**Supplementary Figure 1. PRISMA 2009 flow diagram**



**Excluded Studies**

**Review Articles**

Alvarez-Jimenez, M., O'Donoghue, B., Thompson, A., Gleeson, J.F., Bendall, S., Gonzalez-Blanch, C., Killackey, E., Wunderink, L., McGorry, P.D., 2016. Beyond Clinical Remission in First Episode Psychosis: Thoughts on Antipsychotic Maintenance vs. Guided Discontinuation in the Functional Recovery Era. CNS Drugs 30 (5), 357-368.

De Hert, M., Sermon, J., Geerts, P., Vansteelandt, K., Peuskens, J., Detraux, J., 2015. The Use of Continuous Treatment Versus Placebo or Intermittent Treatment Strategies in Stabilized Patients with Schizophrenia: A Systematic Review and Meta-Analysis of Randomized Controlled Trials with First- and Second-Generation Antipsychotics. CNS Drugs 29 (8), 637-658.

Doyle, R., Turner, N., Fanning, F., Brennan, D., Renwick, L., Lawlor, E., Clarke, M., 2014. First-episode psychosis and disengagement from treatment: a systematic review. Psychiatr Serv 65 (5), 603-611.

Goff, D.C., Falkai, P., Fleischhacker, W.W., Girgis, R.R., Kahn, R.M., Uchida, H., Zhao, J., Lieberman, J.A., 2017. The Long-Term Effects of Antipsychotic Medication on Clinical Course in Schizophrenia. Am J Psychiatry 174 (9), 840-849.

Karson, C., Duffy, R.A., Eramo, A., Nylander, A.G., Offord, S.J., 2016. Long-term outcomes of antipsychotic treatment in patients with first-episode schizophrenia: a systematic review. Neuropsychiatr Dis Treat 12, 57-67.

Leucht, S., Tardy, M., Komossa, K., Heres, S., Kissling, W., Salanti, G., Davis, J.M., 2012. Antipsychotic drugs versus placebo for relapse prevention in schizophrenia: a systematic review and meta-analysis. Lancet 379 (9831), 2063-2071.

Zhang, J.P., Gallego, J.A., Robinson, D.G., Malhotra, A.K., Kane, J.M., Correll, C.U., 2013. Efficacy and safety of individual second-generation vs. first-generation antipsychotics in first-episode psychosis: a systematic review and meta-analysis. Int J Neuropsychopharmacol 16 (6), 1205-1218.

**Not Only First Episode Patients Study**

Wiedemann, G., Hahlweg, K., Muller, U., Feinstein, E., Hank, G., Dose, M., 2001. Effectiveness of targeted intervention and maintenance pharmacotherapy in conjunction with family intervention in schizophrenia. Eur Arch Psychiatry Clin Neurosci 251 (2), 72-84.

**Identical Studies**

Gaebel, W., Frick, U., Kopcke, W., Linden, M., Muller, P., Muller-Spahn, F., Pietzcker, A., Tegeler, J., 1993. Early neuroleptic intervention in schizophrenia: are prodromal symptoms valid predictors of relapse? Br J Psychiatry Suppl(21), 8-12.

Gaebel, W., Riesbeck, M., Wolwer, W., Klimke, A., Eickhoff, M., von Wilmsdorff, M., Heuser, I., Maier, W., Klosterkotter, J., Falkai, P., Schlosser, R., Schmitt, A., Riedel, M., Klingberg, S., Kopcke, W., Ohmann, C., Moller, H.J., 2014. Rates and predictors of remission in first-episode schizophrenia within 1 year of antipsychotic maintenance treatment. Results of a randomized controlled trial within the German Research Network on Schizophrenia. Schizophr Res 152 (2-3), 478-486.

Godemann, F., Linden, M., Gaebel, W., Kopke, W., Muller, P., Muller-Spahn, F., Tegeler, J., Pietzcker, A., 2003. Is interval medication a successful treatment regimen for schizophrenic patients with critical attitudes towards treatment? Eur Psychiatry 18 (2), 82-84.

Muller, P., Bandelow, B., Gaebel, W., Kopcke, W., Linden, M., Muller-Spahn, F., Pietzcker, A., Schaefer, E., Tegeler, J., 1992. Intermittent medication, coping and psychotherapy. Interactions in relapse prevention and course modification. Br J Psychiatry Suppl(18), 140-144.

Wunderink, L., Nieboer, R.M., Wiersma, D., Sytema, S., Nienhuis, F.J., 2013. Recovery in remitted first-episode psychosis at 7 years of follow-up of an early dose reduction/discontinuation or maintenance treatment strategy: long-term follow-up of a 2-year randomized clinical trial. JAMA Psychiatry 70 (9), 913-920.

**Supplementary Figure 2. Risk of bias summary**

**Supplementary Figure 3. Forest plot for the relapse rate at 12 months**

**Supplementary Figure 4. Funnel plot**

**Supplementary Figure 5. Forest plot for the relapse rate at 1 month**

**Supplementary Figure 6. Forest plot for the relapse rate at 2 months**

**Supplementary Figure 7. Forest plot for the relapse rate at 3 months**

**Supplementary Figure 8. Forest plot for the relapse rate at 6 months**

**Supplementary Figure 9. Forest plot for the relapse rate at 9 months**

**Supplementary Figure 10. Forest plot for the relapse rate at 18–24 months**

**Supplementary Figure 11. Forest plot for discontinuation due to all causes**

**Supplementary Figure 12. Forest plot for discontinuation due to adverse events**

**Supplementary Figure 13. Forest plot for discontinuation because of withdrawn consent**

**Supplementary Figure 14. Forest plot for discontinuation due to loss to follow-up**

**Supplementary Figure 15. Forest plot for Positive and Negative Syndrome Scale positive subscale scores**

**Supplementary Figure 16. Forest plot for Positive and Negative Syndrome Scale negative subscale scores**

**Supplementary Figure 17. Forest plot for Positive and Negative Syndrome Scale general subscale scores**

**Supplementary Figure 18. Forest plot for quality of life scores**

**Supplementary Figure 19. Forest plot for extrapyramidal symptoms scores**

**Supplementary Figure 20. Forest plot for the use of anticholinergic drugs/incidence of tremor**

**Supplementary Table 1. Definitions of remission and relapse**

|  |  |  |
| --- | --- | --- |
|  | Remission | Relapse |
| Boonstra 2011 | > 1 PANSS core psychosis item score (delusions, conceptual disorganization, hallucinatory behavior, suspiciousness or persecution) ≤ 3 for > 1 year | > 1 PANSS core psychosis item score (delusions, conceptual disorganization, hallucinatory behavior, suspiciousness or persecution) > 4 and PANSS total score > 20% increase or hospitalization for any psychiatric indication. |
| Chen 2010 | PANSS delusions score ≤ 2, conceptual disorganization score ≤ 3, hallucinatory behavior score ≤ 2, suspiciousness score ≤ 4, unusual thought content score ≤ 3, CGI-S ≤ 2 for > 8 weeks | PANSS delusions score > 3, conceptual disorganization score > 4, hallucinatory behavior score > 3, suspiciousness score > 5, unusual thought content score > 4, CGI-S > 3, CHI-I > 5 for > 1 week |
| Crow 1986 | Discharge maintained for > 30 days post index episode | Hospitalization or imminent relapse requiring antipsychotic medication |
| Gaebel 2002 | NR | BPRS psychosis item score (hostile suspiciousness, though disturbance, activation) > 10, GAS < 20, CGI-S > 6, clinician’s judgement |
| Gaebel 2011 | NR | PANSS positive score > 10 increase, GAF > 20 decrease, CGI-C > 6 |
| Hogarty 1973 | NR | Clinical deterioration of such magnitude that hospitalization appeared imminent |
| Kane 1982 | NR | Substantial clinical deterioration with a potential for marked social impairment |
| McCreadie 1989 | NR | Hospitalization |
| Rifkin 1979 | No positive symptoms | Significant clinical deterioration with a potential for, or actual, marked social impairment |
| Wunderink 2007 | Sustained improvement of positive symptoms as measured byPANSS reﬂecting symptom severity levels at or below the level of response (i.e., clinical improvement to a non-ﬂorid psychotic state for > 1 week, reported by clinician and conﬁrmed by PANSS positive subscale score) for > 6 months | Clinical deterioration for > 1 week having consequences(increased antipsychotic dose, hospitalization, increased frequency of consultations) reported by clinician and conﬁrmed by > 1 PANSS positive subscale items score > 5 |

BPRS: Brief Psychiatric Rating Scale, CGI-C: Clinical Global Impression-Global Change, CGI-I: Clinical Global Impression-Global Improvement, CGI-S: Clinical Global Impressions-Severity Illness Scale, GAF: Global Assessment of Functioning, GAS: Global Assessment Scale, NR: not report, PANSS: Positive and Negative Syndrome Scale

**Supplementary Table 2. Results of the subgroup analyses**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Modulators | Subgroup | N | n | RR | 95% CI | p | I2 | NNT | p for subgroup difference |
| Antipsychotic class | SGAs (quetiapine) alone | 1 | 178 | 0.48 | 0.34–0.69 | <0.0001 | na | 3 | 0.76 |
| SGAs and FGAs | 3 | 192 | 0.27 | 0.09–0.80 | 0.02 | 52% | 2 |
| FGAs alone | 5 | 254 | 0.51 | 0.31–0.84 | 0.009 | 31% | 3 |
| Unknown | 1 | 115 | 0.43 | 0.21–0.87 | 0.02 | na | 3 |
| Placebo use | Placebo-controlled studies | 6 | 432 | 0.53 | 0.39–0.71 | <0.0001 | 22% | 3 | 0.26 |
| Non-placebo-controlled studies | 4 | 307 | 0.37 | 0.21–0.64 | 0.0005 | 26% | 3 |
| Diagnosis | Schizophrenia-only studies | 5 | 223 | 0.20 | 0.04–0.95 | 0.04 | 66% | 3 | 0.31 |
| Studies with various psychotic disorders | 5 | 516 | 0.45 | 0.35–0.58 | <0.00001 | 0% | 3 |
| Sponsorship | Industry-sponsored studies | 4 | 341 | 0.45 | 0.33–0.61 | <0.00001 | 0% | 3 | 0.08 |
| Non-industry-sponsored studies | 5 | 278 | 0.37 | 0.22–0.65 | 0.0005 | 17% | 3 |
| Unknown | 1 | 120 | 0.69 | 0.50–0.97 | 0.03 | na | 5 |
| Antipsychotic discontinuation | Studies with abrupt discontinuation of antipsychotics | 4 | 134 | 0.40 | 0.23–0.68 | 0.0009 | 0% | 3 | 0.98 |
| Studies where the antipsychotics were discontinued after gradually tapering the dose over several months | 6 | 605 | 0.48 | 0.34–0.69 | <0.0001 | 47% | 3 |
| Remission at baseline | Studies that included only patients remitted at baseline | 5 | 370 | 0.45 | 0.33–0.61 | <0.00001 | 0% | 3 | 0.55 |
| Other studies | 5 | 369 | 0.45 | 0.25–0.79 | 0.006 | 59% | 3 |
| Wunderink 2007 study | Wunderink 2007 study | 1 | 128 | 0.47 | 0.24–0.91 | 0.03 | na | 6 | 0.92 |
| Other studies | 9 | 611 | 0.45 | 0.32–0.64 | <0.00001 | 39% | 3 |
| Psychological intervention | Studies with known psychological intervention | 7 | 481 | 0.46 | 0.31–0.69 | 0.0001 | 46% | 3 | 0.82 |
| Other studies | 3 | 258 | 0.43 | 0.27–0.69 | 0.0005 | 0% | 4 |

95% CI: 95% confidence interval, FGAs: First-generation antipsychotics, N: number of studies, n: number of patients, na: not applicable, NNT: number-needed-to-treat, RR: risk ratio, SGAs: second generation antipsychotics

**Supplementary Table 3. Results of the meta-regression analysis**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Number of studies | Coefficient | Standard error | 95% confidence interval | Z | p |
| Total number of patients | 10 | 0.0043 | 0.0032 | –0.0019 to 0.0106 | 1.35 | 0.177 |
| Study duration | 10 | 0.0122 | 0.0255 | –0.0377 to 0.0621 | 0.48 | 0.632 |
| Publication year | 10 | –0.0068 | 0.0102 | –0.0268 to 0.0132 | –0.67 | 0.506 |
| Percentage of males | 7 | –0.0050 | 0.0174 | –0.0391 to 0.0290 | –0.29 | 0.773 |
| Age | 7 | –0.0664 | 0.0741 | –0.212 to 0.0787 | –0.90 | 0.370 |
| Duration of illness | 5 | 0.0024 | 0.0191 | –0.0350 to 0.0398 | 0.13 | 0.899 |
| Antipsychotic dose at baseline | 4 | –1.78 | 1.07 | –3.88 to 0.321 | –1.66 | 0.0968 |

**Supplementary Table 4. Results of the meta-regression analysis: relapse rate and length of time from tapering antipsychotic to antipsychotic discontinuation (6 studies, 605 patients)**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Point estimate | Standard error | 95% confidence interval | Z | p |
| Relapse rate at 1 month | –0.119 | 0.0896 | –0.294 to 0.0571 | –1.32 | 0.186 |
| Relapse rate at 2 months | –0.0959 | 0.0568 | –0.207 to 0.0155 | –1.69 | 0.0915 |
| Relapse rate at 3 months | 0.00602 | 0.0442 | –0.0807 to 0.0927 | 0.136 | 0.892 |
| Relapse rate at 6 months | –0.0103 | 0.0315 | –0.0721 to 0.0515 | –0.328 | 0.743 |
| Relapse rate at 9 months | 0.0120 | 0.0265 | –0.0400 to 0.0641 | 0.454 | 0.650 |
| Relapse rate at 12 months | 0.0102 | 0.0241 | –0.0370 to 0.0575 | 0.425 | 0.671 |