33 | 0.17 – 1.45 | 88.3 |
| Nicotinic | Dexmecamylamine | 1 | 980 | 1.13 | 0.18 | 0.78 – 1.49 | n/a |
| Antiglucocorticoid | Metyrapone | 1 | 69 | 0.63 | 0.13 | 0.37 – 0.89 | n/a |
| **Pill placebo** | | **16** | **1552** | **0.78** | **0.07** | **0.66 – 0.91** | **68.8** |
| **Psychological therapies** | **All** | **3** | **276** | **1.43** | **0.23** | **0.50 – 2.36** | **95.3** |
| MBCT | 1 | 67 | 0.99 | 0.21 | 0.58 – 2.41 | n/a |
| LTPP | 1 | 67 | 0.59 | 0.13 | 0.33 – 0.85 | n/a |
| CBT | 1 | 142 | 1.74 | 0.20 | 1.35 – 2.13 | n/a |
| **Psychological comparators** | **All** | **3** | **162** | **0.94** | **0.30** | **0.36 – 1.52** | **89.1** |
| TAU | 2 | 98 | 0.77 | 0.37 | 0.06 – 1.49 | 88.0 |
| Active control | 1 | 64 | 1.27 | 0.17 | 0.94 – 1.59 | n/a |

Results of meta-analyses assessing treatment effectiveness, at a category, class and individual intervention level - identical to Table 2, but describes results prior to separation of trials with short therapeutic durations or high risk of bias.

NMDA = N-methyl-D-aspartate; SARI = Serotonin antagonist and reuptake inhibitor; MBCT = mindfulness-based cognitive therapy; LTPP = long-term psychoanalytic psychotherapy; CBT = cognitive behavioural therapy; TAU = treatment-as-usual; k = number of studies; n = number of patients; ES = effect size (Hedges’ g); SE = standard error; 95% CI = 95% confidence interval.