National clinical recommendations for Combination Therapy with Antipsychotics and ADHD Medication for Patients with Primary Psychotic Disorders

Quick guide

ADHD medication as add-on to antipsychotic treatment in patients with schizophrenia or other primary psychotic disorders and disabling attention deficits

Do not use methylphenidate, dexamphetamine, or lisdexamphetamine as add-on to antipsychotic treatment in patients (from 12 years and up) with stable schizophrenia or other primary psychotic disorders and disabling attention deficits, as these drugs may potentially have serious harmful effects.

Strong recommendation against

See the rationale under the next recommendation

Only consider using atomoxetine as add-on to antipsychotic treatment in patients (from 12 years and up) with stable schizophrenia or other primary psychotic disorders and disabling attention deficits after careful consideration, as the beneficial effect is small. For children/adolescents and adults, guanfacine is an alternative treatment. For adults, modafinil is an alternative treatment.

Weak recommendation against

Rationale for the recommendation

To be considered for ADHD medication as add-on, the patient must be clinically stable and well-managed for the primary psychotic disorder. Stability means the absence of significant fluctuations in symptom and functional levels, including no recent hospitalizations. Well-managed refers to significant relief from psychotic symptoms due to appropriate antipsychotic treatment. Full remission of psychotic symptoms is not required.

Atomoxetine is the first-line treatment. Guanfacine is an alternative treatment (second to atomoxetine) for children/adolescents and adults, because its efficacy in combination with antipsychotics is highly uncertain. Modafinil is an alternative treatment (secondary to atomoxetine and possibly guanfacine) for adults, because there is no experience with using modafinil in Denmark to treat attention disorders in general, and its use has been linked to isolated cases of severe skin manifestations. For this reason, modafinil should not be prescribed for children.

Since the balance between beneficial and harmful effects, based on the evidence reviewed, is not clear, individual clinical factors will determine in which selected patients within the defined target group a trial with atomoxetine (or guanfacine/modafinil) may be relevant. These individual clinical factors will be based on knowledge of the specific patient and the medication, which may include considerations such as the likelihood of adherence to more complex medication regimens, the patient's current life situation, and the support available in their immediate network to support adjunctive treatment.

Patients who have previously been diagnosed with ADHD and have been treated with and tolerated stimulant medications constitute a special group where methylphenidate treatment may be considered if sufficient effect cannot be achieved with atomoxetine (and possibly guanfacine). In such special cases, if one chooses to initiate adjunct treatment with methylphenidate, it should be noted that the product information lists the treatment as contraindicated for patients with psychosis or schizophrenia. However, recent observational studies reviewed during the development of this national clinical recommendation do not confirm the risk of symptom worsening (measured as the risk of psychiatric hospitalization). Other stimulant medications (dexamphetamine and lisdexamfetamine) will rarely be relevant due to their stronger stimulant effect and presumed increased risk of worsening psychosis.

Patients with schizophrenia or other primary psychotic disorders who are not receiving antipsychotic treatment are not covered by this national clinical recommendation, as this population was not included in the evidence base. None of the patients in the evidence base were diagnosed with ADHD/ADD. Disorders in other cognitive domains in addition to attention are also included in this recommendation.

In patients who have not been diagnosed with ADHD/ADD, adjunctive treatment with ADHD medication will be off-label, and the patient should be informed that the treatment is outside the approved indication, and the indication will not be found in the package leaflet. Modafinil is not approved for the treatment of ADHD in Denmark.

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If adjunctive treatment with ADHD medication is chosen, careful monitoring with relevant rating scales should be conducted to ensure that the therapeutic effect outweighs the side effects. Monitoring should assess the intensity of psychotic symptoms (e.g., PANSS or SAPS), psychosocial functioning (e.g., PSP GAPD in children/adolescents), and side effects (e.g., general UKU) before treatment initiation and every two weeks (weekly for stimulant medications) until the target dose is reached and the expected effect of the chosen adjunctive medication has occurred. Thereafter, monitoring should be done monthly (biweekly for stimulant medications) until six months of treatment, and then semi-annually (monthly to bi-monthly for stimulant medications) as long as the treatment continues. Medications can be discontinued without tapering in the event of unacceptable side effects (including worsening psychosis), though gradual tapering is preferred if discontinuation is due to lack of efficacy. Specifically for guanfacine, tapering is recommended before discontinuation due to the risk of increased heart rate and blood pressure.

It is the responsibility of a doctor working in a psychiatric or child and adolescent psychiatric setting to initiate treatment with ADHD medication as add-on to antipsychotic treatment. The prescription must also follow the guidelines in the Danish Health Authority's guidance on pharmacological treatment of adults with mental and behavioral disorders and, for stimulant medications, the guidance on prescribing dependency-inducing medications.

Rationale for the recommendations

A total of 11 randomized studies were found that examined the effects of treatment with atomoxetine or modafinil, while only a single study was identified that assessed the effects and side effects of other central stimulant treatments, specifically lisdexamfetamine. This single study was not designed to address the current PICO question, and thus, its results cannot be considered reliable. As a result, the evidence base lacks controlled data on treatment with methylphenidate, dexamphetamine, and lisdexamfetamine. For atomoxetine/modafinil, no data were available for the critical outcome measure of ADHD symptoms, but data were available for the critical outcome measure of worsening of psychotic symptoms, where no difference was found between groups, indicating no evidence for worsening of psychotic symptoms. Likewise, for the important outcome measures of attention and executive function, there was no difference between groups, though a difference favoring the intervention group was observed for overall symptom level. The confidence in the evidence was very low, but it was assessed that most patients in the target group would accept the treatment if offered. No differences in efficacy or side effects were found between atomoxetine and modafinil, leading them to be assessed together.

The quality of the evidence was rated as low to very low. For guanfacine, one randomized study was identified, showing neither positive nor harmful effects.

Observational evidence from the included registry-based studies did not find an association between treatment with central stimulants and an increased risk of psychiatric hospitalization in patients with psychosis; rather, a trend in the opposite direction was observed. This should not be interpreted as a protective effect of stimulant adjunctive treatment but rather underscores that, in these observational studies, treatment was not associated with an increased risk of psychiatric hospitalization. However, this observational evidence likely carries a substantial risk of bias.

The lack of data on critical outcome measures for atomoxetine/guanfacine/modafinil and the absence of evidence from controlled clinical trials for the classic central stimulants are decisive factors for both the weak and strong recommendations against using ADHD medication as an adjunct to antipsychotic treatment in the defined patient group.

Delimitation

The national clinical guideline provides action-oriented instructions for selected and well-defined clinical issues ("focus points in the patient pathway"). These issues have been prioritized by the expert working group as the areas where it is most important to clarify the evidence. Thus, the national clinical guideline addresses a specific area of treatment efforts. The outcome measures used have been preselected by the working group.

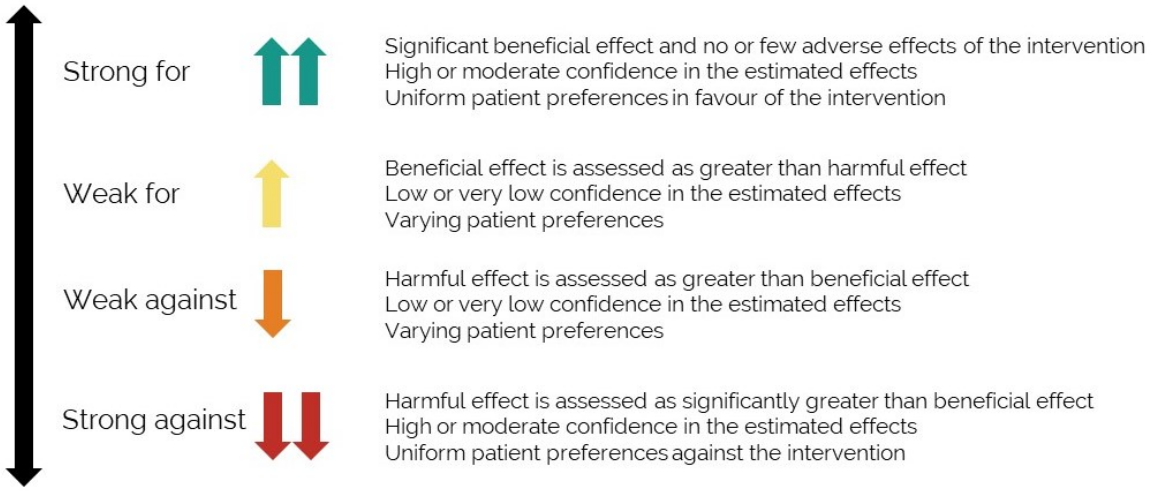
The patient group includes individuals with schizophrenia or another primary psychotic disorder who simultaneously experience impaired cognitive function, particularly related to attention deficits and executive difficulties. Most patients with schizophrenia experience a reduced level of cognitive functioning compared to expected levels; however, this encompasses a wide range of cognitive domains and does not always include attention deficits and executive difficulties. The patient group also includes individuals with a comorbid ADHD disorder.

Attention deficits refer to a reduced ability to maintain sustained focus over time, diminished capacity to exclude irrelevant stimuli, and challenges with switching/divided attention. Executive difficulties refer to reduced abilities in self-regulation (impulse control), planning and organization, initiation, word retrieval, and cognitive flexibility.

Patients with impairments in other cognitive domains in addition to those mentioned above are also covered by this recommendation.

The full version of the national clinical guidelines, including a detailed review of the underlying evidence, can be accessed on the Danish Health Authority's website (www.sst.dk).

What does a weak or strong recommendation mean?



What is a national clinical recommendation?

A national clinical recommendation is delimited to a specific problem in the course of the patient's treatment. Therefore, a national clinical recommendation cannot stand alone, but is complemented and supplemented by other guidelines and treatment guides. This may, for example, be interdisciplinary and intersectoral guidelines for other parts of the course of the patient's treatment or other patient populations, guidelines prepared by societies and professional organisations, as well as regional and municipal guidelines and instructions.

National clinical recommendations are classified as professional advice, which means that the Danish Health Authority recommends that the relevant professionals adhere to the recommendations. The national clinical recommendations are not legally binding,

and a professional assessment in the specific clinical situation will always be of decisive importance to the decision on appropriate and correct healthcare services.

Collaboration

The recommendations have been developed in collaboration with a guideline panel that included representatives from:

- Danish Psychiatric Association
- Danish Child and Adolescent Psychiatry Association
- Danish Society for General Practice
- Danish Multidisciplinary Psychiatric Groups (DMPG)
- Danish Psychological Association
- Alcohol Professional Forum
- Danish Society for Addiction Medicine
- Danish Nursing Society
- Danish Society for Physiotherapy
- Danish Association of Occupational Therapists
- The National Association for Mental Health (SIND)
- ONE OF US
- Danish Patients
- Center for Substance Abuse Research
- Competence Center for Dual Diagnoses
- Youth Alliance