DANISH HEALTH AUTHORITY

NATIONAL CLINICAL GUIDELINE FOR THE PHARMACOLOGICAL TREATMENT OF BIPOLAR DISORDER – ADD-ON MAINTENANCE TREATMENT FOLLOWING DEPRESSION

Quick guide

Maintenance treatment of adult patients with bipolar disorder, type I – with a combination of two drugs	
Whether to offer add-on treatment with an antipsychotic, an anticonvulsant or an antidepressant to adults with bipolar disorder in remission following a depressive episode, despite maintenance treatment with lithium	
↑	Consider continuing maintenance treatment with quetiapine or lamotrigine (if the drug had an effect on the preceding acute depressive episode) as an add-on to ongoing lithium treatment.(⊕⊕○○)
↓	Maintenance treatment with aripiprazole, olanzapine*, oxcarbazepine, paliperidone, risperidone, valproate* and ziprasidone should only be *continued* as an add-on to ongoing lithium treatment in special cases. There is no documentation of a preventive effect on depression. (⊕⊕○○)
√	It is good practice to *initiate* maintenance treatment with quetiapine or lamotrigine, rather than aripiprazole, olanzapine*, oxcarbazepine, paliperidone, risperidone, valproate* or ziprasidone, as an add-on to ongoing lithium treatment.
√	It is not good practice to *initiate or continue* maintenance treatment with a typical antipsychotic as an add-on to ongoing lithium treatment. Based on clinical experience, these drugs may cause depression in patients with bipolar disorder. Their use for long-term treatment entails a documented risk of onset of extrapyramidal adverse reactions, including tardive dyskinesias.
√	It is not good practice to *initiate* maintenance treatment with an antidepressant as an add-on to ongoing lithium treatment. This is due to the uncertainty of the beneficial effect. Also, it is being debated whether treatment with antidepressants increases the risk of developing a manic episode.
√	It is not good practice to *continue* maintenance treatment with an antidepressant as an add-on to ongoing lithium treatment. This applies unless there was an effect on the preceding acute depression, where acute treatment with, e.g., lamotrigine or quetiapine was insufficient or not possible, and unless there are no previous signs of or suspected destabilising effect of antidepressants (such as the development of mixed states or rapid cycling). Additional caution is recommended in case of previous depressive episodes with manic symptoms.
√	It is not good practice to *initiate or continue* maintenance treatment with other antipsychotics or anticonvulsants, rather than the above-mentioned drugs, as an add-on to ongoing lithium treatment. This applies to bipolar disorder in remission following a depressive episode.

* Please note: Special circumstances for olanzapine and valproate

Whether to offer add-on treatment with an anticonvulsant, an antidepressant or lithium to adults with bipolar disorder in remission following a depressive episode despite maintenance treatment with an atypical antipsychotic	
↑	Consider *initiating* maintenance treatment with lithium, rather than lamotrigine or valproate, as an add-on to ongoing treatment with an atypical antipsychotic. (⊕○○○)
↑	Consider *continuing* maintenance treatment with lithium or lamotrigine (if the drug had an effect on the preceding acute depressive episode), rather than valproate*, as an add-on to ongoing treatment with an atypical antipsychotic.(⊕○○○)
↓	Maintenance treatment with valproate* should only be *continued* as an add-on to ongoing treatment with an atypical antipsychotic in special cases. There is no documentation of a preventive effect on depression. (⊕○○○)
√	It is not good practice to *initiate* maintenance treatment with an antidepressant as an add-on to ongoing treatment with an atypical antipsychotic. The beneficial effect is uncertain, and it is being debated whether treatment with antidepressants increases the risk of developing a manic episode.
√	It is not good practice to *continue* maintenance treatment with an antidepressant as an add-on to ongoing treatment with an atypical antipsychotic. This applies unless there was an effect on the preceding acute depression, where acute treatment with, e.g., lamotrigine or lithium was insufficient or not possible, and unless there are no previous signs of or suspected destabilising effect of antidepressants (such as the development of mixed states or rapid cycling). Additional caution is recommended in case of previous depressive episodes with manic symptoms.
√	It is not good practice to combine two antipsychotics as a maintenance treatment as an add-on to ongoing treatment with an atypical antipsychotic. This is due to the uncertainty of the beneficial effect and the fact that it involves a risk of interactions and unacceptable adverse effects.
√	It is not good practice to *initiate or continue* maintenance treatment with other anticonvulsants than lamotrigine and valproate as an add-on to ongoing treatment with an atypical antipsychotic. This applies to bipolar disorder in remission following a depressive episode.

* Please note: Special circumstances for valproate

Whether to offer add-on treatment with an antidepressant, another anticonvulsant, lithium or an atypical antipsychotic to adults with bipolar disorder in remission following a depressive episode despite maintenance treatment with an anticonvulsant	
↑	Consider *initiating* maintenance treatment with lithium, rather than lamotrigine, olanzapine*, quetiapine or valproate*, as an add-on to ongoing treatment with an anticonvulsant.(⊕○○○)
↑	Consider *continuing* maintenance treatment with lamotrigine, lithium or quetiapine (if the drug had an effect on the preceding acute depression) as an add-on to ongoing treatment with an anticonvulsant. The Danish Health Authority recommends for lamotrigine, lithium or quetiapine and against aripiprazole, olanzapine*, oxcarbazepine, paliperidone, risperidone, valproate* and ziprasidone. (⊕○○○)
↓	Maintenance treatment with aripiprazole, olanzapine*, oxcarbazepine, paliperidone, risperidone, valproate* and ziprasidone should only be *continued* as an add-on to ongoing treatment with an anticonvulsant in special cases. There is no documentation of a preventive effect on depression. (⊕○○○)
√	It is not good practice to *initiate* maintenance treatment with an antidepressant as an add-on to ongoing treatment with an anticonvulsant. This is due to the uncertainty of the beneficial effect. Also, it is being debated whether treatment with antidepressants increases the risk of developing a manic episode.
√	It is not good practice to *continue* maintenance treatment with an antidepressant as an add-on to ongoing treatment with an anticonvulsant. This applies unless there was an effect on the preceding acute depression, where acute treatment with, e.g., lithium or quetiapine was insufficient or not possible, and unless there are no previous signs of or suspected destabilising effect of antidepressants (such as the development of mixed states or rapid cycling). Additionally, based on the previous course, it should be deemed likely that an effective mania prophylaxis has been established, i.e. that the patient has had no manic episodes during the primary treatment with an anticonvulsant. Additional caution is recommended in case of previous depressive episodes with manic symptoms.
√	It is not good practice to *initiate or continue* maintenance treatment with a typical antipsychotic as an add-on to ongoing treatment with an anticonvulsant. Add-on antipsychotics for long-term treatment may entail a risk of developing a depressive episode and a risk of onset of extrapyramidal adverse reactions, including tardive dyskinesias.
√	It is not good practice to initiate or continue maintenance treatment with other antipsychotics or anticonvulsants, rather than any of the above-mentioned drugs, as an add-on to ongoing treatment with an anticonvulsant. This applies to preventive treatment of bipolar disorder in remission following a depressive episode.

* Please note: Special circumstances for olanzapine and valproate

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About the quick guide

This quick guide contains the key recommendations from the national clinical guideline for the pharmacological treatment of bipolar disorder.
The guideline was prepared by the DHA.

The national clinical guideline for the pharmacological treatment of bipolar disorder focuses on maintenance treatment of adults with bipolar disorder, type I, with a combination of two drugs. The guideline recommendations distinguish between *continuing* treatment administered for the preceding acute depressive episode and *initiating* treatment with a product that wasn't administered for the preceding acute depressive episode.

The guideline contains recommendations for selected parts of the field only. Therefore, the guideline must be seen alongside the other guidelines, recommendations, process descriptions etc. in this field.

The recommendations are preceded by the following indications of their strength:

↑↑= a strong recommendation for
↓↓ = a strong recommendation against
↑ = a weak/conditional recommendation for
↓= a weak/conditional recommendation against

The symbol (√) stands for good practice. This symbol is used in case of lack of evidence, when the DHA wants to emphasise particular aspects of the established clinical practice.

The recommendations are followed by the following symbols which indicate the strength of the underlying evidence – from high to very low:

(⊕⊕⊕⊕) = high
(⊕⊕⊕◯) = moderate
(⊕⊕◯◯) = low
(⊕◯◯◯) = very low

In case of lack of evidence, a recommendation is not followed by a symbol. This applies to recommendations based on good practice.

Further information at sundhedsstyrelsen.dk
At sundhedsstyrelsen.dk, a full-length version of the national clinical guideline is available, including a detailed review of the underlying evidence for the recommendations.

About the national clinical guidelines
The national clinical guideline is one of 50 national clinical guidelines (NCGs) to be prepared by the DHA during the period 2013-2016.

Further information about the choice of subjects, method and process is available at sundhedsstyrelsen.dk.