Newer antipsychotics for maintenance treatment of bipolar disorder

SBU ALERT REPORT | EARLY ASSESSMENT OF NEW HEALTH TECHNOLOGIES

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Summary and conclusions

Bipolar disorder generally requires lifelong medication. Today, second generation antipsychotics (SGA) are sometimes used for maintenance treatment, either as monotherapy or in combination with lithium or other mood stabilisers.

SGA is prescribed in relatively high numbers of cases of bipolar disorder. According to The Swedish National Quality Register for Bipolar Disorder, a combination of SGA and mood stabilisers was prescribed in 2014 for 20% of all patients registered for follow-up, but SGA was prescribed as monotherapy for only a very small percent.

The purpose of this project is to evaluate the benefits and risks of maintenance treatment of bipolar disorder with SGA (of at least six months' duration), with special reference to medical, ethical and health economic perspectives.

Conclusions

In the long-term

- As there are no studies of more than two years' duration, it is not possible to assess the long-term benefits and risks of SGA for maintenance treatment of bipolar disorder.

In the short-term

Bipolar disorder type I

- For patients with bipolar disorder type I who have responded to aripiprazole, quetiapine or ziprasidone as adjunct to mood stabilisers in the manic acute phase, the risk of relapse is reduced when these drugs are used during maintenance.
- There is insufficient quality of studies in order to evaluate the effects of maintenance treatment using olanzapine and risperidone.
- In some patients, quetiapine could be an alternative to lithium for reducing the risks of relapse and treatment discontinuation. While the risk of serious side effects must be considered, to date no long term studies are available.
- Weight gain is frequently associated with all of the SGA investigated. Aripiprazole causes slightly more tremors and tingling in the legs than mood stabilisers. Olanzapine and quetiapine are associated with more daytime drowsiness and less insomnia than mood stabilisers. It is a requirement that side effects are reported to the Medical Products Agency and should be followed up in quality registers.
- Drugs which prevent relapses have the potential to redeem much of their cost by reducing the healthcare costs associated with relapses. Fewer relapses improve quality of life and survival.

Bipolar disorder type II

- In the absence of studies, no conclusions can be drawn about the effect of SGA as maintenance treatment for bipolar disorder type II.

Economic aspects

The annual cost per patient of medication with SGA is around SEK 700 for quetiapin and around SEK 16 000 for aripiprazol. The patent for aripiprazol expired recently and the price will probably drop as generic alternatives become commercially available. However, whether SGA treatment can be considered to be good use of resources, compared with either mood-stabilising pharmaceuticals alone or in conjunction with SGA, depends primarily on the effectiveness of SGA drugs in reducing the number of manic and depressive relapses. Fewer relapses are associated with better quality of life, increased survival rates and reduced societal costs. SGA which are effective in preventing relapses have the potential to save a considerable amount of the cost of the medication

by reducing the health and medical costs associated with relapse. Assessment of the cost-effectiveness of the methods should however, also take into account the influence of the medication on costs and quality of life and the consequences of side effects.

Ethical aspects

Only limited information is available about the long-term effects and side effects of antipsychotic drugs. It is therefore important that currently available information about side effects is factual and objective and that the psychiatrist, in consultation with the patient, assesses whether the risk of side effects is outweighed by the anticipated benefits of the treatment. Periods of illness cause a reduction in functional level and quality of life and can lead to compulsory admission for institutional care, which is a major uppheaval for both the patient and close relatives. Because of the sporadic nature of the illness, conflict may arise between patient and healthcare personnel as to the need for maintenance treatment. This is particularly obvious under periods of neutral or slightly elevated moods when the patient feels well, but his/her decision-making capacity may be impaired. Healthcare professionals may then be tempted "in the best interests of the patient" to try to force or at least to influence the patient to continue medication against their will. This could then be perceived as a conflict between the obligation under the Health and Medical Services Act for the health services to achieve good health and quality of life for the patient and the patient's rights, according to the legislation, requiring informed consent for treatment.

Patient benefit, Bipolar disorder type I

Effect measure	Action	Comparison	Result	Number of participants/ studies	Scientific data[1]
SGA as supplemental treatment (+ Lithium or Valproate) (for treatment of 6–24 months)					
Discontinuation	Aripiprazole	Placebo	Aripriprazole not better than placebo	688/2	⊕⊕○○
Relapse all	Aripiprazole	Placebo	Aripriprazole better than placebo	688/2	⊕⊕⊕○
Relapse mania	Aripiprazole	Placebo	Aripriprazole better than placebo	688/2	⊕⊕⊕○
Relapse depression	Aripiprazole	Placebo	Aripriprazole not better than placebo	688/2	⊕⊕○○
Discontinuation	Quetiapine	Placebo	Quetiapine better than placebo	1326/2	⊕⊕○○
Relapse all	Quetiapine	Placebo	Quetiapine better than placebo	1326/2	⊕⊕⊕○
Relapse mania	Quetiapine	Placebo	Quetiapine better than placebo	1326/2	⊕⊕⊕○
Relapse depression	Quetiapine	Placebo	Quetiapine better than placebo	1326/2	⊕⊕⊕○
Discontinuation	Ziprasidone	Placebo	Ziprasidone better than placebo	238/1	⊕⊕○○
Relapse all	Ziprasidone	Placebo	Ziprasidone better than placebo	238/1	⊕⊕○○
SGA as monotherapy (for treatment of 12–24 months)					
Discontinuation	Quetiapine	Lithium	Quetiapine better than Lithium	768/1	⊕⊕○○
Relapse all	Quetiapine	Lithium	Quetiapine better than Lithium	768/1	⊕⊕○○
Relapse depression	Quetiapine	Lithium	Quetiapine better than Lithium	768/1	⊕⊕○○
Relapse depression	Olanzapine	Lithium/ Valproate	Olanzapine not better than Lithium/Valproate	682/2	⊕⊕○○

Bipolar disorder type I

- There is insufficient scientific data to assess the effect of olanzapine transdermal as adjuvant therapy to lithium or valproate during maintenance treatment of bipolar disorder type I, measured as discontinuation and relapse.
- There is insufficient scientific data to compare olanzapine treatment of bipolar disorder type 1 with lithium and valproate, in terms of discontinuation and relapse, independent of polarity and relapse into mania.
- There is insufficient scientific data to compare the effects of quetiapine and lithium for treatment of bipolar disorder type I, in terms of relapse into mania.

Bipolar disorder type II

- Because of the lack of studies, there is insufficient scientific data to assess the effect of SGA during maintenance treatment of bipolar disorder type II.

[1] *Where appropriate, deductions have been made on the grounds of study quality, conformity or precision (see GRADE tables 1–3 in the report)*

For experts and scientific reviewers, see the full report, www.sbu.se/201502