Second-generation antipsychotics in major depressive disorder: update and clinical perspective
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CRD summary
The authors concluded that second-generation antipsychotic monotherapy and adjunctive therapy both showed greater efficacy in the treatment of major depressive disorder than placebo. The conclusion represented the evidence presented, but the limited search, small number of studies, lack of study quality assessment and lack of reporting on review processes made its reliability unclear.

Authors' objectives
To evaluate the efficacy and safety of second-generation antipsychotics (SGAs) as monotherapy or adjunctive therapy for nonpsychotic major depressive disorder (MDD) in adults.

Searching
PubMed was searched from 1 January 1966 to 1 June 2010 for articles published in English. Search terms were reported. References lists of identified articles were searched.

Study selection
Randomised double-blind controlled trials that enrolled at least 40 adult (≥18 years old) patients with nonpsychotic MDD were eligible for inclusion in the review. Trials on bipolar disorder, schizophrenia, schizoaffective disorder or psychotic depression were excluded. Outcomes of interest were change from baseline to endpoint in the severity of depressive symptoms, remission rates and the number needed to treat (NNT) for response (defined as ≥50% reduction in depressive symptom severity). Safety was measured by the withdrawal rate due to adverse events.

In included trials SGA monotherapy included quetiapine (extended release formulation 50mg to 300mg per day), sulpiride (150mg to 300mg per day) and amisulpride (50mg per day). Comparators were placebo or an antidepressant. SGAs quetiapine (normal formulation 200mg to 600mg per day, extended release 150mg to 300mg), aripiprazole (2mg to 20mg per day), olanzapine (6mg to 18mg per day), olanzapine-fluoxetine combination (6mg, 12mg or 18mg olanzapine combined with 50mg fluoxetine) and risperidone (0.25mg to 3mg per day) were used as adjunctive therapy to antidepressants, which were mainly selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs). Most studies of monotherapy included patients with single or recurrent episodes of MDD. Most studies of adjunctive therapy included patients with treatment resistant depression; definition of treatment resistance varied between studies. Most studies measured severity of depression using the Montgomery-Asberg Depression Rating Scale (MADRS). Study duration ranged from six to 42 weeks; most were six or eight weeks.

The authors did not state how many reviewers performed study selection.

Assessment of study quality
The authors did not state whether study quality was assessed.

Data extraction
Data were extracted to calculate change from baseline to endpoint.

The authors did not state how many reviewers performed data extraction

Methods of synthesis
The authors presented the results in a narrative synthesis. Study details and results were presented in a table.

Results of the review
Eighteen studies were included in the review. Sample size ranged from 58 to 1,293 patients. Six studies evaluated SGAs as monotherapy and 12 studies evaluated SGAs as adjunctive therapy.
**Quetiapine monotherapy:** Two eight-week placebo-controlled studies each found a statistically significant greater mean change in MADRS total score from baseline to endpoint with 50mg (mean change from baseline -13.6, p<0.05 versus placebo), 150mg (-14.8, p<0.01) and 300mg (-15.3, p<0.01) of quetiapine extended release compared with placebo.

**Sulpride and amisulpride monotherapy:** One study found a statistically significant greater mean change in the 21-item Hamilton Depression Rating Scale with 150mg to 300mg sulpride compared with placebo (-10 versus -8, p<0.01). One study for amisulpride found a statistically significant greater mean change in MADRS with 50mg amisulpride compared with placebo (-12.7 versus -7.6, p<0.01) and with 100mg imipramine compared with placebo (-12.2 versus -7.6, p<0.05).

Results for other outcomes and for studies without placebo groups were reported.

**Quetiapine adjunctive therapy:** One study in treatment-resistant depressed patients found a statistically significant greater mean change in MADRS total score with 150mg and 300mg extended release quetiapine combined with antidepressants compared with placebo combined with antidepressants (-15.3/-14.9 versus -12.2, p<0.01). A second study found a statistically significant greater mean change in MADRS total score with 300mg extended release quetiapine combined with antidepressants compared with placebo combined with antidepressants (-14.7 versus -11.7, p<0.01), but found no difference between 150mg extended release quetiapine combined with antidepressants compared with placebo combined with antidepressants.

**Aripiprazole adjunctive therapy:** Three studies all found statistically significant greater mean change in MADRS total score from baseline to endpoint with 2mg to 20mg aripiprazole combined with SSRIs/SNRIs compared with placebo combined with SSRIs/SNRIs (-10.1 versus -6.4, p<0.01, -8.5 versus -5.7, p<0.01 and -8.8 versus -5.8, p<0.01)

**Olanzapine in combination with fluoxetine:** One study of olanzapine in combination with fluoxetine showed a statistically significant greater mean change in MADRS total score from baseline to endpoint compared with olanzapine alone or fluoxetine alone (-12.6 versus -8.9/-9.2, p<0.01). One RCT that compared olanzapine in combination with fluoxetine to venlafaxine and one study that compared olanzapine in combination with fluoxetine with nortriptyline found greater mean change in MADRS total score in the course of the trials, but no difference by the endpoints.

**Risperidone:** One study found a statistically significant greater mean change in the 17-item Hamilton Depression Rating Scale with risperidone 1mg to 2mg combined with antidepressants compared with placebo combined with antidepressants (-10.8 versus -8.2, p<0.01)

Results for other outcomes were reported.

Safety/withdrawal due to adverse events was one- to three-fold higher with SGA than with placebo. Discontinuations were dose related. This was especially so in quetiapine trials, where patients who took lower doses withdrew less frequently. The most common events for withdrawal were sedation/somnolence (quetiapine, aripiprazole, risperidone, sulpride), akathisia/restlessness (aripiprazole) and weight gain/increased appetite (olanzapine-fluoxetine combination, risperidone).

**Authors’ conclusions**
Second-generation antipsychotic monotherapy and adjunctive therapy both showed greater efficacy in the treatment of major depressive disorder than placebo.

**CRD commentary**
The review addressed a clear research question and was supported by adequate inclusion criteria. The search was limited to studies published in English and only one database was searched, so some relevant studies may have been missed. The authors stated that only randomised controlled trials were eligible for inclusion in the review, but there was no formal assessment of study quality was so the reliability of the evidence presented was unclear.

Heterogeneity between the studies made a narrative synthesis appropriate. Individual study details were provided, but there were discrepancies between the text and the table. The authors did not state how the review processes were performed, so it was unclear whether these could have been subject to reviewer error or bias.
The authors’ conclusion represented the evidence presented, but the limited search, small number of studies, lack of study quality assessment and lack of reporting on review processes made its reliability unclear.

**Implications of the review for practice and research**

**Practice:** The authors stated that when prescribing SGAs, clinicians should tailor the pharmacologic approach based on underlying psychiatric and medical comorbidities, side effect burden and patient preference. Clinicians should routinely monitor for cardio-metabolic side effects and extrapyramidal symptoms during SGA therapy.

**Research:** The authors did not state any implications for research.

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