What are first and second-generation antipsychotics?

First-generation ‘typical’ antipsychotics are an older class of antipsychotic than second-generation ‘atypical’ antipsychotics. First-generation antipsychotics are used primarily to treat positive symptoms such as hallucinations and delusions. Second-generation antipsychotics are also effective for the positive symptoms of schizophrenia, and it is sometimes claimed that they are more effective than first-generation antipsychotics in treating the negative symptoms of schizophrenia. Negative symptoms include a lack of ordinary mental activities such as emotional expression, social engagement, thinking and motivation. High-potency first-generation antipsychotics usually have high affinity for the dopamine receptor and therefore induce extrapyramidal side effects by the blockade of these dopamine receptors. Extrapyramidal side effects include dyskinesias (repetitive, involuntary, and purposeless body or facial movements), Parkinsonism (cogwheel muscle rigidity, pill-rolling tremor and reduced or slowed movements); akathisia (motor restlessness, especially in the legs, and resembling agitation), and dystonias (muscle contractions causing unusual twisting of parts of the body, most often in the neck). Second-generation antipsychotics generally have a lower affinity for the dopamine receptor and also block serotonin receptors, so may be associated with lower risk of these side effects.

What is the evidence for first versus second-generation antipsychotics?

Efficacy

Moderate to high quality evidence suggests a small effect of improved overall symptoms with second-generation antipsychotics, particularly olanzapine, amisulpride, and risperidone, compared to first-generation antipsychotics, particularly high-dose haloperidol (>12mg/day), which is not as effective as lower doses. There is a small effect of less all-cause study discontinuation with olanzapine, risperidone, or amisulpride compared to haloperidol in the short-term. Moderate quality evidence suggests only olanzapine may result in less long-term discontinuation due to drug intolerability or inefficiency. Moderate to high quality evidence suggests olanzapine and risperidone may improve cognition more effectively than haloperidol, and moderate quality evidence suggests amisulpride, clozapine and sertindole may improve quality of life more effectively than first-generation antipsychotics in general.

Side effects

Moderate quality evidence suggests a medium-sized effect of less extrapyramidal side effects with second-generation antipsychotics, particularly olanzapine and risperadone, than with haloperidol. Clozapine, olanzapine, and risperidone may also produce fewer extrapyramidal side effects when compared to low-potency first-generation antipsychotics. Moderate quality evidence suggests clozapine, quetiapine, and zotepine may be more sedating, and aripiprazole less sedating, than haloperidol. Compared with low-potency first-generation antipsychotics, only clozapine may be more sedating. Moderate to high quality evidence suggests low use of benzodiazepines, anticholinergic medications, and beta-blockers with olanzapine than with haloperidol. Moderate quality evidence suggests amisulpride, clozapine, olanzapine, quetiapine, risperidone, sertindole, and zotepine may be associated with more weight gain than haloperidol, with no differences when compared to low-potency first-generation antipsychotics. Moderate quality evidence suggests more cholesterol change with olanzapine than haloperidol, and more tryglyceride change with amisulpride than haloperidol.

For more information see the technical table

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