Focused clinical question regarding
National Clinical Recommendation on the use of mild tranquilizers
Version 3.0 approved 11.02.2022

Indhold

PICO: *Which minor tranquilizers may be prescribed for short-term treatment of unspecific symptoms of anxiety or distress where pharmacological treatment is required?*

Background:

Focus on limitations in the use of benzodiazepines has led to a significant decline in the number of patients treated with benzodiazepines as well as a decline in the number of long-term users and a reduction in the total amount consumed. However, data from the Danish Health Data Authority show an increase in the use of other sedative/anxiolytic drugs such as low-dose quetiapine. Benzodiazepines have a rapid anxiolytic effect, but at the same time also a potential risk for tolerance and dependency. Other sedative drugs used in clinical practice have well known side effects such as anticholinergic side effects e.g. dry mouth, constipation, dizziness, but also neurological and metabolic side effects, which can affect the patient in the long run. The guideline panel will investigate the benefits and harms regarding the different treatment options to determine which drug with sedative and anxiolytic properties is most appropriate in short-term treatment of anxiety.

Population

Adults with recent-onset of symptoms of anxiety and distress, including related sleeping problems, in need of brief pharmacological treatment (maximum up to 4 weeks). This may include patients with symptoms of anxiety and stress, who may be in distress/crisis as a result of illness, death, accident or other stressful life events. This includes patients with acute stress or adjustment disorder. It includes both patients without prior known psychiatric disorder as well as patients diagnosed with mild-moderate depression or anxiety disorder. Regarding the latter, the psychiatric comorbidity should be treated in accordance with current guidelines, and treatment must be optimized before considering adding a short-term sedative/anxiolytic drug. Thus, patients with comorbidity may be included if treatment with rapid onset action is required and if the distress/anxiety is considered to be transient. Patients with ongoing diagnostic assessment may be included in the population.

The population only includes patients that are stable enough to receive treatment without requiring hospitalization, i.e. patients in primary care and possibly outpatient settings. The population does not include patients diagnosed with organic mental disorders (F00-09), psychotic disorders (F20-29), bipolar disorder, severe depression or OCD.

Patients with expected need of longer (>4 weeks) pharmacological treatment are not included.

To explain potential heterogeneity in the results and to elaborate the recommendation in relation to subpopulations, we will extract data regarding psychiatric comorbidity and age.

Search terms:

Anxiety, Anxious, Anxiety Disorder, Neurotic disorder, Neurosis, Acute stress disorder, Stress, Mental stress, Adjustment disorder, distress, crisis.

Intervention

The following interventions will be investigated:

- Benzodiazepines
- Antipsychotics with sedative effects (for example quetiapine, olanzapine in low doses)
- Sedative antidepressants (mirtazapin, mianserin)
- Antihistamines with sedation (for example promethazine)
- Melatonin
- Z-drugs (zopiclone, zolpidem)
- Pregabalin

All interventions will be investigated for both regular dosage and as needed dosage (PRN) and only for oral administration of the drug. Length of treatment up to 4 weeks.
The interventions can be given as monotherapy or in combination with other psychopharmacologic or non-pharmacologic treatment.

To explain potential heterogeniety in the results and to elaborate the recommendation, data will be extracted regarding any additional pharmacological or non-pharmacological treatment.

Suggested search terms:

”Hypnotics and sedatives”, minor tranquilizer, ”benzodiazapin”, ”BZD”, “Abecarnil”, “Adinazolam”, “Alprazolam”, ”Arfendazam”, ”Bentazepam”, ”Bretazenil” , ”Bromazepamor Brotizolam”, ”Camazepam” , ”Chlordiazepoxide” ,”Chlordesmethyldiazepam”, ”Cinolazepam” , ”Clobazam”, ”Clonazepam”, ”Clo-razepate”, ”Chlorazepate”, ”Clotiazepam”, ”Cloxazolam”, ”Delorazepam” , Demoxepam” , Desmethyldiazepam”, ”Desoxydemoxepamor Devazepide” , ”Diazepam” , ”Doxefazepam” , ”Estazolam”, ”Fludiazepamor”, ”Flunitrazepam” , ”Flurazepam”, ”dealkylflurazepam”, ”Flutoprazepam”, ”Fosazepam” , ”Gidazepam” ”Girisopam”, ”Halazepamor”, ”Haloxazolam”, ”Ketazolam”, ”Loflazepate” ,” Loprazolam” , ”Lorazepam” , ”Lormetazepam” , ”Meclonazepam or Medazepam orMetaclazepam or Mexazolam or Midazolam or Nerisopam or

Nimetazepam", "Nitrazepam" , "Norchlordiazepoxide" , "Norclobazamor", "Nordazepam", "Norfludiazepam", "Norflunitrazepam" , "Oxazepam" , "Oxazolam" , Phenazepamor", "Pinazepam" "Prazepam", "Premazepam", "Propazepam", "Quazepam", "Ripazepam", "Serazepine", "Sograzepide" , "Talampanelor Tarazepide", "Temazepam" , "Tetrazepam", "Tofisopam", "Triazolam","drug therapy", "anti-anxiety agents", "sedatives", "antipsychotics", "antipsychotic agent", "antipsychotic drug", "mirtazapine", "mianserin", "sedating antihistamines", "antihistamines", "H1 antagonists", "Histamine H1 blockers", "promethazine", "melatonin", "zopiclone", "Zolpidem", z-drugs, quetiapine, olanzapine, melperone, chlorprothixen, levompromazine, risperidone.

Comparison

Comparators will include both no farmacological treatment and the other drugs included as interventions.

If possible, a network meta-analysis will be performed, where estimates for all mutual comparisons between interventions and between no treatment (e.g. placebo) will be calculated based on direct and indirect comparisons.

All interventions will be compared in direct head-to-head meta-analyses, whenever data is available for a comparison These analyses will serve as sensitivity analyses for an eventual network meta-analysis.

All interventions will be compared to no treatment (e.g. placebo) in an overall meta-analysis, with subgroups according to the different drug classes.

Outcomes	**Priority scales and minimum clinical important difference (MCID)**	**Time**	**Critical/important**
Serious adverse events		*Within 4 weeks*	*Critical*
Anxiety	*Priority* *1) Hamilton Rating scale for anxiety (HAM-A)* *2) Beck Anxiety Inventory*	*Within 4 weeks*	*Critical*

	3) *State Trait Anxiety Inventory (STAI) and other scales with self-reported outcomes* *An external partner (McMaster University) will estimate the MCID for HAM-A based on a systematic literature review of studies reporting anchor-based MCIDs.*		
Function of daily living/Disability	*Priority* 1) *Scales that are interviewer-administered, for example WHODAS 12-item.* 2) *Scales with self-reported outcomes as Sheehan Disability Scale or Social Adjustment Scale-Self report (SAS-SR)* 3) *Un specific scales e.g. GAS or GAF* *An external partner (McMaster University) will estimate the MCID for WHODAS 12-itwm based on a systematic literature review of studies reporting anchor-based MCIDs.*	*Within 4 weeks*	*Critical*
Quality of life	*Priority scales SF-36, SF-12 or EuroQol-5 Domain*	*Within 4 weeks*	*Important*
Suicidal thoughts/attempts		*Within 1 year after start of short term treatment (up to 4 weeks)*	*Important*

Addiction	*e.g.* *Withdrawal symptoms* *Craving* *Tolerance*	*Within ½year after start of short term treatment (up to 4 weeks)*	*Important*
Fractures	*1) Fractures* *2) Falls*	*Within 4 weeks*	*Important*
Changes in weight	Weight gain/weight loss	*Within 4 weeks*	*Important*
Cardial side-effects	*Including: Prolonged QT and Other arrhythmia*	*Within 4 weeks*	*Important*
Extrapyramidal symptoms		*Within 4 weeks*	*Important*
Quality of sleep	*Measured on a compositscala as e.g. Pittsburg Sleep Quality Index (PSQI) or as single reports of e.g. time to sleep onset, number of awakenings or total sleep time*	*Within 4 weeks*	*Important*
Drowsiness during daytime		*Within 4 weeks*	*Important*
Dizziness		*Within 4 weeks*	*Important*

Amendants

11.02.22 Changes for the critical outcome anxiety

Per 4. February 2022 McMaster University have carried out a report regarding MCID for HAM-A. No studies reporting Anchor-based MCIDs for the HAM-A have been identified. On this basis the guideline panel on a meeting the 10. February 2022 decided to use a SMD of 0.3 as the minimal clinically important difference. A SMD of 0.3 was chosen instead of 0.5 because our population of interest is patients where non pharmacological treatment have been tried or considered and deemed irrelevant.

11.02.22 Changes for the critical outcome function of daily living/disability

Per 18. January 2022 McMaster University have carried out a report regarding MCID for WHODAS-2. One study that reported 3 different anchor-based MCIDs for WHODAS-12 where identified. The Report from McMaster concludes taht the optimal MCID for WHODAS-12 is a change of 5 points. The reported optimal MCID of 5 points have been evaluated in a population of surgical patients with increased risk of surgical complications undergoing major abdominal surgery. It is unclear whether the estimated optimal MCID is applicabale to other clinical context. On this basis the guideline panel on

a meeting the 10. February 2022 decided to use a SMD of 0.3 as the minimal clinically important difference. A SMD of 0.3 was chosen instead of 0.5 because our population of interest is patients where non pharmacological treatment have been tried or considered and deemed irrelevant.

07.06.22 Changes for interventions

During the literature screening of primary studies from the included systematic reviews, we identified more primary studies evaluating the effect of pregabalin on anxiety symptoms. Pairwise meta analyses showed effect of pregabalin on anxiety symptoms, therefor the guideline panel on at panel meeting on 6th June 2022 decided to include pregabalin as an intervention of interest.