**Supplementary Material**

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**Supplementary Material 1.** Search strategy

**PubMed**

("Schizophrenia Spectrum and Other Psychotic Disorders"[Mesh] OR "Psychotic Disorders"[Mesh] OR "Schizophrenia"[Mesh] OR schizophren\*[tiab] OR psychosis[tiab] OR psychot\*[tiab] OR schizoaffective[tiab]) AND (“Anti-Inflammatory Agents"[Mesh] OR antiinflammatory[tiab] OR Anti-Inflammatory[tiab] OR "Anti-Inflammatory Agents, Non-Steroidal"[Mesh] OR NSAID\*[tiab] OR "Aspirin"[Mesh] OR aspirin\*[tiab] OR "Celecoxib"[Mesh] OR celecoxib[tiab] OR "Ibuprofen"[Mesh] OR ibuprofen[tiab] OR "Diclofenac"[Mesh] OR diclofenac[tiab] OR "Naproxen"[Mesh] OR naproxen[tiab] OR davunetide[tiab] OR "Fatty Acids"[Mesh] OR fatty acid\*[tiab] OR "Estrogens"[Mesh] OR estrogen\*[tiab] OR 17β-estradiol[tiab] OR raloxifene[tiab] OR "Tamoxifen"[Mesh] OR tamoxifen[tiab] OR acetylcysteine\*[tiab] OR "Acetylcysteine"[Mesh] OR N-acetylcysteine\*[tiab] OR NAC[tiab] OR corticosteroid\*[tiab] OR "Prednisone"[Mesh] OR prednisone[tiab] OR "Prednisolone"[Mesh] OR prednisolone\*[tiab] OR "Hydrocortisone"[Mesh] OR hydrocortisone\*[tiab] OR "methylprednisolone"[Mesh] OR methylprednisolone\*[tiab] OR "dexamethasone"[Mesh] OR dexamethasone\*[tiab] OR "Dexmedetomidine"[Mesh] OR dexmedetomidine[tiab] OR "Cortisone"[Mesh] OR cortisone\*[tiab] OR "Triamcinolone"[Mesh] OR triamcinolone\*[tiab] OR "Betamethasone"[Mesh] OR betamethasone[tiab] OR "Tacrolimus"[Mesh] OR tacrolimus[tiab] OR "Cyclosporine"[Mesh] OR "Cyclosporins"[Mesh] OR cyclosporine[tiab] OR cyclosporins[tiab] OR "Everolimus"[Mesh] OR everolimus[tiab] OR sirolimus[tiab] OR mycophenolate mofetil[tiab] OR "Cytostatic Agents"[Mesh] OR cytostatic\*[tiab] OR bexarotene[tiab] OR "Bone Marrow Transplantation"[Mesh] OR bone marrow irradiation\*[tiab] OR bone marrow transplantation\*[tiab] OR "Methotrexate"[Mesh] OR methotrexate[tiab] OR "Cyclophosphamide"[Mesh] OR cyclophosphamide[tiab] OR "Melatonin"[Mesh] OR melatonin\*[tiab] OR "Ketamine"[Mesh] OR ketamine[tiab] OR parecoxib[tiab] OR "Erythromycin"[Mesh] OR "Piracetam"[Mesh] OR piracetam[tiab] OR statins[tiab] OR "Pregabalin"[Mesh] OR pregabalin[tiab] OR "Lidocaine"[Mesh] OR lidocaine\*[tiab] OR "Propofol"[Mesh] OR propofol[tiab] OR "Thiopental"[Mesh] OR thiopental[tiab] OR "Xenon"[Mesh] OR xenon[tiab] OR "Magnesium"[Mesh] OR magnesium[tiab] OR "Erythropoietin"[Mesh] OR erythropoietin\*[tiab] OR erythromycin[tiab] OR "Minocycline"[Mesh] OR minocycline[tiab] OR "Anti-Bacterial Agents"[Mesh] OR antibiotic\*[tiab]))

Publication year restriction: 2012-2018.

**PubMed**

("Schizophrenia Spectrum and Other Psychotic Disorders"[Mesh] OR "Psychotic Disorders"[Mesh] OR "Schizophrenia"[Mesh] OR schizophren\*[tiab] OR psychosis[tiab] OR psychot\*[tiab] OR schizoaffective[tiab]) AND (OR 17β-estradiol[tiab] OR "Ketamine"[Mesh] OR ketamine[tiab] OR parecoxib[tiab] OR "Erythromycin"[Mesh] OR "Piracetam"[Mesh] OR piracetam[tiab] OR statins[tiab] OR "Pregabalin"[Mesh] OR pregabalin[tiab] OR "Lidocaine"[Mesh] OR lidocaine\*[tiab] OR "Propofol"[Mesh] OR propofol[tiab] OR "Thiopental"[Mesh] OR thiopental[tiab] OR "Xenon"[Mesh] OR xenon[tiab] OR "Magnesium"[Mesh] OR magnesium[tiab] OR "Erythropoietin"[Mesh] OR erythropoietin\*[tiab] OR erythromycin[tiab] OR "Anti-Bacterial Agents"[Mesh] OR antibiotic\*[tiab varenicline[tiab] OR "Varenicline"[Mesh]))

Publication year restriction: none.

**Embase**

'schizophrenia spectrum disorder' OR schizophrenia OR 'schizophreniform disorder' OR 'paranoid psychosis' OR 'paranoid schizophrenia' OR psychosis OR 'schizoaffective psychosis'

schizophren\* or psychotic or psychosis.ab,kw,ti

Anti-inflammatory OR Antiinflammatory OR NSAID\* OR aspirin\* OR celecoxib OR ibuprofen OR diclofenac OR naproxen OR davunetide OR fatty acid\* OR estrogen\* OR 17β-estradiol OR raloxifene OR tamoxifen OR acetylcysteine\* OR N-acetylcysteine\* OR NAC OR corticosteroid\* OR prednisone OR prednisolone\* OR hydrocortisone\* OR methylprednisolone\* OR dexamethasone\* OR dexmedetomidine OR cortisone\* OR triamcinolone\* OR betamethasone OR tacrolimus OR cyclosporine OR cyclosporins OR everolimus OR sirolimus OR mycophenolate mofetil OR cytostatic\* OR bexarotene OR bone marrow irradiation\* OR bone marrow transplantation\* OR methotrexate OR cyclophosphamide OR melatonin\* OR ketamine OR parecoxib OR piracetam OR statins OR pregabalin OR lidocaine\* OR propofol OR thiopental OR xenon OR magnesium OR erythropoietin\* OR erythromycin OR minocycline OR antibiotic.ab,kw,sh,ti

Publication year restriction: 2012-2018.

**Embase**

'schizophrenia spectrum disorder' OR schizophrenia OR 'schizophreniform disorder' OR 'paranoid psychosis' OR 'paranoid schizophrenia' OR psychosis OR 'schizoaffective psychosis'

schizophren\* or psychotic or psychosis.ab,kw,ti

17β-estradiol cyclosporine OR ketamine OR parecoxib OR piracetam OR statins OR pregabalin OR lidocaine\* OR propofol OR thiopental OR xenon OR magnesium OR erythropoietin\* OR erythromycin OR antibiotic OR varenicline.ab,kw,sh,ti

Publication year restriction: none.

**The National Institutes of Health website: http://www.clinicaltrials.gov**

'schizophrenia spectrum disorder' OR schizophrenia OR 'schizophreniform disorder' OR 'paranoid psychosis' OR 'paranoid schizophrenia' OR psychosis OR 'schizoaffective psychosis'

Anti-inflammatory OR Antiinflammatory OR NSAID\* OR aspirin\* OR celecoxib OR ibuprofen OR diclofenac OR naproxen OR davunetide OR fatty acid\* OR estrogen\* OR 17β-estradiol OR raloxifene OR tamoxifen OR acetylcysteine\* OR N-acetylcysteine\* OR NAC OR corticosteroid\* OR prednisone OR prednisolone\* OR hydrocortisone\* OR methylprednisolone\* OR dexamethasone\* OR dexmedetomidine OR cortisone\* OR triamcinolone\* OR betamethasone OR tacrolimus OR cyclosporine OR cyclosporins OR everolimus OR sirolimus OR mycophenolate mofetil OR cytostatic\* OR bexarotene OR bone marrow irradiation\* OR bone marrow transplantation\* OR methotrexate OR cyclophosphamide OR melatonin\* OR ketamine OR parecoxib OR piracetam OR statins OR pregabalin OR lidocaine\* OR propofol OR thiopental OR xenon OR magnesium OR erythropoietin\* OR erythromycin OR minocycline OR antibiotic\*

Publication year restriction: none.

**Cochrane Reviews**

"Schizophrenia" OR "Psychotic " OR schizophren\* OR psychosis OR psychot\* OR schizoaffective

AND

Anti-inflammatory OR Antiinflammatory OR NSAID\* OR aspirin\* OR celecoxib OR ibuprofen OR diclofenac OR naproxen OR davunetide OR fatty acid\* OR estrogen\* OR 17β-estradiol OR raloxifene OR tamoxifen OR acetylcysteine\* OR N-acetylcysteine\* OR NAC OR corticosteroid\* OR prednisone OR prednisolone\* OR hydrocortisone\* OR methylprednisolone\* OR dexamethasone\* OR dexmedetomidine OR cortisone\* OR triamcinolone\* OR betamethasone OR tacrolimus OR cyclosporine OR cyclosporins OR everolimus OR sirolimus OR mycophenolate mofetil OR cytostatic\* OR bexarotene OR bone marrow irradiation\* OR bone marrow transplantation\* OR methotrexate OR cyclophosphamide OR melatonin\* OR ketamine OR parecoxib OR piracetam OR statins OR pregabalin OR lidocaine\* OR propofol OR thiopental OR xenon OR magnesium OR erythropoietin\* OR erythromycin OR minocycline OR antibiotic\*

Publication year restriction: 2012-2018.

**Cochrane Reviews**

"Schizophrenia" OR "Psychotic " OR schizophren\* OR psychosis OR psychot\* OR schizoaffective

AND

17β-estradiol OR ketamine OR parecoxib OR piracetam OR statins OR pregabalin OR lidocaine\* OR propofol OR thiopental OR xenon OR magnesium OR erythropoietin\* OR erythromycin OR antibiotic\*

Publication year restriction: none.

Note: this search strategy was an update from a previously published study (Sommer, I. E., van Westrhenen, R., Begemann, M. J., de Witte, L. D., Leucht, S., Kahn, R. S. (2014). Efficacy of anti-inflammatory agents to improve symptoms in patients with schizophrenia: an update. Schizophrenia bulletin 40, 181-91).

**Supplementary Material** **2.**Effects of anti-inflammatory agents on positive and negative symptoms

The results of aspirin, estrogens, minocycline, and *N-*acetylcysteine (NAC) were significant in meta-analysis of at least two studies. An overview is presented in Supplementary Table 5.

*Effects on positive symptoms*

Positive symptoms were improved by the anti-inflammatory agents estrogens (ES: 0.48; 95% CI, 0.15 to 0.81; *p*=0.004; I2=76%) and celecoxib (ES: 0.54; 95%CI, 0.22 to 0.85; *p*=0.001; I2=0%). Bexarotene, melatonin, and pioglitazone seem to have promising effects on improving positive symptoms, but were investigated in single studies only (Supplementary Figures 20–33).

*Effects on negative symptoms*

Negative symptoms are relatively resistant to antipsychotics and are associated with worse social functioning (Howes *et al.* 2017). It is therefore important, to consider the possibility of additional treatment strategies which could treat negative symptoms. Augmentation therapy with minocycline (ES: 0.50; 95% CI, 0.17 to 0.84; *p*=0.003; I2=82%), NAC (ES: 0.75; 95% CI, 0.19 to 1.32; *p*=0.009; I2=88%), and estrogen (ES: 0.45; 95% CI, 0.13 to 0.77; *p*=0.006; I2=73%) showed positive results on improving negative symptoms. The following agents were investigated in only single studies and seem to have beneficial effects on negative symptoms: melatonin, pioglitazone, piracetam, pregnenolone, and withania somnifera extract (WSE).

In perspective, we like to point out that additional strategies for improving negative symptoms warrant additional research (Supplementary Figures 34-46).

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Supplementary Table 1.** Baseline characteristics of the included studies. | | | | | | | | | | | | | | | |
|
|  |  | **Sample Size, No.** |  | **Males, No. / Females, No.** |  | **Age, Mean (SD)** |  | **Duration of Illness (years)** |  |  |  |  |  | **Baseline Severity, PANSS Total, Mean (SD)** | |
| **Study** | **Anti-Inflammatory Agent** | **Treatment / Placebo** |  | **Treatment / Placebo** |  | **Treatment / Placebo** |  | **Treatment / Placebo** |  | **Daily Treatment Dose** | **Duration of Treatment** | **Illness Stage** |  | **Treatment** | **Placebo** |
| **Laan et al., 201** | Aspirin | 33 / 37 |  | 25/8 / 33/4 |  | 31.6 (8.9) / 30.6 (9.2) |  | 4.1 (3.0) / 3.4 (2.5) |  | 1000 mg | 3 months | Early-phase |  | 71.1 (10.6) | 73.1 (10.3) |
| **Weiser et al., 2012** | Aspirin | 100 / 100 |  | n/a |  | 43.2 (10.5) / 41.4 (10.4) |  | n/a |  | n/a | 12 weeks | n/a |  | n/a | n/a |
| **Lerner et al., 2013** | Bexarotene | 45 / 45 |  | 41/4 / 40/5 |  | 41.2 (12.4) / 41.7 (10.0) |  | n/a |  | 75 mg | 6 weeks | Chronic |  | 73.2 (18.9) | 74.9 (24.0) |
| **Akhondzadeh et al., 2007** | Celecoxib | 30 / 30 |  | 18/12 / 17/13 |  | 33.10 (7.29) / 34.30 (7.21) |  | 7.79 (5.87) / 7.98 (5.87) |  | 400 mg | 6 weeks | Early-phase |  | n/a | n/a |
| **Müller et al., 2002** | Celecoxib | 25 / 25 |  | 14/11 / 11/14 |  | 35.9 (12.8) / 35.5 (13.6) |  | n/a |  | 400 mg | 5 weeks | Early-phase |  | n/a | n/a |
| **Müller et al., 2010** | Celecoxib | 25 / 25 |  | 14/11 / 16/9 |  | 26.2 (7.7) / 30.9 (8.1) |  | 16.0 (5.0) / 14.9 (4.6) [months] |  | 400 mg | 6 weeks | FEP |  | 94.5 (16.2) | 95.9 (19.1) |
| **Rapaport et al., 2005** | Celecoxib | 18 / 17 |  | 16/2 / 13/4 |  | 44.1 (9.2) / 47.3 (11.4) |  | n/a |  | 400 mg | 8 weeks | Early-phase |  | 84.1 (11.4) | 84.2 (12.9) |
| **Rappard & Müller 2004** | Celecoxib | 138 / 132 |  | n/a |  | n/a |  | n/a |  | 400 mg | 11 weeks | Early-phase |  | n/a | n/a |
| **Javitt et al. 2012 (30 mg)\*** | Davunetide | 21 / 22 |  | n/a |  | n/a |  | n/a |  | 30 mg | 12 weeks | n/a |  | BPRS: 29.1 (6.1) | BPRS: 29.3 (7.6) |
| **Javitt et al. 2012 (5 mg)\*** | Davunetide | 20 / 22 |  | n/a |  | 45.2 (8.2) / 41.4 (10.4) |  | n/a |  | 5 mg | 12 weeks | n/a |  | BPRS: 31.2 (5.5) | BPRS: 29.3 (7.6) |
| **Lee et al., 2015** | Dextromethorphan | 74 / 75 |  | 44/30 / 46/29 |  | 30.6 (8.2) / 30.0 (7.2) |  | n/a |  | 60 mg | 11 weeks | n/a |  | 86.3 (12.6) | 86.9 (14.9) |
| **Akhondzadeh et al., 2003** | Estrogen (ethinyl estradiol) | 16 / 16 |  | 0/16 / 0/16 |  | 32.128 (6.31) / 33.37 (6.72) |  | 96.87 (90.52) / 87.37 (49.13) [months] |  | 0.5 mg | 8 weeks | Chronic |  | n/a | n/a |
| **Ghafari et al., 2013** | Estrogen (conjugated estrogen) | 15 / 15 |  | 0/15 / 0/15 |  | 34.2 (9.1) / 34.8 (8.3) |  | n/a |  | 0.625 mg | 4 weeks | Chronic |  | n/a | n/a |
| **Khodaie-Ardakani et al., 2015** | Estrogen (raloxifene) | 21 / 21 |  | 21/0 / 21/0 |  | 31.4 (5.9) / 32.4 (7.8) |  | 89.3 (70.9) / 96.2 (45.9) [months] |  | 120 mg | 8 weeks | Chronic |  | 101.6 (13.5) | 100.7 (15.5) |
| **Kianimehr et al., 2014** | Estrogen (raloxifene) | 25 / 25 |  | 0/25 / 0/25 |  | 61.96 (4.49) / 60.44 (5.28) |  | 17.24 (12.03) / 13.64 (12.41) |  | 120 mg | 8 weeks | Chronic |  | 105.52 (16.96) | 105.00 (11.68) |
| **Kulkarni et al., 2001 (0.05 mg)\*** | Estrogen (transdermal estradiol) | 12 / 12 |  | 0/12 / 0/12 |  | 34.00 (9.2) / 34.91 (7.6) |  | 5.5 (5.3) / 10.33 (8.7) |  | 0.05 mg every 4 days | 4 weeks | Chronic |  | 68.17 (10.8) | 67.58 (14.5) |
| **Kulkarni et al., 2001 (10 mg)\*** | Estrogen (transdermal estradiol) | 12 / 12 |  | 0/12 / 0/12 |  | 32.83 (8.6) / 34.91 (7.6) |  | 7.38 (7.1) / 10.33 (8.7) |  | 0.10 mg every 4 days | 4 weeks | Chronic |  | 75.83 (18.8) | 67.58 (14.5) |
| **Kulkarni et al., 2008** | Estrogen (transdermal estradiol) | 56 / 46 |  | 0/56 / 0/46 |  | 33.5 (8.8) / 33.8 (7.7) |  | n/a |  | 0.10 mg every 3.5 days | 28 days | Chronic |  | 77.48 (20.0) | 73.40 (12.5) |
| **Kulkarni et al., 2011 (only men included)** | Estrogen (estradiol valerate) | 26 / 27 |  | 26/0 / 27/0 |  | 32.9 (10.2) / 31.2 (12.4) |  | 7.6 (7.7) / 6.1 (7.1) |  | 2 mg | 14 days | Chronic |  | 72.6 (10.7) | 73.5 (9.2) |
| **Kulkarni et al., 2016** | Estrogen (raloxifene) | 26 / 30 |  | 0/26 / 0/30 |  | 52.92 (8.07) / 53.07 (7.43) |  | 24 (11) |  | 120mg | 12 weeks | Chronic |  | 79.96 (15.91) | 77.03 (14.85) |
| **Louzã et al., 2004** | Estrogen (conjugated estrogen) | 21 / 19 |  | 0/21 / 0/19 |  | 34.1 (7.9) / 30.4 (8.3) |  | n/a |  | 0.625 mg | 4 weeks | Chronic |  | n/a | n/a |
| **Usall et al., 2016** | Estrogen (raloxifene) | 38 / 32 |  | 0/38 / 0/32 |  | 62.03 (9.39) / 61.34 (10.41) |  | n/a |  | 60 mg | 24 weeks | Chronic |  | 80.47 (14.30) | 74.66 (13.26) |
| **Weiser et al., 2017** | Estrogen (raloxifene) | 100 / 100 |  | 0/100 / 0/100 |  | 56.6 (4.6) / 55.8 (4.7) |  | n/a |  | 120 mg | 16 weeks | Chronic |  | 101.7 (18.5) | 101.2 (18.1) |
| **Bentsen et al. 2013 (EPA)\*** | Fatty acids (EPA) | 33 / 24 |  | 20/13 / 17/7 |  | 25.7 (5.4) / 28.3 (5.8) |  | Median: 2 (1-5.5) / 7 (2-10) |  | 2000 mg EPA | 16 weeks | n/a |  | 78 (16) | 82.5 (19) |
| **Bentsen et al. 2013 (EPA+vitamins E&C)\*** | Fatty acids (EPA) | 19 / 24 |  | 12/7 / 17/7 |  | 27.6 (7.1) / 28.3 (5.8) |  | Median: 3.5 (1-6.5) / 7 (2-10) |  | 2000 mg EPA + 364 mg RRR-α-tocopherol + 1000 mg slow release ascorbic acid | 16 weeks | n/a |  | 94.5 (30) | 82.5 (19) |
| **Berger et al. 2007 (EPA)** | Fatty acids (EPA) | 35 / 34 |  | 25/10 / 28/7 |  | 20.5 (3.8) / 20.6 (3.7) |  | 7.2 (10) / 10.0 (13.1) [months] |  | 2 g | 12 weeks | FEP |  | BPRS: 61.6 (9.6) | BPRS: 62.8 (13.8) |
| **Boskovic et al. 2016 (EPA+vitamin E)\*** | Fatty acids (omega-3: EPA, DHA, ALA, OE) | 9 / 11 |  | 4/5 / 4/7 |  | 53.6 (8.7) / 45.6 (8.7) |  | 201 (94) / 190 (116) [months] |  | Omega-3 (EPA 132 mg, DHA 88 mg, ALA 94 mg, and OE 52 mg) | 4 months | Chronic |  | 58 .9 (21.5) | 57.8 (14.2) |
| **Boskovic et al. 2016 (EPA+DHA+ALA+OE)\*** | Fatty acids (omega-3: EPA, DHA, ALA, OE) | 9 / 11 |  | 6/3 / 4/7 |  | 54.8 (9.6) / 45.6 (8.7) |  | 184 (18) / 190 (116) [months] |  | Omega-3 + vitamin E 600 IU | 4 months | Chronic |  | n/a | n/a |
| **Emsley et al. 2002 (3g EPA)** | Fatty acids (EPA) | 20 / 20 |  | n/a |  | 46.2 (10.6) / 43.6 (13.9) |  | 23.1 / 22.2 |  | 3 g | 12 weeks | Chronic |  | n/a | n/a |
| **Emsley et al. 2006 (2g EPA)** | Fatty acids (EPA) | 39 / 38 |  | 27/12 / 24/14 |  | 42.4 (10.3) / 43.4 (10.9) |  | 16.0 (10.5) / 16.8 (10.4) |  | 2 g | 12 weeks | Chronic |  | 59.2 (13.0) | 57.5 (11.8) |
| **Emsley et al. 2014 (1g DHA+2g EPA+ α-LA)** | Fatty acids (omega-3) | 21 / 12 |  | 16/5 / 8/4 |  | 30.6 (7.4) / 28.1 (8.9) |  | n/a |  | Omega-3 (EPA 2 g + DHA 1 g + 300 mg α-LA) | 2 years or until relapse | Early-phase |  | 36.1 (4.2) | 38.2 (4.0) |
| **Fenton et al. 2001 (EPA)** | Fatty acids (EPA) | 43 / 44 |  | 53/34 |  | 40 (10) |  | n/a |  | 3 g | 16 weeks | Chronic |  | 74 (16) | 76 (18) |
| **Jamilian et al. 2017 (omega-3)** | Fatty acids (omega-3) | 30 / 30 |  | 16/14 / 15/15 |  | 32.01 (7.13) / 31.01 (8.81) |  | n/a |  | 1 g | 8 weeks | Chronic |  | 96.13 (9.61) | 98.26 (4.51) |
| **Pawelcyk et al. 2016 (EPA+DHA)** | Fatty acids (omega-3: EPA and DHA) | 36 / 35 |  | 19/17 |  | 23.2 (4.8) / 23.3 (4.8) |  | 3.1 (4.2) / 2.7 (3.5) [months] |  | Omega-3 2.2g  (EPA 1.32 g and DHA 0.88 g) | 26 weeks | FEP |  | 98.4 (13.22) | 96.8 (12.01) |
| **Peet and Horobin 2002 (EPA)** | Fatty acids (DHA) | 9 / 7 |  | n/a |  | n/a |  | n/a |  | 4 g | 12 weeks | n/a |  | 73.4 (17.9) | 76.2 (20.6) |
| **Peet et al. 2001 (DHA)\*** | Fatty acids (EPA) | 16 / 14 |  | 12/4 / 8/6 |  | 42.0 (10.6) / 43.8 (10.8) |  | n/a |  | 2 g | 12 weeks | n/a |  | 73.4 (17.9) | 76.2 (20.6) |
| **Peet et al. 2001 (EPA)\*** | Fatty acids (EPA) | 15 / 14 |  | 10/5 / 8/6 |  | 44.2 (11.3) / 43.8 (10.8) |  | n/a |  | 2 g | 12 weeks | n/a |  | 69.9 (12.9) | 76.2 (20.6) |
| **Modabbernia et al., 2014** | Melatonin | 18 / 18 |  | 13/5 / 12/6 |  | 32.7 (7.3) / 32.8 (8.2) |  | n/a |  | 3 mg | 8 weeks | FEP |  | 113.5 (12.7) | 103.5 (18.0) |
| **Chaudhry et al., 2012 (Brazil)** | Minocycline | 15 / 15 |  | 41/30 / 45/28 |  | 25.87 (7.07) / 26.59 (8.26) |  | < 5 |  | start dose: 50 mg; end dose: 200 mg | 8 weeks | Early-phase |  | 63.00 (17.19) | 57.87 (13.25) |
| **Chaudhry et al., 2012 (Pakistan)** | Minocycline | 56 / 58 |  | 41/30 / 45/28 |  | 25.87 (7.07) / 26.59 (8.26) |  | < 5 |  | start dose: 50 mg; end dose: 200 mg | 8 weeks | Early-phase |  | 82.24 (21.55) | 83.84 (20.64) |
| **Chaves et al., 2015** | Minocycline | 16 / 14 |  | 13/3 / 11/3 |  | 24 (5.02) / 25 (6.37) |  | 31.8 (21.98) / 29.1 (17.9) [months] |  | 200 mg | 12 months | Early-phase |  | n/a | n/a |
| **Deakin et al., 2018** | Minocycline | 103 / 103 |  | 77/27 / 73/30 |  | 25.5 (5.2) / 25.7 (5.1) |  | < 5 |  | start dose: 200 mg; end dose: 300 mg | 12 months | Early-phase |  | 67.1 (13.2) | 69.3 (15.4) |
| **Ghanizadeh et al., 2014** | Minocycline | 21 / 22 |  | 15/6 / 19/3 |  | 31.0 (7.6) / 30.2 (8.9) |  | 3.8 (1.7) / 3.2 (1.6) |  | 200 mg | 8 weeks | Early-phase |  | 43.9 (14.9) | 40.3 (10.8) |
| **Kelly et al., 2015** | Minocycline | 27 / 23 |  | 20/8 / 18/5 |  | 42.9 (14.2) / 42.3 (11.0) |  | 24.4 |  | 200 mg | 10 weeks | Chronic |  | BPRS: 44.9 (8.7) | BPRS: 44.0 (7.9) |
| **Khodaie-Ardakani et al., 2014** | Minocycline | 20 / 20 |  | 14/6 / 15/5 |  | 41.05 (7.47) / 38.95 (7.78) |  | 20.90 (8.02) / 18.75 (7.55) |  | start dose: 100 mg; end dose: 200 mg | 8 weeks | Chronic |  | 71.35 (4.54) | 71.90 (7.14) |
| **Levkovitz et al., 2010** | Minocycline | 36 / 18 |  | 3/10 / 3/15 |  | 24.8 (4.01) / 25.5 (4.06) |  | 3.78 / 3.73 |  | 200 mg | 6 months | Early-phase |  | 80.37 (12.77) | 82.86 (13.90) |
| **Liu et al., 2014** | Minocycline | 39 / 40 |  | 25/14 / 24/16 |  | 27.05 (5.68) / 27.70 (7.27) |  | 21.00 (13.84) / 27.45 (14.25) [months] |  | 200 mg | 16 weeks | Early-phase |  | 81.28 (12.88) | 83.35 (10.65) |
| **Weiser et al., 2019** | Minocycline | 100 / 100 |  | n/a |  | 43.4 (10.5) / 43.5 (9.7) |  | 17.2 / 17.2 |  | 200 mg | 16 weeks | Chronic |  | 94.6 (14.3) | 96.5 (16.0) |
| **Zhang et al., 2018 (100 mg minocycline)\*** | Minocycline | 25 / 25 |  | 13/12 / 12/13 |  | 33.04 (7.78) / 33.68 (6.18) |  | 6.28 (1.82) / 6.27 (1.71) |  | 100 mg | 3 months | n/a |  | 79.04 (5.04) | 78.08 (4.71) |
| **Zhang et al., 2018 (200 mg minocycline)\*** | Minocycline | 25 / 25 |  | 12/13 / 12/13 |  | 33.24 (6.48) / 33.68 (6.18) |  | 5.98 (1.78) / 6.27 (1.71) |  | 200 mg | 3 months | n/a |  | 78.52 (4.58) | 78.08 (4.71) |
| **Berk et al., 2008** | *N*-acetylcysteine | 69 / 71 |  | 48/21 / 50/21 |  | 37.2 (10.1) / 36.1 (11.7) |  | 12.4 (8.2) / 12.1 (9.6) |  | 2000 mg | 24 weeks | Chronic |  | 64.0 (15.4) | 64.4 (16.3) |
| **Breier et al., 2018** | *N*-acetylcysteine | 30 / 30 |  | 23/7 / 24/6 |  | 22.2 (4.2) / 25.0 (5.2) |  | 1.3 (1.2) / 1.4 (1.1) |  | 3600 mg | 52 weeks | Early-phase |  | 56.7 (15.0) | 56.4 (12.0) |
| **Farokhnia et al., 2013** | *N*-acetylcysteine | 21 / 21 |  | 9/12 / 11/10 |  | 32.23 (6.12) / 33.38 (6.97) |  | 83.23 (41.02) / 88.95 (44.66) [months] |  | 2000 mg | 8 weeks | Blank |  | 113.42 (9.05) | 114.61 (10.09) |
| **Sepehrmanesh et al., 2018** | *N*-acetylcysteine | 40 / 39 |  | 22/18 / 19/20 |  | 38.7 (1.9) / 39.4 (2.2) |  | 13.8 (9.9) / 17 (11.6) |  | 1200 mg | 12 weeks | Blank |  | 104.0 (27.0) | 87.7 (17.4) |
| **Zhang et al., 2015** | *N*-acetylcysteine | 61 / 60 |  | 32/29 |  | 34.6 (8.4) |  | 6.6 (5.1) [months] |  | 600 mg | 8 weeks | FEP |  | 113.87 (3.57) | 113.67 (4.36) |
| **Iranpour et al., 2016** | Pioglitazone | 21 / 21 |  | 14/7 / 15/6 |  | 38 (8.99) / 37 (7.69) |  | 16.25 (8.94) / 13.60 (8.21) |  | 30 mg | 8 weeks | n/a |  | 70.45 (5.54) | 68.50 (5.46) |
| **Noorbala et al., 1999** | Piracetam | 14 / 16 |  | 18/16 |  | n/a |  | n/a |  | 3200 mg | 8 weeks | n/a |  | n/a | n/a |
| **Ritsner et al., 2014** | Pregnenolone | 25 / 27 |  | 22/3 / 23/4 |  | 26.9 (5.2) / 27.8 (6.0) |  | 2.5 (1.4) / 2.8 (1.5) |  | 50 mg | 8 weeks | Early-phase |  | 58.2 (11.9) | 63.7 (10.5) |
| **Tajik-Esmaeeli et al., 2017** | Statin (Simvastatin) | 33 / 33 |  | 31/2 / 28/5 |  | 43.18 (8.89) / 44.64 (9.11) |  | 20.55 (10.79) / 19.60 (10.23) |  | 40 mg | 8 weeks | n/a |  | 47.09 (7.60) | 48.18 (7.70) |
| **Vincenzi et al., 2014** | Statin (Pravastatin) | 30 / 30 |  | 22/8 / 16/14 |  | 42.57 (11) / 44.53 (12.55) |  | 20.89 (13.13) / 22.03 (6.74) |  | 40 mg | 12 weeks | n/a |  | 75.16 (21.87) | 79.93 (18.53) |
| **Hong et al., 2011** | Varenicline | 32 / 32 |  | 20/12 / 22/10 |  | 44.03 / 41.57 |  | n/a |  | 1 mg | 8 weeks | n/a |  | BPRS: 34.13 (1.44) | BPRS: 34.69 (1.52) |
| **Smith et al., 2016** | Varenicline | 42 / 45 |  | 35/7 / 39/6 |  | 46.6 (8.9) / 43.6 (10.6) |  | n/a |  | 2 mg | 8 weeks | Chronic |  | 56.2 (14.9) | 58.8 (15.7) |
| **Chengappa et al., 2018** | Withania somnifera extract | 34 / 34 |  | 21/13 / 14/20 |  | 45.18 (12.90) / 47.38 (11.37) |  | 20.85 (12.26) / 23.38 (11.61) |  | 1000 mg | 12 weeks | Chronic |  | 69.88 (8) | 69.48 (8.45) |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| α-LA, alpha-lipoic acid ; ALA, α-linolenic acid; BPRS, Brief Psychiatric Rating Scale; Chronic, chronic schizophrenia with an illness duration > 5 years; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; Early-phase, early-phase schizophrenia with an illness duration ≤ 5 years; FEP, first-episode psychosis; OA, oleic acid; n/a, not applicable; PANSS, Positive and Negative Syndrome Scale; SD, standard deviation. \*Different treatment doses or treatment types were applied within the same study | | | | | | | | | | | | | | | |
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| **Supplementary Table 2.** Results of the Cochrane risk of bias tool for randomized trials | | | | | | | |
| **Study** | **Random sequence generation** | **Allocation concealment** | **Blinding of participants and personnel** | **Blinding of outcome assessment** | **Incomplete outcome data** | **Selective reporting** | **Total** |
| Akhondzadeh et al., 2003 | **+** | **+** | **+** | **+** | **+** | **+** | **4** |
| Akhondzadeh et al., 2007 | **+** | **+** | **+** | **+** | **+** | **+** | **4** |
| Berger et al., 2007 | **+** | **+** | **+** | **+** | **+** | **+** | **4** |
| Berk et al., 2008 | **+** | **+** | **+** | **+** | **+** | **+** | **4** |
| Boskovic et al., 2016 | **?** | **?** | **+** | **+** | **+** | **+** | **3** |
| Breier et al., 2018 | **?** | **+** | **+** | **+** | **+** | **+** | **3** |
| Chaudhry et al., 2012 | **+** | **+** | **+** | **+** | **+** | **+** | **4** |
| Chaves et al., 2015 | **+** | **+** | **+** | **+** | **+** | **+** | **4** |
| Chengappa et al., 2018 | **+** | **+** | **+** | **+** | **+** | **+** | **4** |
| Deakin et al., 2018 | **+** | **+** | **+** | **+** | **+** | **+** | **4** |
| Emsley et al., 2002 | **?** | **?** | **+** | **+** | **+** | **+** | **3** |
| Emsley et al., 2006 | **+** | **+** | **+** | **+** | **+** | **+** | **4** |
| Emsley et al., 2014 | **+** | **+** | **+** | **+** | **+** | **+** | **4** |
| Farokhnia et al., 2013 | **+** | **+** | **+** | **+** | **+** | **+** | **4** |
| Fenton et al., 2001 | **?** | **+** | **+** | **+** | **+** | **+** | **3** |
| Ghafari et al., 2013 | **+** | **?** | **+** | **+** | **+** | **+** | **3** |
| Ghanizadeh et al., 2014 | **+** | **+** | **+** | **+** | **+** | **+** | **4** |
| Hong et al., 2011 | **?** | **?** | **+** | **+** | **+** | **+** | **3** |
| Iranpour et al., 2016 | **+** | **+** | **+** | **+** | **+** | **+** | **4** |
| Jamilian et al., 2017 | **?** | **+** | **+** | **+** | **+** | **+** | **3** |
| Javitt et al. 2012 | **?** | **?** | **+** | **+** | **+** | **+** | **3** |
| Kelly et al., 2015 | **+** | **+** | **+** | **+** | **+** | **+** | **4** |
| Khodaie-Ardakani et al., 2014 | **+** | **+** | **+** | **+** | **+** | **+** | **4** |
| Khodaie-Ardakani et al., 2015 | **+** | **+** | **+** | **+** | **+** | **+** | **4** |
| Kianimehr et al., 2014 | **?** | **?** | **+** | **+** | **+** | **+** | **3** |
| Kulkarni et al., 2001 | **?** | **+** | **+** | **+** | **+** | **+** | **3** |
| Kulkarni et al., 2008 | **+** | **+** | **+** | **+** | **+** | **+** | **4** |
| Kulkarni et al., 2011 | **?** | **?** | **+** | **+** | **+** | **+** | **3** |
| Kulkarni et al., 2016 | **+** | **+** | **+** | **+** | **+** | **+** | **4** |
| Laan et al., 201 | **-** | **-** | **+** | **+** | **+** | **+** | **3** |
| Lee et al., 2015 | **?** | **?** | **+** | **+** | **+** | **+** | **3** |
| Lerner et al., 2013 | **+** | **+** | **+** | **+** | **+** | **+** | **4** |
| Levkovitz et al., 2010 | **?** | **?** | **+** | **+** | **+** | **+** | **3** |
| Liu et al., 2014 | **?** | **+** | **+** | **+** | **+** | **+** | **3** |
| Louzã et al., 2004 | **?** | **?** | **+** | **+** | **+** | **+** | **3** |
| Modabbernia et al., 2014 | **+** | **+** | **+** | **+** | **+** | **+** | **4** |
| Müller et al., 2002 | **?** | **+** | **+** | **+** | **+** | **+** | **3** |
| Müller et al., 2010 | **?** | **+** | **+** | **+** | **+** | **+** | **3** |
| Noorbala et al., 1999 | **?** | **?** | **+** | **+** | **+** | **+** | **3** |
| Pawełczyk et al., 2016 | **+** | **-** | **+** | **+** | **+** | **+** | **3** |
| Peet and Horobin et al., 2002 | **+** | **+** | **+** | **+** | **+** | **+** | **4** |
| Peet et al., 2001 | **+** | **+** | **+** | **+** | **+** | **+** | **4** |
| Rapaport et al., 2005 | **?** | **?** | **+** | **+** | **+** | **+** | **3** |
| Rappard & Müller 2004 [abstract] | **n/a** | **n/a** | **n/a** | **n/a** | **n/a** | **n/a** | **n/a** |
| Ritsner et al., 2014 | **+** | **?** | **+** | **+** | **+** | **+** | **3** |
| Sepehrmanesh et al., 2018 | **+** | **+** | **+** | **+** | **+** | **+** | **4** |
| Smith et al., 2016 | **+** | **+** | **+** | **+** | **+** | **+** | **4** |
| Tajik-Esmaeeli et al., 2017 | **+** | **+** | **+** | **+** | **+** | **+** | **4** |
| Usall et al., 2016 | **+** | **+** | **+** | **+** | **+** | **+** | **4** |
| Vincenzi et al., 2014 | **?** | **?** | **+** | **+** | **+** | **+** | **3** |
| Weiser et al., 2012 [abstract] | **n/a** | **n/a** | **n/a** | **n/a** | **n/a** | **n/a** | **n/a** |
| Weiser et al., 2017 | **?** | **?** | **+** | **+** | **+** | **+** | **3** |
| Weiser et al., 2019 | **+** | **?** | **+** | **+** | **+** | **+** | **3** |
| Zhang et al., 2015 (Chinese article) | **?** | **?** | **+** | **+** | **+** | **+** | **3** |
| Zhang et al., 2018 | **+** | **+** | **+** | **+** | **+** | **+** | **4** |
|  |  |  |  |  |  |  |  |
| **Key** |  |  |  |  |  |  |  |
| **+** | **Low risk of bias** | |  |  |  |  |  |
| **-** | **High risk of bias** | |  |  |  |  |  |
| **?** | **Unclear risk of bias** | |  |  |  |  |  |

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| **Supplementary Table 3.** Subgroup analysis and moderators | | | | | |
|
| **Anti-inflammatory agent** | **No. analyses** | **Hedges' *g*** | **95% lower limit** | **95% upper limit** | **P value** |
|  |  |  |  |  |  |
| **Celecoxib** |  |  |  |  |  |
| QASS (reference 4) | 4 | -0.663 | -1.720 | 0.394 | 0.219 |
|  |  |  |  |  |  |
| Illness stage |  |  |  |  |  |
| FEP | 1 | 0.531 | -0.024 | 1.087 | 0.061 |
| Chronic | 4 | 0.051 | -0.899 | 1.001 | 0.916 |
|  |  |  |  |  |  |
| **EPA and DHA Fatty Acids** |  |  |  |  |  |
| QASS (reference 4) | 12 | 0.059 | -0.377 | 0.496 | 0.790 |
| Illness duration | 12 | 0.004 | -0.026 | 0.034 | 0.783 |
| Treatment duration | 14 | 0.007 | -0.023 | 0.036 | 0.658 |
| Treatment dose | 14 | 0.000 | -0.000 | 0.000 | 0.074 |
| Baseline symptom severity | 13 | 0.001 | -0.011 | 0.013 | 0.889 |
|  |  |  |  |  |  |
| Illness stage |  |  |  |  |  |
| FEP | 2 | 0.312 | -0.018 | 0.642 | 0.064 |
| Early-phase | 1 | 0.569 | -0.136 | 1.275 | 0.114 |
| Chronic | 6 | 0.155 | -0.124 | 0.434 | 0.276 |
|  |  |  |  |  |  |
| **Estrogens** |  |  |  |  |  |
| QASS (reference 4) | 12 | -0.259 | -1.092 | 0.575 | 0.543 |
| Illness duration | 7 | -0.011 | -0.078 | 0.056 | 0.753 |
| Treatment duration | 12 | -0.024 | -0.092 | 0.043 | 0.479 |
| Treatment dose | 9 | -0.006 | -0.016 | 0.004 | 0.216 |
| Baseline symptom severity | 9 | 0.001 | -0.024 | 0.026 | 0.943 |
|  |  |  |  |  |  |
| **Minocycline** |  |  |  |  |  |
| QASS (reference 4) | 12 | -0.364 | -1.045 | 0.318 | 0.296 |
| Illness duration | 9 | 0.014 | -0.027 | 0.056 | 0.495 |
| Treatment duration | 12 | -0.012 | -0.029 | 0.006 | 0.198 |
| Treatment dose | 12 | -0.003 | -0.009 | 0.004 | 0.394 |
| Baseline symptom severity | 10 | -0.013 | -0.037 | 0.012 | 0.305 |
| Illness stage |  |  |  |  |  |
| Early-phase | 7 | 0.381 | -0.016 | 0.778 | 0.060 |
| Chronic | 3 | 0.617 | -0.267 | 1.501 | 0.171 |
|  |  |  |  |  |  |
| ***N*-acetylcysteine** |  |  |  |  |  |
| QASS (reference 4) | 5 | 0.359 | -0.404 | 1.123 | 0.356 |
| Illness stage |  |  |  |  |  |
| FEP | 1 | 1.417 | 1.020 | 1.813 | **0.000** |
| Early-phase | 1 | 0.977 | 0.448 | 1.506 | **0.000** |
| Chronic | 1 | 0.441 | 0.107 | 0.774 | **0.010** |
|  |  |  |  |  |  |
| Chronic, chronic schizophrenia with an illness duration > 5 years; Early-phase, early-phase schizophrenia with an illness duration ≤ 5 years; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; FEP, first-episode psychosis; QASS, quality assessment score. | | | | | |
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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Supplementary Table 4.** Effects of anti-inflammatory agents on cognitive domains | | | | | | | | | | | | | | | | | |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | **Aspirin** | **Davunetide** | **Fatty acids** | | **Estrogens** | | **Minocycline** | | | | | | **NAC** | | **Statin** | **Varenicline** | |
| ***Study*** | *Laan et al., 2010* | *Javitt et al., 2012* | *Fenton et al., 2001* | *Emsley et al., 2014* | *Kulkarni et al., 2016* | *Weiser et al., 2017* | *Chaudhry et al., 2012* | *Deakin et al., 2018* | *Levkotvitz et al., 2010* | *Liu et al., 2014* | *Weiser et al., 2019* | *Kelly et al., 2015* | *Breier et al., 2018* | *Sepehrmanesh et al., 2018* | *Vincenzi et al., 2014* | *Hong et al. 2011* | *Smith et al., 2016* |
| **Attention / vigilance** | **-** | **-** | **-** | **-** | **-** | **-** | **-** | n/a | **-** | **+** | **-** | **-** | **-** | n/a | **-** | **-** | **-** |
| **Communication** | n/a | **-** | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a |
| **Comprehension/ Planning** | n/a | **-** | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a |
| **Executive functions** | n/a | n/a | n/a | n/a | n/a | **-** | **-** | n/a | **+** | **-** | **-** | n/a | **-** | n/a | n/a | n/a | n/a |
| **Financial Skills** | n/a | **-** | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a |
| **Fine locomotor skills** | **-** | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | **-** | n/a | n/a | n/a | n/a | n/a | n/a | n/a |
| **Household Management** | n/a | **-** | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a |
| **IQ** | n/a | n/a | n/a | n/a | n/a | n/a | n/a | **-** | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a |
| **Language** | n/a | n/a | **-** | n/a | **-** | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a |
| **Medication Management** | n/a | **-** | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a |
| **Memory** | **-** | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a |
| **Memory (delayed memory)** | n/a | n/a | **-** | n/a | **-** | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a |
| **Memory (immediate memory)** | n/a | n/a | **-** | n/a | **-** | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a |
| **Memory (verbal memory)** | n/a | n/a | n/a | n/a | n/a | **-** | n/a | n/a | n/a | n/a | **-** | n/a | **-** | n/a | n/a | n/a | n/a |
| **Memory (visuospatial memory)** | n/a | n/a | n/a | n/a | n/a | n/a | **-** | n/a | **+** | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a |
| **Memory (working memory)** | n/a | **+ (5 mg only)** | n/a | **-** | n/a | **-** | n/a | n/a | n/a | **-** | **-** | **-** | **-** | n/a | **-** | n/a | **-** |
| **Motor speed** | n/a | n/a | n/a | n/a | n/a | **-** | n/a | n/a | n/a | n/a | **-** | n/a | **-** | n/a | n/a | n/a | n/a |
| **Problem solving** | n/a | n/a | n/a | **-** | n/a | n/a | n/a | n/a | n/a | **-** | n/a | **-** | n/a | n/a | **-** | n/a | **-** |
| **Processing speed** | n/a | **-** | n/a | **-** | n/a | n/a | n/a | **-** | n/a | **-** | n/a | **-** | n/a | n/a | n/a | **-** | **-** |
| **Psychomotor skills** | **-** | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | **-** | n/a | n/a | n/a | n/a | n/a | n/a | n/a |
| **Psychomotor speed** | n/a | n/a | n/a | n/a | n/a | n/a | **-** | n/a | **-** | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a |
| **Reasoning / problem-solving** | n/a | **-** | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a |
| **Social cognition** | n/a | **-** | n/a | **-** | n/a | n/a | n/a | n/a | n/a | n/a | n/a | **-** | n/a | n/a | **-** | n/a | **-** |
| **Transportation** | n/a | **-** | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a |
| **Verbal fluency** | n/a | n/a | n/a | n/a | n/a | **-** | n/a | n/a | n/a | **-** | **-** | n/a | **-** | n/a | n/a | n/a | n/a |
| **Verbal learning** | n/a | **+ (5 mg only)** | n/a | **-** | n/a | n/a | n/a | n/a | n/a | **-** | n/a | **-** | n/a | n/a | **-** | n/a | **-** |
| **Visual learning** | n/a | **-** | n/a | **-** | n/a | n/a | n/a | n/a | n/a | **-** | n/a | **-** | n/a | n/a | **-** | n/a | **-** |
| **Visuospatial / constructional** | n/a | n/a | **-** | n/a | **-** | n/a | n/a | n/a | n/a | **-** | n/a | n/a | n/a | n/a | n/a | n/a | n/a |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Cognitive tools** | RAVLT; HQ-CPT; PPT; TMT | UPSA; MCCB | RBANS | MCCB | RBANS | BACS | CANTAB | Wechsler Adult Intelligence Scale III | CANTAB | MCCB; WCST | BACS | MATRICS/MCCB | BACS | MMSE; DSFBT; DSST; SCWT | MATRICS; UPSA-B | MCCB | MCCB |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |

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| ***Study*** | *Sepehrmanesh et al., 2018* |  |  |  |  |  |  |  |  |  |  |
| **MMSE (visuospatial / language / attention / concentration / memory recall / orientation)\*** | **+** |  |  |  |  |  |  |  |  |  |  |
| **The Digit Span test, Backward (Verbal ability / Memory short term)\*** | **+** |  |  |  |  |  |  |  |  |  |  |
| **The Digit Span test, Forward (Verbal ability / Memory short term)\*** | **+** |  | BACS, Brief Assessment of Cognition in Schizophrenia; CANTAB, Cambridge Neuropsychological Test Automated Battery; DGSBT, Digit Span Forward and Backward Test; DSST, Digit Symbol Substitution Test; HQ-CPT, HQ Continuous Performance Test; IQ, Intelligence Quotient; MCCB, MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) Consensus Cognitive Battery; MMSE, Mini-Mental State Examination; n/a, not available; NAC, *N*-acetylcysteine; PPT, Purdue Pegboard Test; RAVLT, Rey Auditory Verbal Learning Test; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; SCWT, Stroop Color-Word Test; TMT, Trail Making Test; UPSA, University of California, San Diego Performance-Based Skills Assessment; Brief Wisconsin Card Sorting Test, WCST. **\*** Cognitive domains were not subdivided; **+**, positive significant effects on improving cognition (p-value < 0.05); **-**, no significant effects on improving cognition. | | | | | | | | |
| **The Digit Symbol Substitution Test (brain damage / dementia / age / depression)\*** | **+** |  |
| **The stroop test (processing speed / executive functions / working memory / cognitive development)\*** | **+** |  |

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| **Supplementary Table 5.** Meta-analysis of RCTs with aspirin, estrogens, minocycline, and *N*-acetylcysteine in schizophrenia: efficacy signal | | | |
| Anti-inflammatory component | Positive symptoms | Negative symptoms | Cognition\* |
|  |  |  |  |
| Aspirin | ES = 0.23; *p* = 0.336 | ES = 0.28; *p* = 0.243 | - |
| Estrogens | **ES = 0.48; *p* = 0.004** | **ES = 0.45; *p* = 0.006** | - |
| Minocycline | ES = 0.14; *p* = 0.094 | **ES = 0.50; *p* = 0.003** | **+/-** |
| *N-*acetylcysteine | ES = 0.21; *p* = 0.124 | **ES = 0.75; *p* = 0.009** | **+/-** |
|  |  |  |  |
| \*Heterogeneity of the used cognitive tests across the studies was too great to make a quantitative review of these effects; -, probably no effects; +/-, probably some beneficial effects. | | | |
| ES, mean weighted effect size; *p*, *p*-value; RCTs, randomized controlled trials. | | | |

**Supplementary Figure 1.** Funnel Plot for Estrogen Analysis



**Supplementary Figure 2.** Funnel Plot for Fatty Acids Analysis

**Supplementary Figure 3.** Funnel Plot for Minocycline Analysis



**Forest Plots Showing Effect Size Estimates for the Total Symptom Scores**

**Supplementary Figure 4.** Forest Plot Showing Effect Sizes for Aspirin Augmentation



**Supplementary Figure 5.** Forest Plot Showing Effect Size for Bexarotene Augmentation



**Supplementary Figure 6.** Forest Plot Showing Effect Sizes for Celecoxib Augmentation



**Supplementary Figure 7.** Forest Plot Showing Effect Sizes for Davunetide Augmentation



**Supplementary Figure 8.** Forest Plot Showing Effect Size for Dextromethorphan Augmentation



**Supplementary Figure 9a.** Forest Plot Showing Effect Sizes for Fatty Acids Augmentation



**Supplementary Figure 9b.** Forest Plot Showing Effect Sizes for Fatty Acids Augmentation



**Supplementary Figure 9c.** Forest Plot Showing Effect Sizes for Fatty Acids Augmentation



**Supplementary Figure 9d.** Forest Plot Showing Effect Sizes for Fatty Acids Augmentation

**Supplementary Figure 10a.** Forest Plot Showing Effect Sizes for Estrogen Augmentation

**Supplementary Figure 10b.** Forest Plot Showing Effect Sizes for Estrogen Augmentation



**Supplementary Figure 10c.** Forest Plot Showing Effect Sizes for Estrogen Augmentation



**Supplementary Figure 11.** Forest Plot Showing Effect Size for Melatonin Augmentation

**Supplementary Figure 12a.** Forest Plot Showing Effect Sizes for Minocycline Augmentation



**Supplementary Figure 12b.** Forest Plot Showing Effect Sizes for Minocycline Augmentation



**Supplementary Figure 13.** Forest Plot Showing Effect Sizes for *N*-acetylcysteine (NAC) Augmentation



**Supplementary Figure 14.** Forest Plot Showing Effect Size for Pioglitazone Augmentation



**Supplementary Figure 15.** Forest Plot Showing Effect Size for Piracetam Augmentation



**Supplementary Figure 16.** Forest Plot Showing Effect Size for Pregnenolone Augmentation



**Supplementary Figure 17.** Forest Plot Showing Effect Sizes for Statin Augmentation



**Supplementary Figure 18.** Forest Plot Showing Effect Sizes for Varenicline Augmentation



**Supplementary Figure 19.** Forest Plot Showing Effect Size for Withania Somnifera Extract (WSE) Augmentation



**Forest Plots Showing Effect Size Estimates for the Positive Symptom Scores**

**Supplementary Figure 20.** Forest Plot Showing Effect Size for Aspirin Augmentation



**Supplementary Figure 21.** Forest Plot Showing Effect Size for Bexarotene Augmentation

**Supplementary Figure 22.** Forest Plot Showing Effect Sizes for Celecoxib Augmentation



**Supplementary Figure 23.** Forest Plot Showing Effect Sizes for Estrogen Augmentation

**Supplementary Figure 24.** Forest Plot Showing Effect Sizes for Fatty Acids Augmentation



**Supplementary Figure 25.** Forest Plot Showing Effect Size for Melatonin Augmentation



**Supplementary Figure 26.** Forest Plot Showing Effect Sizes for Minocycline Augmentation



**Supplementary Figure 27.** Forest Plot Showing Effect Sizes for NAC Augmentation



**Supplementary Figure 28.** Forest Plot Showing Effect Size for Pioglitazone Augmentation 

**Supplementary Figure 29.** Forest Plot Showing Effect Size for Piracetam Augmentation



**Supplementary Figure 30.** Forest Plot Showing Effect Size for Pregnenolone Augmentation



**Supplementary Figure 31.** Forest Plot Showing Effect Sizes for Statin Augmentation



**Supplementary Figure 32.** Forest Plot Showing Effect Size for Varenicline Augmentation



**Supplementary Figure 33.** Forest Plot Showing Effect Size for WSE Augmentation



**Forest Plots Showing Effect Size Estimates for the Negative Symptom Scores**

**Supplementary Figure 34.** Forest Plot Showing Effect Size for Aspirin Augmentation



**Supplementary Figure 35.** Forest Plot Showing Effect Size for Bexarotene Augmentation   


**Supplementary Figure 36.** Forest Plot Showing Effect Sizes for Celecoxib Augmentation



**Supplementary Figure 37.** Forest Plot Showing Effect Sizes for Estrogen Augmentation



**Supplementary Figure 38.** Forest Plot Showing Effect Sizes for Fatty Acids Augmentation



**Supplementary Figure 39.** Forest Plot Showing Effect Size for Melatonin Augmentation



**Supplementary Figure 40.** Forest Plot Showing Effect Sizes for Minocycline Augmentation



**Supplementary Figure 41.** Forest Plot Showing Effect Sizes for NAC Augmentation



**Supplementary Figure 42.** Forest Plot Showing Effect Size for Pioglitazone Augmentation  


**Supplementary Figure 43.** Forest Plot Showing Effect Size for Pregnenolone Augmentation

**Supplementary Figure 44.** Forest Plot Showing Effect Sizes for Statin Augmentation



**Supplementary Figure 45.** Forest Plot Showing Effect Size for Varenicline Augmentation  


**Supplementary Figure 46.** Forest Plot Showing Effect Size for WSE Augmentation



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