



Snips from the journals

Update on therapeutics

Shehan Williams and Thilini Rajapakse

Antipsychotic drugs versus placebo for relapse prevention in schizophrenia: a systematic review and meta-analysis.(1).

This is a systematic review and meta-analysis which aims to answer the question, are antipsychotics effective in preventing relapse for patients with schizophrenia? The primary outcome was relapse occurring between 7 and 12 months. Secondary outcomes include readmission, dropout, improvement of disease, death, violence or aggressive behaviour, adverse events, quality of life, satisfaction with care and employment.

The Cochrane Schizophrenia Group's specialised register for reports published before Nov 11, 2008; and PubMed, Embase, and ClinicalTrials.gov for those before June 8, 2011 were searched. They also contacted pharmaceutical companies and searched the reference lists of included studies and previous reviews. Randomised trials of patients with schizophrenia continued on or withdrawn from any antipsychotic drug regimen after stabilisation were eligible. They used the random effects model for analysis and verified results for the primary outcome with a fixed effects model. Heterogeneity was investigated with subgroup and meta-regression analyses. The study was funded by the German ministry of education and research.

They identified 116 suitable reports from 65 trials, with data for 6493 patients. Antipsychotic drugs significantly reduced relapse rates at 1 year (drugs 27% vs placebo 64%; risk ratio [RR] 0.40, 95% CI 0.33-0.49; number needed to treat to benefit [NNTB] 3, 95% CI 2-3). Fewer patients given antipsychotic drugs than placebo were readmitted (10% vs 26%; RR 0.38, 95% CI 0.27-0.55; NNTB 5, 4-9), but less than a third of relapsed patients had to be admitted. Limited evidence suggested better quality of life (standardised mean difference -0.62, 95% CI -1.15 to -0.09) and fewer aggressive acts (2% vs 12%; RR 0.27, 95% CI 0.15-0.52; NNTB 11, 6-100) with antipsychotic drugs than with placebo. Employment data were scarce and too few deaths were reported to allow significant differences to be identified. More patients given antipsychotic drugs than placebo gained weight (10% vs 6%; RR 2.07, 95% CI 2.31-3.25), had movement disorders (16% vs 9%; RR 1.55, 95% CI 1.25-1.93), and experienced sedation (13% vs 9%; RR 1.50, 95% CI 1.22-1.84). Substantial heterogeneity in size of effect was recorded. In subgroup analyses, number of episodes, whether patients were in remission, abrupt or gradual withdrawal of treatment, length of stability before trial entry, first-generation or second-generation drugs, and allocation concealment method did not significantly affect relapse risk. Depot preparations reduced relapse (RR 0.31, 95% CI 0.21-

0.41) more than did oral drugs (RR 0.46, 95% CI 0.37-0.53); depot haloperidol (RR 0.14, 95% CI 0.04-0.55) and fluphenazine (RR 0.23, 95% CI 0.14-0.39) had had larger effects than other drugs. The effects of antipsychotic drugs were greater in two unblinded trials (0.26, 0.17-0.39) than in blinded trials (RR 0.42, 95% CI 0.35-0.51; $p=0.03$). In a meta-regression, the difference between drug and placebo decreased with study length.

This study strengthens current practice of maintenance treatment with antipsychotic drugs for patients with schizophrenia. In the Sri Lankan context, the use of depot preparation especially the low cost fluphenazine decanoate for maintenance treatment is also justified.

Adverse effects of second-generation antipsychotics in children and adolescents: a Bayesian meta-analysis (2).

This is a systematic review and meta-analysis which aims to answer the question, what are the most common short-term side effects of second-generation antipsychotics (SGAs) in children and adolescents? The main outcomes considered were: Clinically significant weight gain as declared by the investigator or as defined in the trial (weight gain 97% or weight gain 95%); change in glucose, cholesterol and triglycerides; change in prolactin; clinically significant hyperprolactinaemia; somnolence/sedation; clinical extrapyramidal symptoms (EPS) and or akathisia. Studies were searched for in MEDLINE and EMBASE (1996-2010), Food and Drug Administration and European Medicines Agency clinical trial registries, and reference lists of review articles. They found 41 short-term (3-12 weeks) controlled studies that evaluated SGA adverse effects in youths. Using Bayesian meta-analysis, they analyzed odds ratios (OR) or mean average effects. Numbers of arms and subjects in the 41 trials were aripiprazole, 10 ($n=671$); olanzapine, 14 ($n=413$); quetiapine, 10 ($n=446$); risperidone, 25 ($n=1040$); ziprasidone, 4 ($n=228$); clozapine, 5 ($n=79$); and placebo/untreated, 23 ($n=1138$), totaling 93 arms (4015 patients). Clozapine was assessed only for weight gain and somnolence. Compared with placebo, significant treatment-related increases were observed for weight gain with olanzapine (mean = 3.99 ± 0.42 kg; 95% credible interval, 3.17-4.84 kg), clozapine (2.38 ± 1.13 kg; 95% credible interval, 0.19-4.62 kg), risperidone (2.02 ± 0.32 kg; 95% credible interval, 1.39-2.66 kg), quetiapine (1.74 ± 0.38 kg; 95% credible interval, 0.99-2.5 kg), and aripiprazole (0.89 ± 0.32 kg; 95% credible interval, 0.26-1.51 kg); glucose levels with risperidone ($3.7 \pm$

1.36 mg/dL; 95% credible interval, 1.08-6.42 mg/dL) and olanzapine (2.09 ± 1.08 mg/dL; 95% credible interval, 0.13-4.32 mg/dL); cholesterol levels with quetiapine (10.77 ± 2.14 mg/dL; 95% credible interval, 6.6-14.95 mg/dL) and olanzapine (4.46 ± 1.65 mg/dL; 95% credible interval, 1.24-7.73 mg/dL); triglyceride levels with olanzapine (20.18 ± 5.26 mg/dL; 95% credible interval, 9.85-30.53 mg/dL) and quetiapine (19.5 ± 3.92 mg/dL; 95% credible interval, 11.84-27.17 mg/dL); hyperprolactinemia with risperidone (OR, 38.63; 95% credible interval, 8.62-125.6), olanzapine (OR, 15.6; 95% credible interval, 4.39-41.1), and ziprasidone (OR, 9.35; 95% credible interval, 1.24-37.03); and EPS with ziprasidone (OR, 20.56; 95% credible interval, 3.53-68.94), olanzapine (OR, 6.36; 95% credible interval, 2.43-13.84), aripiprazole (OR, 3.79; 95% credible interval, 2.17-6.17), and risperidone (OR, 3.71; 95% credible interval, 2.18-6.02).

All other SGAs except quetiapine significantly increased the risk of EPS compared with the placebo. All SGAs increased the risk of somnolence/sedation compared to placebo.

Efficacy and safety of individual second-generation vs. first-generation antipsychotics in first-episode psychosis: a systematic review and meta-analysis (3).

Because early treatment choice is critical in first-episode schizophrenia-spectrum disorders (FES), this meta-analysis compared efficacy and tolerability of individual second-generation antipsychotics (SGAs) with first-generation antipsychotics (FGAs) in FES. They conducted a systematic literature search (until 12 December 2010) and meta-analysis of acute, randomized trials with FGA vs. SGA comparison; patients in their first episode of psychosis and diagnosed with schizophrenia-spectrum disorders; available data for psychopathology change, treatment response, treatment discontinuation, adverse effects, or cognition. Across 13 trials ($n = 2509$), olanzapine (seven trials) and amisulpride (one trial) outperformed FGAs (haloperidol: 9/13 trials) in 9/13 and 8/13 efficacy outcomes, respectively, risperidone (eight trials) in 4/13, quetiapine (one trial) in 3/13 and clozapine (two trials) and ziprasidone (one trial) in 1/13, each. Compared to FGAs, extrapyramidal symptom (EPS)-related outcomes were less frequent with olanzapine, risperidone and clozapine, but weight gain was greater with clozapine, olanzapine and risperidone. Pooled SGAs were similar to FGAs regarding total psychopathology change, depression, treatment response and metabolic changes. SGAs significantly outperformed FGAs regarding lower treatment discontinuation, irrespective of cause, negative symptoms, global cognition and less EPS and akathisia, while SGAs increased weight more ($p < 0.05-0.01$). Results were not affected by FGA dose or publication bias, but industry-sponsored studies favoured SGAs more than federally funded studies. To summarize, in FES, olanzapine, amisulpride and, less so, risperidone and quetiapine showed superior efficacy, greater treatment persistence and less EPS than FGAs.

However, weight increase with olanzapine, risperidone and clozapine and metabolic changes with olanzapine were greater. Additional FES studies including broader based SGAs and FGAs are needed.

One-year, randomized, open trial comparing olanzapine, quetiapine, risperidone and ziprasidone effectiveness in antipsychotic-naïve patients with a first-episode psychosis (4).

The aim of this study was to compare the 12-month effectiveness of several second-generation antipsychotic drugs, with that of haloperidol in never-treated patients with first-episode psychosis. In total, 114 patients without life time exposure to any psychotropic medication were randomized to haloperidol, olanzapine, risperidone, quetiapine or ziprasidone. Primary outcome was time to all-cause discontinuation. Secondary outcomes included discontinuation rates and symptom change as measured by the Positive and Negative Syndrome Scale (PANSS). The overall discontinuation rate was 64%. At 12 months, the proportion of patients discontinuing treatment was 40.0% for olanzapine, 56.5% for quetiapine, 64.0% for risperidone, 80.0% for ziprasidone and 85.7% for haloperidol. Mean time to antipsychotic discontinuation was higher in patients randomized to second-generation antipsychotics than in those taking haloperidol. Significantly lower discontinuation was noted in patients on olanzapine than on haloperidol, or ziprasidone. The results suggest that olanzapine might lead to longer treatment continuation in treatment naïve FEP patients than haloperidol and, possibly ziprasidone. Global psychopathology was significantly less reduced by haloperidol than with each individual SGA in this earliest phase of treatment.

The findings of this randomised control study lend support to the use of SGA in antipsychotic-naïve patients with first episode psychosis.

Polypharmacy with antipsychotics, antidepressants, or benzodiazepines and mortality in schizophrenia (5).

Polypharmacy is widely used in the treatment of schizophrenia, although guidelines discourage this practise. This was a registry based case linkage study that investigated the use of benzodiazepines, antidepressants, or multiple concomitant antipsychotics and its association with increased mortality among patients with schizophrenia. This study linked national databases of mortality and medication prescriptions among a complete nationwide cohort of 2588 patients hospitalized in Finland for the first time with a diagnosis of schizophrenia between January 1, 2000, and December 31, 2007.

Hazard ratios (HRs) were computed for all-cause mortality during the use of antipsychotics, antidepressants, or benzodiazepines in outpatient care,

adjusting for the effects of socio-demographic and clinical variables, geographic location, and current and past pharmacological treatments.

Compared with antipsychotic monotherapy, concomitant use of 2 or more antipsychotics was not associated with increased mortality (HR, 0.86; 95% CI, 0.51-1.44). Similarly, antidepressant use was not associated with a higher risk for mortality (HR, 0.57; 95% CI, 0.28-1.16) and was associated with markedly decreased suicide deaths (HR, 0.15; 95% CI, 0.03-0.77). However, benzodiazepine use was associated with a substantial increase in mortality (HR, 1.91; 95% CI, 1.13-3.22), and this was attributable to suicidal deaths (HR, 3.83; 95% CI, 1.45-10.12) and to non-suicidal deaths (HR, 1.60; 95% CI, 0.86-2.97). In total, 826 of 904 patients (91.4%) who used benzodiazepines had purchased prescriptions that contained more than 28 defined daily doses, violating treatment guidelines.

Benzodiazepine use was associated with a marked increase in mortality among patients with schizophrenia, whereas the use of an antidepressant or several concomitant antipsychotics was not. Antidepressant use was associated with decreased suicide deaths.

Although polypharmacy is best avoided, it is useful to keep these findings in mind when rational polypharmacy is deemed necessary in certain clinical situations.

Antidepressant agents and suicide death among US Department of Veterans Affairs patients in depression treatment (6).

This is a retrospective cohort study with a period of follow up of five years that looked at the risk of suicide of people with depression on anti-depressants. They assessed associations between suicide death and treatment with the 7 most commonly used antidepressants in a US national sample of Department of Veterans Affairs patients in depression treatment. Multiple analytic strategies were used to address potential selection biases. Department of Veterans Affairs patients with depression diagnoses and new antidepressant starts between April 1, 1999, and September 30, 2004 (N = 502,179) were included. Conventional Cox regression models, Cox models with inverse probability of treatment weighting, propensity-stratified Cox models, marginal structural models (MSM), and instrumental variable analyses were used to examine relationships between suicide and exposure to bupropion, citalopram, fluoxetine, mirtazapine, paroxetine, sertraline, and venlafaxine. Crude suicide rates varied from 88 to 247 per 100,000 person-years across antidepressant agents. The highest rate per 100 000 person-years was among those prescribed mirtazapine (247, 95% CI 138 to 407), followed by venlafaxine (195), paroxetine (180),

citalopram (165), sertraline (110), fluoxetine (102) and bupropion (88).

Most antidepressants did not differ in their risk for suicide death. However, across several analytic approaches, although not instrumental variable analyses, fluoxetine and sertraline had lower risks of suicide death than paroxetine. These findings are congruent with the Food and Drug Administration meta-analysis of randomized controlled trials reporting lower risks for "suicidality" for sertraline and a trend toward lower risks with fluoxetine than for other antidepressants. Nevertheless, divergence in findings by analytic approach suggests caution when interpreting results.

Shehan Williams Senior Lecturer,
Department of Psychiatry, Faculty of Medicine,
University of Kelaniya, Sri Lanka
Thilini Rajapakse Senior Lecturer,
Department of Psychiatry, Faculty of Medicine,
University of Peradeniya, Sri Lanka

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