Nordic Network for Neurorehabilitation, Brain Injury pharmacotherapy interest group (BIPIG)

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Introduction

This document is a result of cooperation through the Nordic Network of Neurorehabilitation Centres (NNNC) https://www.nordisk-netvaerk-neurorehab.com/ . Physicians in the specialized centres for neurorehabilitation in the Nordic countries summarize their consensus recommendations for pharmacological treatment of agitation in adult patients with acquired brain injury (ABI) in this guideline.

The main target group is patients with moderate to severe traumatic brain injury (TBI) in a posttraumatic confusional state (PTCS) in the subacute phase (ref 1). Patients with other causes of acquired brain injuries such as stroke, anoxia, infections and encephalopathy may present similar symptoms of agitation, and the recommendations may have relevance for clinical management.

The guidelines have been created to support logical prescribing and are envisaged as a first step towards data-driven development of care. At present there are no medications approved specifically for agitation after brain injury, and significant barriers exist to accumulating data on use of these medications in routine clinical practice.

Recommendations are based on clinical experience of the members of the BIPIG, systematic reviews published in 2016 and 2019 (ref 2, 3), and the BIPIG-participants' discussions with pharmacologists. The evidence to support the choice of pharmacological treatment of agitation is however very limited (ref 2-4). In order to advance patient care, there is a need both for further research studies and for systematic follow up of routine clinical practice. To this end, clear documentation in medical journals and prescriptions (for example regarding indication for treatment) should be prioritized, and future development work will be needed to establish standards for documentation to allow optimal clinical audit.

Responsibility for treatment remains that of the prescriber and patient-specific factors should always be considered. Within a brief guideline it is not possible to give a complete description of the pharmacological characteristics of specific medications; the reader is referred to established sources for such information (specifications of pharmaceutical companies, national formularies).

The recommendations are presented first, followed by background, discussion and references. The inclusion of several options reflects variation in current clinical practice in the Nordic countries.

Recommendations:

Agitation

First line:

Propranolol 10 mgx3, orally -increase every 2-3 day to max 40 mgx3 (rare cases max 80 mg x3).
Titrate according to agitation, pulse, blood pressure.
Contraindications: sick sinus syndrome, AV block grade 3, asthma and COPD.
Discontinue if there is no effect.

Second line:

Second generation neuroleptics or antiepileptics (can be added to propranolol if propranolol had some effect):

1) Quetiapine orally, start 25 mgx2 d1, 50 mgx2 d2, max 200 mgx2. Contraindication glaucoma, hypotension, bradycardia.
   Or Olanzapine orally, start with 5 mg x 1, can be increased to 10 mg x 1 after 24 hours. Avoid dosage over 20 mg x1 (30 mg can be used in smokers)
2) Valproate orally, 300 mg x2, 300 mgx3, thereafter increase with 300 mg pr day up to daily dose 1200-1500 mg. Contraindication reduced liver function, pregnancy, bleeding
3) Carbamazepine orally, 100 mgx3 max 900 mg /d. Contraindication hyponatremia, porphyria, bone marrow depression

Other alternatives for persistent agitation: Combination of quetiapine and valproate
Avoid: Benzodiazepines, haloperidol, risperidone, clomethiazole

In special situations, such as critical agitation with need for very rapid effect or other situations:

- Olanzapine for intravenous or intramuscular injection or as orally disintegrating tablets
  Example of dose – 5mg i.m. (short term use only intramuscularly, 2.5 mg start dose if aged over 60 years), can be repeated after 2 hours, max 3 times in 24 hours.
  Alternative, depending on local preference Quetiapine in tablet form
- Diazepam
  - example of dose – 5 mg intramuscularly or as slow intravenous injection, can be increased to 5-10mg up to 3 times a day.
- Oxazepam as tablets
- Atypical neuroleptics
- Haloperidol for injection – last choice (*possible negative effects on neuroplasticity)*

Note that prolonged use of “as required” medications/prescription is not recommended.

Sleep Disturbance

Sleep disturbance commonly occurs during PTCS (ref 5). The preferred treatments of nighttime sleeplessness are the following:

1) Melatonin 3-6 mg and/or melatonin with slow release (Circadin) 2-4 mg (Melatonin 2 mg if over 55 years old) *or*
2) Mianserin 10-20 mg, max 60 mg (CAVE enzyme induction when combination with carbamazepine) (*used in some Norwegican centres) or alternatively*
   Mirtazapine 7,5 – 30mg (antidepressive effect only at higher doses) (*used in Swedish centres).* Mianserin or mirtazapine should not be used if the patent already is on atypical antipsychoics, they are sufficiently sedating.

Antihistamines, including promethazine, and benzodiazepines should be avoided.

Background

Agitation after traumatic brain injury

Early recovery for persons with significant TBI is characterized by a period of disorientation and impaired cognitive abilities with other neurobehavioral disturbances (ref 1,6). The term PTCS refers to the clinical presentation during early recovery from TBI of a confusional state as opposed to simply an amnestic state and is therefore preferred to the older term "post-traumatic amnesia", used to refer to the same state. PTCS is a heterogeneous disorder characterized by disorientation and disturbance of attention and memory, which tend to fluctuate in severity during the course of the day. In addition, PTCS can include emotional and/or behavioral disturbances (in some cases including agitation and aggression), sleep-wake cycle disturbances, delusions, perceptual disturbance or confabulations (ref 1). These symptoms should be assessed and followed up as a basis for decisions on non-pharmacological and pharmacological interventions during PTCS. Duration of PTCS is known to have prognostic relevance; it has been used as an index of injury severity and is predictive of outcome. Prospective assessment of patients gives the most accurate estimation of PTCS duration.

Clinical assessment of the features of PTCS may be supported by the use of assessment scales, either with focus on one symptom (e.g. GOAT, O-log or Westmead protocols for assessing orientation and amnesia (ref 7), agitated behavior scale (ABS) for agitation, (ref 8)) or by protocols incorporating a broader set of symptoms. An example of the latter is The Confusion Assessment Protocol (CAP), (ref 9). The multidimensional assessment of confusion provided by the CAP is considered to provide useful data for clinicians; it can be used to identify patients who may require additional supervision or special arrangements for therapy activities.

Confused patients have an increased risk for injury to themselves and others, have poor compliance with treatment, and their state may be emotionally upsetting to family/significant others.

Of the many psychiatric symptoms that may result from TBI, agitation is often the most troublesome for carers and patients and often occurs early, during care on medical or surgical wards immediately following injury. There is good evidence that patients with a head injury have an increased risk of agitation. For example, when patients with TBI were compared with patients suffering multiple traumatic injuries, but without head injury, three times as many patients with TBI showed significant aggression during the first 6 months post injury.

Non-pharmacological treatment should always be considered first (ref 6). Non-pharmacological treatment may involve adaptation of the environment, reduction of physical restraints, resting periods, and modification of the approach and attitude of caregivers and relatives. The effect of non-pharmacological measures is presented in a recent systematic review (ref 10). Factors that may trigger agitation should be assessed and treated. Medical complications (infections, pain, hypoxia, hypoglycemia, epilepsy), unwanted side effects of drugs, excessive stimulation, sleep disturbance should be considered. Evaluation is also required as to whether the agitation is a component of an agitated depression, anxiety disorder, or other psychiatric illness. With such

factors excluded or optimally treated, pharmacological treatment targeting agitation may be needed if the agitation is of a severity that hampers the rehabilitation process or puts the patient or staff at risk. Situations may occur where a very rapid effect of medication is essential due to the severity of agitation and of possible consequences (e.g. immediate risk of injury to the patient or others, or when a confused patient needing medical care who due to brain injury is unable to understand the medical risks, attempts to leave the hospital).

Although the use of such medications is sometimes unavoidable, their use, especially if more than occasional, is thought to have some risks in terms of prolonging the duration of PTCS. Studies also suggest that some medications (for example Haloperidol) may have negative effects on cognition and neuroplasticity. Benzodiazipines may have paradoxical effects with increased agitation and through negative effects on cognition may affect the patient's participation in rehabilitation.

If critical situations recur several times over a period of hours to days, strategies to prevent their occurrence are needed, incorporating both non-pharmacological interventions and regular medication: A parallel pharmacological strategy is needed over the longer term with regular administration of medications to minimize the risk that agitation leads to a critical situation and to minimize disruption to the patient's care.

Before starting any intervention, an adequate base-line assessment is necessary. Possible tools for operational assessment are, among others, the Agitation Behavior Scale (ABS) and the Brøset violence checklist. ABS is included in the CAP protocol. The assessment scales should be used consistently and at predefined intervals during the treatment of agitation.

This guideline also gives brief recommendations for the treatment of sleep disturbance which is common during PTCS.

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