Brain injury pharmacotherapy interest group, Nordic Network in Neurorehabilitation

Recommendations for pharmacotherapy in prolonged disorders of consciousness

Background

Patients with a severe acquired brain injury (ABI) usually emerge from coma and gradually regain a greater or lesser degree of independence. A small group of patients, however, open their eyes but show no or extremely limited signs of consciousness, and are described as having a Disorder of Consciousness (DOC). Prolonged DOC (PDOC) (≥4 weeks) encompasses Unresponsive Wakefulness Syndrome (UWS, previously called vegetative state) (Laureys et al 2010), where patients show no behavioral signs of consciousness, and Minimally Conscious State (MCS) where patients show "clearly discernible" but inconsistent signs of consciousness (Giacino et al,2002). Emergence from MCS is marked by the emergence of functional communication and/or functional object use (3).

Definitions

UWS (unresponsive wakefulness syndrome = vegetative state):

A state of wakefulness without awareness in which there is preserved capacity for spontaneous or stimulus-induced arousal, evidenced by sleep-wake cycles and a range of reflexive and spontaneous behaviours. UWS is characterized by complete absence of behavioural evidence for self- or environmental awareness. (RCP, 2013, Giacino 2002).

MCS (minimally conscious state):

A state of severely altered consciousness in which minimal but clearly discernible behavioural evidence of self- or environmental awareness is demonstrated. MCS is characterized by inconsistent, but reproducible, responses above the level of spontaneous or reflexive behaviour, which indicate some degree of interaction with their surroundings. (RCP, 2013, Giacino 2002).

Target group for pharmacotherapy

- Patients with UWS or MCS at least 4 weeks after severe ABI.
- ABI is defined here as brain injury due to a sudden onset insult (injury or illness) to a previously healthy adult brain. Underlying causes include trauma, hypoxia, vascular events, infections, and toxic or metabolic causes. Progressive conditions, for example dementia and multiple sclerosis, do not fall within this definition.

Aim of pharmacotherapy (indication)

- Promoting recovery of consciousness, and increasing levels of consciousness, in patients with PDOC (UWS and MCS) after ABI.

Drug recommendations

On-label

There are no drugs approved for this indication in the Nordic countries or elsewhere (2022). Use of other sedating drugs that could worsen responsiveness should be minimized.

Off-label – based on current evidence to August 2022

First line: Amantadine

Recommended for patients in PDOC, 4-16 weeks after traumatic brain injury (TBI)

Should be considered for patients in PDOC longer after TBI and with PDOC of other causes.

Insufficient evidence for use within the first 4 weeks after brain injury.

Second line: Zolpidem

Should be considered for patients with PDOC in whom Amantadine has not had an effect, or cannot be used due to contraindications or adverse effects.

Not recommended: (insufficient evidence of effect) - Methylphenidate, apomorphine

Amantadine (=Amantadin) to treat patients with PDOC after ABI

*Note/disclaimer – the following summary information is provided to assist in orienting the prescriber but is not intended to be comprehensive. Consult the product information before prescribing. Amantadine is also marketed under the name "*Symmetrel*".*

Formalities and administrative aspects for the prescriber:

- In Sweden amantadine was for many years deregistered, meaning that the prescriber had to apply for a license ("licenspreparat"). Recently an Amantadine medication "Dinetrel" became registered, making prescription easier. Remaining difficulties are that the official information from the pharmaceutical company recommends swallowing the medication whole, i.e. administration via PEG is not recommended. However, the pharmaceutical properties of Amantadine (highly water soluble) suggest that opening the capsules for dilution in water directly before administration should not change its effect. The prescriber should themselves make an assessment as this is not in keeping with the company's recommendation. An alternative is to apply for a license for an alternative preparation.

Published pharmacological information om Amantadine:

1. Norwegian drug formulary, information given refers to the on-label use of Amantadine for L-dopa related dyskinesias in Parkinson disease: L6.3.5.1 Amantadin | Legemiddelhåndboka (legemiddelhandboka.no) (accessed 2022-08-16)
2. Product information on the Amantadine Hydrochloride preparation "Symmetrel", FDA website *(*accessed 2017-11-08) https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/016023s041,018101s016lbl.pdf
3. Information in the British National Formulary (subscription required).

Action: N-methyl-D-aspartate antagonist and indirect dopamine agonist.

Indication: Promoting recovery of consciousness in patients with PDOC after ABI. (Off-label)

Evidence for effect:

Traumatic brain injury - A methodologically sound, international, multicenter, randomized, controlled trial (Giacino et al 2012, NEJM) involving 184 patients with **post-traumatic** disorders of consciousness, found that the administration of amantadine between 4 and 16 weeks after injury significantly improved the rate of functional recovery over the 4-week period of treatment, as compared with placebo. Use of Amantadine was not associated with any difference in incidence of serious adverse effects compared to placebo. Grade 1+ evidence.
Anoxic brain injury – Only case studies, but reasonable to extrapolate from the evidence for traumatic brain injury.
Stroke – Only case studies, but reasonable to extrapolate from the evidence for traumatic brain injury.

Other uses:

- Originally developed as an antiviral (no longer used for this indication due to resistance).
- Also used in the treatment of Parkinson disease, but has fallen out of common use due to limited effect.

- An RCT (2017) has shown effect of an extended release preparation in reducing levodopa induced dyskinesias in Parkinson disease, and at the time of writing it remains to be seen whether this becomes a common use.
- As Amantadine has been in clinical use for these indications for many years, there is good knowledge of adverse effects.

Putative mechanisms for effect of Amantadine in promoting consciousness in PDOC:

- Promotion of dopaminergic activity by facilitating presynaptic release and blocking postsynaptic uptake (Giacino et al 2012).
- Enhanced neurotransmission in the nigrostriatal, mesolimbic and frontostriatal circuits dopaminergic circuits responsible for arousal, drive and attention, is thought to mediate the effect. This via an effect on the medium spiny neurons of the striatum (mesocircuit hypothesis, Schiff 2010).
- Unclear how important the NMDA-mediated effect is.

Pharmacokinetics: Well absorbed after oral administration. Biological availability 80-90%. Maximal concentration after approximately 2-4 hours. Half life approximately 15 hours. Largely renal elimination (approx. 90%).

Dose

- A range of dosing regimes used in the Nordic countries (start dose, rate of titration, max dose) were discussed at the Nordic network meeting in 2016.
- There is insufficient evidence on which to make a definitive statement on optimal dosing. The following is therefore for guidance, based on incomplete consensus.
- When two doses are given, these should be in the morning and at lunch, to avoid sleep disturbance.
- Evaluation of effect with standardized methods, such as the Coma Recovery Scale Revised, is advised.

Start dose 100mg (single dose in the morning, or 50mg twice a day)

Titration: increase the dose after 4-7 days if insufficient effect and if the absence of significant adverse effects, initially to 100mg twice a day. Further dose increases at a minimum 1 week interval, in steps of 100mg.

Max dose – 400mg daily. Note – some consider 300mg to be a more appropriate max dose due to increased adverse effects without increased effect on consciousness at 400mg.

Duration of therapy: The existing evidence is based on relatively short term treatment (6 weeks). This treatment duration in the Giacino 2012 RCT was however largely due to practical and logistical considerations integral to the trial design, and many practitioners continue Amantadine in the medium to long term. If this is done, the continued effect should be evaluated at regular intervals (minimum 1 year), by performing a controlled gradual cessation of therapy with evaluation of the patient's function before and after. Reintroduction of Amantadine may be needed if cessation is associated with worsening function. (*consensus recommendation).*

Contraindications: Allergy. Epileptic seizure during the preceding month, or electrographic seizure activity on EEG (ref Giacino et al 2012).

Cautions: Epilepsy.

Other cautions - Renal failure, liver failure, congestive heart failure, peripheral oedema (may precipitate deterioration, monitoring needed), orthostatic hypotension.

Interactions: (list from British National Formulary)

Antimuscarinic drugs (increased risk of antimuscarinic effects), antipsychotic medications, metoclompramide, tetrabenaxin (increased risk of extrapyramidal adverse effects), Bupropiron (Voxra, Wellbutrin, Zyban), Memantin (Ebixa, Axura) increased risk of adverse effects.

Adverse effects: Note that in the multicenter, placebo controlled RCT, there was no difference in the incidence of adverse effects in the Amantadine and placebo groups. The following have however been reported (source - product information for Symmetrel):

Common (5-10%): nausea, dizziness (lightheadedness), and insomnia.

Less frequent (1-5%): depression, anxiety and irritability, hallucinations, confusion, anorexia, dry mouth, constipation, ataxia, livedo reticularis, peripheral edema, orthostatic hypotension, headache, somnolence, nervousness, dream abnormality, agitation, dry nose, diarrhea and fatigue.

Infrequent (0.1-1%): congestive heart failure, psychosis, urinary retention, dyspnea, skin rash, vomiting, weakness, slurred speech, euphoria, thinking abnormality, amnesia, hyperkinesia, hypertension, decreased libido, and visual disturbance, including punctate subepithelial or other corneal opacity, corneal edema, decreased visual acuity, sensitivity to light, and optic nerve palsy.

Rare (less than 0.1%): convlusions, leukopenia, neutropenia, eczematoid dermatitis, oculogyric episodes, suicidal attempt, suicide, and suicidal ideation.¨

See product information *for other adverse events reported in post-marketing surveillance.*

Pregnancy: Inadequately tested in pregnancy (category C).

Lactation: Excreted in breast milk – should not be used in lactating mothers.

Zolpidem (=Stilnoct) to treat patients with PDOC after ABI

Note/disclaimer – the following summary information is provided to assist in orienting the prescriber but is not intended to be comprehensive. Consult national formularies and product information before prescribing.

Published pharmacological information om Zolpidem:

1. Norwegian drug formulary, information given refers to the "on-label" use to treat insomnia: L5.1.2.1 Zolpidem | Legemiddelhåndboka (legemiddelhandboka.no) (accessed 2022-08-16)
2. Swedish drug formulary, information given refers to the "on-label" use to treat insomnia: http://www.fass.se/LIF/substance?userType=0&substanceId=IDE4POFIUB0C5VERT1 (accessed 2022-08-16)
3. Information in English, registered at the FDA (accessed 2022-08-16) (https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/019908s027lbl.pdf

Action: Non-benzodiazepine hypnotic, potentiates GABA A receptors.

Indication: Promoting recovery of consciousness in patients with PDOC after ABI. (Off-label)

Evidence for effect: Moderate (2)

- Good effect, but only in a small minority of patients.
- One double-blind, placebo-controlled, crossover design (n=15) found an effect in one patient (5%) (Whyte et al 2009).
- A follow-up, open label study (Thonnard et al 2013) in 60 patients failed to demonstrate "clinically significant" improvement in any patient. The definition of "clinically significant" improvement, was however narrow: 20% in fact showed improved behaviors and/or CRS-R total scores, but without changing clinical diagnostic category (UWS/MCS/emerged from MCS).

Other uses: - Originally developed to treat insomnia.
- As Zolpidem has been in clinical use for many years, there is good knowledge of adverse effects.

Putative mechanisms for effect of Zolpidem in promoting consciousness in PDOC:

- In PDOC, Zolpidem can have a paradoxical effect in **improving** arousal and behavioural responses.
- In PDOC, the activity of the medium spiny neurons of the striatum is reduced due to brain injury, releasing the inhibition of the globus pallidus interna (GPi) which then has an **increased** inhibitory input to the central thalamus (mesocircuit hypothesis, Schiff 2010).
- Zolpidem is thought to normalize central thalamic activity by directly inhibiting the GPi and thus lifting inhibition of the thalamus.

Pharmacokinetics: Good absorption after oral administration. Biological availability approx. 70%. Maximal concentration after approximately 0,5 – 3 hours (large individual variation). Half-life approximately 1- 3 hours. Eliminated as an inactive metabolite in the urine (56%) and faeces (30-40%).

Dose

- 10mg once a day
- Suggest beginning treatment mid-afternoon, to minimize disruption of the sleep-wake cycle if Zolpidem has the usual effect of initiating sleep, rather than the desired paradoxical effect of promoting consciousness.
- Evaluation of effect with standardized methods, such as the Coma Recovery Scale Revised, is advised, 1-2 hours after administration (i.e. at the time of expected maximal concentration). Note that time to maximal concentration shows large variability, so be alert to possible late effects and plan for increased nursing observations for 8 hours after administration.

Duration of therapy: Optimal duration of therapy (once effect is established) is unknown. When used for longer periods (months to years), continued effect should be evaluated at regular intervals (minimum 1 year), by performing a controlled gradual cessation of therapy with evaluation of the patient's function before and after. Reintroduction of Zolpidem may be needed if cessation is associated with worsening function. (*consensus recommendation).*

Contraindications:

Allergy, Severe liver disease, Obstructive sleep apnoea, Myasthenia gravis, Acute and/or sever respiratory failure.

Cautions: Reduce lose in mild-moderate liver dysfunction and in elderly patients. See also national formularies.

Interactions: (from the Swedish national formulary, www.fass.se)

- Combination with other drugs with a suppressive effect on the CNS can lead to an increase in the psychomotor retardation and sleepiness.
- Cases of visual hallucinations have been reported when Zolpidem is combined with antidepressants such as bupropion, desipramine, fluoxetine, sertraline och venlafaxine.
- Zolpidem is metabolized via several cytochrome P-450 enzymes, and so substances that inhibit cytochrome P-450 can lead to an increased concentration and effect of Zolpidem. Cytochrome P-450 inducers (e.g. Rifampicin, Joannes Wort), can reduce the concentration and thereby effect of Zolpidem.
- Administration together with Ciprofloxacin or Fluvoxamin can lead to increased Zolpidem concentration and is therefore not recommended.
- An increased sedative effect can be expected when combined with Ketakonazol. A change in dose is not usually needed.

Adverse effects: (from the Swedish national formulary, www.FASS.se, refers to "Stilnoct")

Very common (>10%) and common (1-10%): sleepiness, headache, dizziness, cognitive changes such as anterograde amnesia, hallucinations, agitation, nightmares.

Infrequent (0.1-1%): confusion, irritability, double vision

Rare (less than 0.1%): none listed.

Unknown frequency: Reduced level of consciousness, restlessness, aggression, delusions, anger, behavioural disturbances, sleep walking, dependency, reduced libido, depression, falls, gait disturbance, muscle weakness, skin rash, itch, urticaria, hyperhidrosis, angioneurotic oedema, raised liver enzymes, liver dysfunction

Pregnancy: Inadequately tested in pregnancy (category C), should be avoided.

Lactation: Excreted in breast milk in small amounts – should not be used in lactating mothers (Group IVb).

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Appendix:

Evidence grading, SIGN (based on GRADE)

KEY TO EVIDENCE STATEMENTS AND GRADES OF RECOMMENDATIONS	
LEVELS OF EVIDENCE	
1^{++}	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1^{+}	Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1^{-}	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2^{++}	High quality systematic reviews of case control or cohort studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2^{+}	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2^{-}	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, eg case reports, case series
4	Expert opinion
GRADES OF RECOMMENDATION	
Note: The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.	
A	At least one meta-analysis, systematic review, or RCT rated as 1^{++}, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1^{+}, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2^{++}, directly applicable to the target population, and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 1^{++} or 1^{+}
C	A body of evidence including studies rated as 2^{+}, directly applicable to the target population and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 2^{++}
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2^{+}