National clinical recommendations for use of minor tranquilizers for short-term symptom relief of newly onset of symptoms of anxiety and distress in adults

Quick guide

Consider benzodiazepine, low-dose quetiapine or pregabalin in preference to other drugs for short-term symptom relief (maximum 4 weeks) of newly onset of symptoms of anxiety and distress in adults where non-pharmacological treatment alone is not effective, possible or relevant.

Weak recommendation for

Patients with severe mental disorders, including psychotic disorders and severe affective disorders such as mania and severe depression as well as dementia and organic delirium, are not covered by the recommendation.

Pharmacological treatment is generally not first-choice treatment for newly onset of symptoms of anxiety and distress. In general, non-pharmacological treatment rather than use of tranquilizers must always be considered.

Benzodiazepines should generally be preferred over quetiapine or pregabalin, as they have been approved for use in anxiety and distress conditions, whereas quetiapine and pregabalin have not been approved. Oxazepam should be preferred over other benzodiazepines as the risk of tolerance, dependence and sedation is lower. If pregabalin or quetiapine has previously been administered with a beneficial effect, it may be considered using this rather than oxazepam.

Treatment with pregabalin and quetiapine for symptoms of anxiety and distress is 'off label'. The patient must here be informed that the treatment falls outside the approved indication and that the indication cannot therefore be found in the package leaflet.

Patients with current or previous abuse of alcohol, medication or other intoxicants, where there is a risk of developing benzodiazepine abuse, can instead be offered treatment with pregabalin or quetiapine. Patients treated with benzodiazepine may develop tolerance as well as physical and psychological dependence if treatment is extended beyond 4 weeks.

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The risk of developing tolerance and dependence in different patient populations is incompletely established for pregabalin and quetiapine, but is assessed to be lower than for benzodiazepine. The Danish Health Authority's guidelines for addictive medicine must be complied with.

The following dosages are recommended as a starting point:

- Oxazepam: 7.5-15 mg, 1-3 times daily. Treatment is commenced with the lowest possible dosage, after which the dose may be increased, depending on efficacy and adverse events.
- Low-dose quetiapine: comprises dosage up to maximum 150 mg quetiapine daily, distributed on doses of 25-50 mg 2-3 times daily. Treatment is commenced with 25-50 mg daily, after which the dose may be increased, depending on efficacy and adverse events.
- Pregabalin: 150-600 mg daily. Treatment is commenced with 150 mg daily, distributed on 2 doses. The dose may be increased to 300 mg daily after 7 days, to 450 mg daily after another 7 days and to a maximum of 600 mg daily after another 7 days, depending on efficacy and adverse events. In patients with known sensitivity to adverse events, a lower start-up dose may be relevant.

For frail elderly people, extra caution should be exercised, and a lower dosage than those recommended above should be used. Frail elderly patients should be monitored closely as there is an increased risk of serious adverse events, including the risk of falls.

When using quetiapine, the QT interval should be checked with an ECG before commencement of treatment. Use of benzodiazepine, quetiapine and pregabalin poses a road safety risk, and a temporary driving prohibition should be issued on commencement of treatment.

After short-term treatment of up to 4 weeks, the medicinal product can usually be discontinued with tapering over a few days. After treatment of longer duration, the dose is slowly tapered over weeks to months, depending on the medicinal product.

Rationale for the recommendation

In formulating the recommendation, it has been emphasised that benzodiazepines, quetiapine and pregabalin having a possible clinically relevant, rapidly onsetting effect on symptoms of anxiety compared to no treatment, while it is uncertain whether there are clinically relevant effects for hydroxyzine, mianserin and agomelatonin. It has also been found important that no certain differences in efficacy on symptoms of anxiety have been observed between benzodiazepine, quetiapine and pregabalin.

Weighed against the beneficial effects of benzodiazepines, quetiapine and pregabalin, it has been found important that it is uncertain whether short-term treatment with benzodiazepine, quetiapine or pregabalin increases the risk of serious adverse events. Furthermore, it has been found important that the recommendation concerns expected short-term use, and that the potential for dependence, abuse and tolerance development is therefore estimated to be lower than in long-term use.

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However, some patients who commence treatment with benzodiazepine, pregabalin and quetiapine continue their treatment for an extended period, and it consequently cannot be excluded that patients commencing short-term treatment may have an increased risk of developing abuse and tolerance in cases where the treatment turns out to be of long duration.

When weighing beneficial effects and adverse event, the guideline panel assesses that the benefits of short-term treatment with benzodiazepines, quetiapine or pregabalin in patients with newly onset of symptoms of anxiety and/or distress outweigh possible adverse events, including the risk of dependence and abuse, although there are uncertainties.

The overall confidence in the evidence is very low. Furthermore, patients are expected to have varying preferences for short-term treatment with benzodiazepines, quetiapine or pregabalin.

Based on these considerations, a weak recommendation is issued for offering short-term treatment with benzodiazepines, quetiapine or pregabalin over other minor tranquilizers to patients with newly onset of symptoms of anxiety and/or distress for whom pharmacological treatment has been found to be indicated.

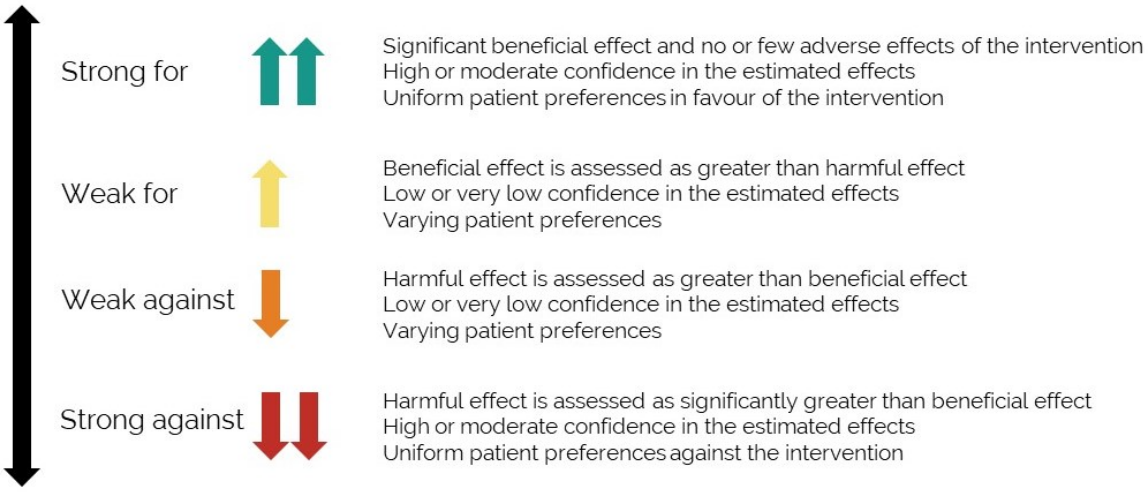
Delimitation

The patient group includes adults with newly onset of symptoms of anxiety and distress with a need for pharmacological treatment with rapidly onsetting effect, where the required pharmacological treatment is expected to be of a short-term duration (maximum 4 weeks). This may apply to patients experiencing a crisis, grief or other strain resulting from illness, death, accident or other stressful life events which, for example, meet the criteria for a diagnosis of acute stress reaction or adjustment disorder, and who present themselves with symptoms of anxiety and distress. This may be both patients with no prior history of mental disorder and patients with mild to moderate depression or anxiety.

Pharmacological treatment need means symptoms of anxiety and distress that affect the patient to such an extent that non-pharmacological treatment alone will not be effective, possible or relevant based on the physician's clinical assessment of the patient's functional level or distress. It must therefore have been clarified that there is an indication for treatment with a minor tranquilizer, which presupposes that non-pharmacological treatment has been tried or considered.

A full-length version of the national clinical recommendations is available at the Danish Health Authority's website (www.sst.dk), including a detailed review of the underlying evidence on which the recommendations are based.

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 drawn up in collaboration with a guideline panel with representatives from:

- Danish College of General Practitioners
- Danish Society of Geriatrics
- Danish Psychiatric Society
- Danish Society of Clinical Pharmacology
- DaneAge Association