**Supplementary Table 1: Trials of antidepressant augmentation of clozapine**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Author, year | Intervention | Sample size | **Mean age in years** | **Gender distribution** | **Definition of clozapine resistance used** | Duration in weeks  | Outcome measure | Effect size | Confidence intervals Lower | Confidence intervals Upper |
| Buchanan et al. 1996 | Fluoxetine | 33 | Flu- 36.8 ±6.4P- 32.8±6.0 | Flu- M- 15, F-3; P- M-8, F-7 | Despite adequate treatment with clozapine (300 mg/day for at least 6 months), continued to exhibit persistent positive or negative symptoms | 8  | BPRS-P | 0.111 | -0.574 | 0.797 |
| Zoccali et al. 2004 | Mirtazapine | 24 | Mir- 30.7±6.5; P- 33.4±9.0 | Mir- M- 6, F-4;P- M- 7, F-3 | Presence of persistent negative symptoms despite receiving an adequate trial of clozapine  | 8  | BPRS  | 5.265 | 3.574 | 6.956 |
| Berk et al., 2009 | Mirtazapine | 38 | Mir – 37.8±10.86; P- 35.9±9.20 | Mir- M-14; F-4; P- M-18, F-2 | Not mentioned specifically | 6 | PANSS-P | -0.570 | -1.229 | 0.072 |
| Mico’ et al. 2011 | Duloxetine | 33 | D- 35.9±7.1P- 34±6.8 | D- M- 13; P- 11 | Presence of persistent positive and negative symptoms (BPRS score of at least 25) despite an adequate trial of clozapine | 16  | PANSS | 1.229 | 0.553 | 1.905 |

BPRS: Brief Psychiatric Rating Scale; BPRS-P: Positive symptom subscale of BPRS; PANSS: Positive and Negative Syndrome Scale

**Supplementary Table 2: Risk of bias in the included studies**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Author(s),year** | **Random sequence** | **Allocation concealment** | **Blinding of participants and personnel** | **Blinding of outcome assessment** | **Incomplete outcome data** | **Jadad score** |
| **Risperidone** | **Josiassen et al.,2005** | **+** | **+** | **+** | **+** | **+** | **5** |
| **Risperidone** | **Anil Yagcioglu et al.,2005** | **+** | **+** | **+** | **+** | **+** | **5** |
| **Risperidone** | **Honer et al.,2006** | **+** | **+** | **+** | **+** | **+** | **5** |
| **Risperidone** | **Freudenreich et al.,2007** | **+** | **+** | **+** | **?NA** | **+** | **4** |
| **Risperidone** | **Weiner et al.,2010** | **?NA** | **?NA** | **+** | **+** | **+** | **3** |
| **Sulpiride** | **Shiloh et al.,1997** | **+** | **+** | **+** | **?NA** | **+** | **4** |
| **Amisulpiride** | **Barnes et al.,2017** | **+** | **+** | **+** | **+** | **+** | **5** |
| **Aripiprazole** | **Chang et al., 2008**  | **+** | **+** | **+** | **+** | **+** | **5** |
| **Aripiprazole** | **Fleischhackeret al., 2010** | **+** | **+** | **+** | **+** | **+** | **5** |
| **Aripiprazole** | **Muscatello et al.,2011** | **+** | **+** | **+** | **+** | **-** | **4** |
| **Sertindole** | **Nielsen et al.,2012** | **+** | **+** | **+** | **+** | **+** | **5** |
| **Pimozide** | **Friedman et al.,2011** | **+** | **+** | **+** | **?NA** | **1** | **4** |
| **Ziprasidone** | **Muscatello et al, 2014** | **+** | **+** | **+** | **+** | **+** | **5** |
| **Haloperidol** | **Mossaheb et al, 2006** | **?NA** | **?NA** | **?NA** | **+** | **?NA** | **1** |
| **Lamotrigine** | **Tiihonen et al.,2003** | **+** | **+** | **+** | **+** | **+** | **5** |
| **Lamotrigine** | **Zoccali et al.,2007** | **+** | **+** | **+** | **+** | **?NA** | **4** |
| **Lamotrigine** | **Vayisoglu et al.,2013** | **+** | **+** | **+** | **+** | **?NA** | **4** |
| **Lamotrigine** | **Kremer et al.,2004** | **+** | **+** | **+** | **+** | **+** | **5** |
| **Lamotrigine** | **Goff et al.,2007** | **+** | **+** | **+** | **+** | **+** | **5** |
| **Topiramate** | **Muscatello et al.,2011** | **+** | **+** | **+** | **+** | **-** | **4** |
| **Topiramate** | **Behadni et al.,2011** | **+** | **+** | **+** | **+** | **?NA** | **4** |
| **Topiramate** | **Tiihonen et al.,2005** | **+** | **+** | **+** | **-** | **-** | **3** |
| **Topiramate** | **Afshar et al.,2009** | **+** | **+** | **+** | **+** | **+** | **5** |
| **Fluoxetine** | **Buchanan et al.,1996** | **?NA** | **?NA** | **+** | **+** | **?NA** | **2** |
| **Mirtazapine** | **Zoccali et al.,2004** | **?NA** | **?NA** | **+** | **?NA** | **?NA** | **1** |
| **Duloxetine** | **Mico et al.,2011** | **+** | **+** | **+** | **+** | **+** | **5** |
| **Memantine** | **De Lucena et al, 2009** | **+** | **?NA** | **?NA** | **?NA** | **+** | **2** |
| **Memantine** | **Veerman et al., 2016** | **+** | **+** | **+** | **+** | **-** | **4** |
| **Glycine** | **Potkin et al.,1999** | **?NA** | **+** | **+** | **+** | **-** | **3** |
| **Glycine** | **Evins et al.,2000** | **?NA** | **+** | **?NA** | **?NA** | **-** | **1** |
| **Glycine** | **Diaz et al.,2005** | **?NA** | **?NA** | **+** | **-** | **-** | **1** |
| **D-Cycloserine** | **Goff et al.,1999** | **?NA** | **+** | **+** | **+** | **+** | **4** |
| **D-serine** | **Tsai et al.,1999** | **?NA** | **+** | **+** | **?NA** | **+** | **3** |
| **Sarcosine** | **Lane et al, 2006** | **+** | **+** | **+** | **+** | **+** | **5** |
| **AmpakineCX516** | **Goff et al.,2001** | **+** | **+** | **?NA** | **+** | **?NA** | **3** |
| **Ginkgo biloba** | **Doruk et al.,2008** | **?NA** | **+** | **+** | **+** | **+** | **4** |
| **Minocycline**  | **Kelly et al.,2015** | **+** | **+** | **+** | **+** | **+** | **5** |
| **Modafinil** | **Freudenreich et al.,2009** | **+** | **+** | **+** | **?NA** | **+** | **4** |
| **N-Acetyl cysteine** | **Dean et al.,2015** | **+** | **+** | **+** | **+** | **?NA** | **4** |
| **ECT** | **Petrides et al.,2015** | **?NA** | **+** | **+** | **+** | **+** | **4** |
| **rTMS** | **Rosa et al.,2007** | **?NA** | **+** | **+** | **+** | **+** | **4** |
| **rTMS** | **de Jesus et al.,2011** | **+** | **+** | **+** | **+** | **+** | **5** |
| **OT** | **Buchain et al, 2003** | **+** | **-** | **-** | **+** | **+** | **3** |
| **CBT** | **Barretto et al, 2009** | **?NA** | **+** | **+** | **+** | **+** | **4** |
| **CBT** | **Morrison et al.,2018** | **+** | **+** | **+** | **+** | **+** | **5** |

**+ – Attribute present; − – Attribute not present; ? NA – Unclear/Not applicable**

**Supplement Figure 1: Forest plot of antipsychotic trials**

****

Shown as standardized mean differences, Values more than 0 favour intervention than placebo.

**Supplementary Figure 2: Forrest plot of mood stabilizers and anticonvulsants for clozapine augmentation**

****

Shown as standardized mean differences, Values more than 0 favour intervention than placebo.

**Supplementary Figure 3: Antidepressant trials for clozapine augmentation**



Shown as standardized mean differences, Values more than 0 favour intervention than placebo.

**Supplementary Figure 4: Forest plot of memantine, amino acids and alternate treatments for augmentation of clozapine**



Shown as standardized mean differences, Values more than 0 favour intervention than placebo.

**Supplementary Figure 5: Forest plot of other interventions for augmentation of clozapine**



Shown as standardized mean differences, Values more than 0 favour intervention than placebo.

**Supplementary Figure 6: Sub-group analyses by types of intervention**



Shown as standardized mean differences, Values more than 0 favour intervention than placebo.

Supplementary Figure-7: Funnel Plot of the all the included studies

