

THERAPEUTICS INITIATIVE

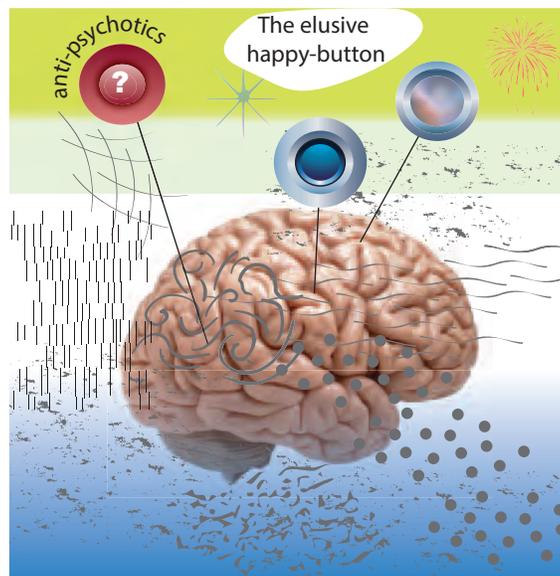
Evidence Based Drug Therapy

Antipsychotics should not be used for non-psychotic depression

This Letter reviews clinical evidence for use of antipsychotics for depression. In Canada, two antipsychotic drugs are approved to treat major depressive disorder (MDD) that is not responsive to other treatment. Quetiapine (Seroquel XR) is approved as monotherapy or in combination with conventional antidepressants for symptomatic relief of MDD “when currently available approved antidepressant drugs have failed”.¹ Aripiprazole (Abilify) is approved only for adjunctive treatment of adults with “inadequate response to prior antidepressant treatments during the current episode”.² Olanzapine, risperidone, ziprasidone, and amisulpride (not available in Canada) have also been evaluated in randomized trials for MDD. **This Letter focuses on quetiapine because it is the most studied antipsychotic in this setting.**

Significant persistent depression that impairs quality of life and affects work, social and family functioning is called MDD. At its worst, it can lead to suicide. **The lifetime prevalence of MDD has been estimated in a systematic review at 6.7 per 100 people.**³ Goals of therapy include amelioration of suffering, suicide prevention and restoration of normal functioning. Maintaining employment, positive social interactions and healthy lifestyle are obvious therapeutic targets, but avoiding drug-induced illness and any deleterious effects are equally important. Clinical trials are typically short, with the only measure of effect being symptom-based depression-rating scales.

Drug treatment of depression dates back to 1957, when Swiss psychiatrist Roland Kuhn claimed that imipramine improved severe depression dramatically and rapidly in hospitalized patients.⁴ The ensuing search for drugs with similar effects led to a number of classes of antidepressant drugs: tricyclics, heterocyclics, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors and others. However, despite widespread use, antidepressants are only marginally better than placebo for all degrees of depression.⁵⁻⁸ Beneficial effects are not dose-dependent.⁹ Older antipsychotics, e.g. chlorpromazine, haloperidol, loxapine, etc. are rarely prescribed for depression, and then only for psychotic symptoms. The newer antipsychotics are also dopamine antagonists and not devoid of their predecessors’ adverse effects.¹⁰



Pharmacology

The marketing label “atypical (second generation) antipsychotic” camouflages properties shared with older antipsychotics. With the exception of clozapine, all antipsychotics block dopamine (D2) receptors, cause extrapyramidal symptoms and signs, tardive dyskinesia and elevate plasma prolactin. The parent drugs or their active metabolites also antagonize serotonin, histamine and alpha-receptors. Quetiapine’s active metabolite, norquetiapine, blocks muscarinic cholinergic receptors, causing dry mouth and other anticholinergic effects.¹

Drugs of this “class” can induce postural hypotension by blocking alpha receptors. They also cause weight gain, diabetes and hypercholesterolemia. Risperidone, quetiapine and aripiprazole increase mortality when used for behaviour control in dementia.^{1,2,11}

Most use of these antipsychotics worldwide is not for schizophrenia, and much is for “off-label” or unapproved conditions.¹² All antipsychotics can impair alertness, concentration and thinking, often in a dose-dependent manner.

Cochrane Systematic Review

The 2012 Cochrane review¹² of “second generation” antipsychotics for MDD and dysthymia in outpatients identified 28 studies using 5 drugs (amisulpride, aripiprazole, olanzapine, quetiapine and risperidone). The trials were short; 22 were 12 weeks or less in duration. Outcomes assessed were typically “response” or “remission” derived from scores on the Hamilton Depression Rating Scale (HAM-D) or the Montgomery Asberg Depression Rating Scale (MADRS). The authors concluded there is “limited” or contradictory evi-

dence either for solo antipsychotic therapy or augmentation therapy and that generally, treatment with second-generation antipsychotic drugs was associated with worse tolerability, mainly due to sedation and weight gain. This review has not yet been updated to include all trials for which results are now available.

Quetiapine for MDD

We identified 10 double blind randomised control trials (RCTs) of quetiapine (25-600 mg/d) for MDD¹³⁻²² and 1 RCT for MDD with “comorbid fibromyalgia”²³. In 9 RCTs, quetiapine monotherapy was compared only with placebo, whereas 2 trials also compared it to duloxetine and escitalopram.^{16,22} In 4 RCTs, quetiapine (or placebo) was added to standard antidepressants. Most trials were of 6-8 weeks duration, and only one was longer than 9 weeks. Astra Zeneca sponsored all trials, and designed, ran and analysed the 8 largest trials. One RCT involved 237 sites, most sites recruiting very few patients.¹⁸

All trials experienced large dropout rates due to adverse effects, higher for quetiapine than placebo. The high incidence of adverse effects made loss of blinding very likely.¹⁴ Selection bias due to early loss of participants, high risk of bias due to loss of blinding, plus other biases made meta-analysis inappropriate, as it would only compound the bias. Quetiapine typically reduced depression scores (vs. placebo) by about 2-3/60 points (MADRS) or 4-5/50 points (HAM-D). “Response” or “remission” rates, defined as arbitrary reductions in rating scores, favoured quetiapine by about 10% absolute improvement. These small effects are not clinically significant⁸ and could easily occur due to biases present in the trials. Furthermore the improvement in the rating scores could be explained by the sedating effect leading to improved sleep. Quetiapine was not better than duloxetine¹⁶ or escitalopram²², and adding quetiapine to fluoxetine in one RCT did not improve any outcomes.¹⁴ The lack of long-term trials has resulted in Astra Zeneca advising physicians in the Product

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For a complete list of references go to: www.ti.ubc.ca/letter95

Monograph to use quetiapine for the shortest time that is clinically indicated: “When lengthier treatment is indicated, the physician must periodically re-evaluate the long-term usefulness of the drug for the individual patient keeping in mind the long-term risks.”¹

Harms caused by quetiapine include somnolence or sedation in up to 69% of patients, and anticholinergic effects in up to 57%. Adverse effects include weight gain, diabetes, extrapyramidal symptoms, dizziness and fatigue. There is no evidence that quetiapine reduces suicidality in MDD and effects on cognition were not reported. A single trial took depressed patients who tolerated and were stabilized on quetiapine and randomized them to continuing quetiapine or placebo. This trial demonstrated that in the first 14 days, treatment discontinuation symptoms were increased in the placebo group as compared to quetiapine. The symptoms included headache, insomnia, sweating, chills, nausea and diarrhea.¹⁸ Long-term harms are unstudied, however quetiapine carries significant long-term risks associated with weight gain, diabetes and anticholinergic effects.²⁴

Other antipsychotics

Trials of aripiprazole and other antipsychotics studied fewer patients, but showed similar results and are limited by the same methodological biases.¹²

Conclusions

- Quetiapine has not been shown to improve overall function as monotherapy or when added to an antidepressant for unresponsive major depressive disorder.
- There is insufficient scientific evidence that quetiapine reduces any depression-rating scores. Quetiapine causes sedation, which improves sleep.
- **Biased trial methodology exaggerates any apparent benefits, and minimizes disadvantages such as weight gain or other long-term harms.**
- Adverse effects include frequent sedation, anticholinergic effects and weight gain. Long-term harms are unknown, but likely include elevated cardiovascular risk related to weight gain and metabolic changes.
- Evidence for other antipsychotics for depression is **not** better.

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