Kliiniline küsimus nr 5

Kas kõigil alkoholi võõrutusseisundis olevatel patsientidel kasutada võõrutussümptomite vähendamiseks farmakoloogilist ravi vs mitte kasutada?

Kriitilised tulemusnäitajad:
Patsiendi rahulolu, võõrutusravi ajal tekkinud komplikatsioonid, võõrutusravi kestus, võõrutusseisundi raskusaste, võõrutussümptomite vähendamiseks kasutatud ravimite koguarv

Ravijuhendid

Kokkuvõte tõendusmaterjali kvaliteedist

Reeglina soovitatakse alustada alkoholi võõrutusseisundis olevatel patsientidel koheselt farmakoloogilise raviga. Mittemedikamentoosset ravi võib proovida patsientidel:

1) kellel ei kaasne võõrutussümptomeid;

2) kes tarbivad alkoholi vähem kui <15 ühikut/päevas (meeste kohta), või <10 ühikut/päevas (naiste kohta);

3) kui patsientide väljahingatavas õhus ei leidu alkoholi;

4) varasemalt pole raskeid alkoholi võõrutussümptomeid esinenud.

Reeglina kasutatakse võõrutusseisundi korral medikamentoosset ravi, sest:

1) on keeruline ennustada, kellel tekivad rasked võõrutussümptomid;

2) ravimata võõrutusseisundi korral esineb suur haigestumus ja suremus võõrutussümptomite komplikatsioonidesse (deliirium, krambid)

3) võõrutusseisundi ja võõrutussümptomite leevendamine on medikamentoosse raviga tunduvalt efektiivsem;

4) medikamentoosset ravi (eelkõige bensodiasepiine) on kerge kasutada, see on efektiivne, odav ja omab vähe kõrvaltoimeid.

Bensodiasepiinid

1 meta-analüüs (Mayo-Smith 1997) hindas 134 uuringut, sealhulgas 65 prospektiivset kontrollitud uuringut, mis hõlmasid 42 erinevat medikamenti. Meta-analüüsi tulemused näitavad, et bensodiasepiinid vähendavad võõrutussümptomite raskust ning deliiriumi võimalikku teket (-4.9 juhtu 100 patsiendi kohta; 95% CI -9.0 - -0.7; p=0.04). Lisaks väheneb bensodiasepiinide kasutamisega krambi tekkerisk (-7.7 juhtu 100 patsiendi kohta; 95% CI -12.0 - -3.5; p=0.003).

1 meta-analüüs (Holbrook et al 1999) koosnes 11 RCT-st (1286 patsienti) ja leidis, et bensodiasepiinid on võõrutussümptomite ravis efektiivsemad kui platseebo (OR 3.28; 95% CI 1.30 – 8.28). Bensodiasepiine võrreldi ka teiste ravimitega (k.a. karbamasepiin), kuid ei nähtud efekti, et karbamasepiin oleks efektiivsem kui bensodiasepiin.

Cochrane'i süstemaatiline ülevaade (Ntais et al 2005) hindas bensodiasepiinide kasutamist alkoholi võõrutussümptomite korral. Kaasati 57 randomiseeritud uuringut 4051 patsiendiga. Leiti, et bensodiasepiinid on võrreldes platseeboga alkoholi võõrutussündroomi korral esinevate krampide ennetuses efektiivsemad (RR 0.16; 95% CI 0.04 – 0.69; p=0.01). Antikonvulsantidega võrreldes oli bensodiasepiinidel sarnane efekt (RR 1.00; 95% CI 0.87 – 1.16) alkoholi võõrutussümptomite ravis. Bensodiasepiinid ennetasid krampe efektiivsemalt kui mitte antikonvulsandid (RR 0.23; 95% CI 0.07 – 0.75; p=0.02). Bensodiasepiinide ja antikonvulsantide võrdluses krampide ennetamises erinevust ei esinenud (RR 1.99; 95% CI 0.46 – 8.65).

Antikonvulsandid (karbamasepiin)

1 meta-analüüs (Mayo-Smith 1997) koosnes 4 RCT-st ja leidis, et karbamasepiin on kerge kuni mõõduka sümptomaatika korral efektiivsem kui platseebo ning efektiivsuselt võrdne fenobarbitaali ja oksasepaamiga. Karbamasepiin vähendab võõrutussümptomite raskust, kuid

tõenduspõhist materjali nende toime kohta krampide ja deliiriumi ennetamises on liialt vähe. Karbamasepiini võib kasutada ainult koos bensodiasepiinidega, kuid mitte monoteraapiana.

1 süstemaatiline ülevaade (Polycarpou et al 2005) koosnes 48st uuringust ja 3610 patsiendist. Antikonvulsante võrreldi platseeboga võõrutussümptomite ravis (RR 1.32; 95% CI 0.92 – 1.91), kuid statistilist erinevust ei leitud. Antikonvulsante võrreldi platseeboga krampide ennetamises (RR 0.57; 95% CI 0.27 – 1.19), kuid statistilist erinevust ei saavutatud. Karbamasepiin võrreldes bensodiasepiiniga omab paremat efekti krampide ennetamises (kaalutud keskmise erinevus -1.04; 95% CI -1.98 - -0.20; p = 0.02). Kuid tulemused baseeruvad vaid 260 randomiseeritud patsiendile. Nende andmete põhjal ei saa väga tugevaid järeldusi teha.

1 süstemaatiline ülevaade (Minozzi et al 2010) koosnes 56 uuringust ja 4076 patsiendist. Võrreldi antikonvulsante platseeboga võõrutussümptomite ravis, kuid statistiliselt olulist erinevust ei leitud. Nende andmete põhjal ei saa väita, et antikonvulsandid on alkoholi võõrutussümptomite korral efektiivsemad kui bensodiasepiinid.

Tiamiin

B-vitamiin puudusel on oluline roll mitmete neuropsühhiaatriliste sündroomide kujunemises (k.a. Wernicke Korsakoff sündroom). Parenteraalse tiamiini manustamisel on väga vähe tõsiseid kõrvaltoimeid ning seetõttu soovitatakse seda kasutada kõigil võõrutusseisundis olevatel patsientidel (Cook 1998).

Cochrane'i süstemaatiline ülevaade (Day 2013) väidab, et tõenduspõhist materjali on liialt vähe, et anda tugevaid soovitusi tiamiini kasutamisel alkoholi võõrutusseisundi korral.

Bensodiasepiinide manustamine

Fikseeritud annus või annustamine vastavalt sümptomitele

Mitmed RCT-d (Saitz et al 1994, Daeppen et al 2002) soovitavad bensodiasepiine kasutada sümptomite esinemise korral, kui on tegu statsionaaris viibiva haigega. Tulemuseks on väiksem bensodiasepiinide koguannus ja lühem ravikestvus.

Saitz et al 1994: keskmine ravikestvus sümptomaatilise annustamise korral on 9 tundi, fikseeritud annuse korral 68 tundi ($p < 0.001$). Sümptomaatilise ravi korral said patsiendid 100 mg kloordiasepoksiidi, fikseeritud annuse korral 425 mg ($p < 0.001$).

Daeppen et al 2002: sümptomaatilise annustamise korral oli oksasepaami annus 37.5 mg, fikseeritud annuse korral 231.4 mg ($p < 0.001$). Sümptomaatilise annustamise korral oli keskmine ravikuur 20 tundi, fikseeritud annuse korral 62.7 tundi ($p < 0.001$).

Ravimi annustamisel sümptomite tekke korral on vajalik on pidev meditsiinipersonali valve. Ambulatoorsetel haigetel on soovitatav kasutada fikseeritud annusega bensodiasepiine.

1 süstemaatiline ülevaade (Liu et al 2013) koosnes 2 RCT uuringust (81 patsienti), mis hindas baklofeeni efektiivsust alkoholi võõrutussümptomite ravis. Üks RCT uuring näitas, et baklofeeni ja bensodiasepiini manustamisel langeb CIWA-Ar skoor (Clinical Institute Withdrawal Assessment of Alcohol Scale Revised) sama efektiivselt. Teine RCT uuring ei näidanud CIWA-Ar skooris erinevusi. On liialt vähe tõenduspõhist infot baklofeeni efektiivsuse kohta võõrutussümptomite ravis.

1 süstemaatiline ülevaade (Sarai et al 2013) koosnes 4 uuringust (317 patsienti), mis hindas magneesiumi kasutamist alkoholi võõrutusseisundi ravis. Ükski uuring ei näidanud statistiliselt olulist erinevust magneesiumi kasutamisel ja võõrutussümptomite vähenemiseks. On liialt vähe tõenduspõhist infot magneesiumi kasutamise ja efektiivsuse kohta võõrutussümptomite ravis.

Statsionaarne vs ambulatoorne ravi

1 RCT (Hayashida 1989) võrdles ambulatoorsete ja statsionaarsete haigete ravi efektiivsust alkoholi võõrutusseisundi korral. Ambulatoorsel ravil olevad patsiendid katkestasid ravi suurema tõenäosusega kui statsionaarsed patsiendid. Statsionaarne ravi oli tunduvalt pikem ja kulukam. Abstinentsi pikkus oli suurem statsionaarsetel haigetel kui ambulatoorsetel. Ambulatoorset ravi võib kasutada kergete-mõõdukate võõrutussümptomite korral.

Võõrutusseisundi ravi võib toimuda ka ambulatoorselt (community detoxifiacation), kuid see peab hõlmama pidevaid meditsiinipersonali (perearstide, pereõdede, psühhiaatria õdede, või farmatseutide) visiite.

Kogukonnas (community) toimuv detoksifikatsioon on paljudel patsientidel efektiivne ning tõenäoliselt kulu-efektiivsem.

Ambulatoorne ravi on vastunäidustatud järgnevatel olukordadel:

1) esineb segasusseisund või hallutsinatsioonid

2) anamneesis rasked võõrutusseisundid

3) anamneesis epilepsia

4) alatoitunud

5) raske oksendamine või diarröoa

6) suitsiidirisk

7) pole koostöövõimeline käima igapäevaselt arsti vastuvõtul

8) varem on ambulatoorne ravi ebaõnnestunud

9) rasked võõrutussümptomid

10) anamneesis psüühikahäire

11) mitmete ainete koos kuritarvitamine

12) pole toetavat kodukeskkonda või patsient on kodutu

13) rasedad, lapsed, eakad

Kokkuvõte ravijuhendites leiduvatest soovitustest

Kümnest ravijuhendist kaheksas (SIGN 2003, NICE 2011, Austraalia 2009, Soome 2010, BAP 2012, WFSBP 2008, NICE 2010a, APA 2006) leidus infot käesoleva küsimuse kohta. 4 ravijuhist (NICE 2011, Austraalia 2009, NICE 2010a, APA 2006) soovitavad reeglina kasutada kõigil alkoholi võõrutusseisundis olevatel patsientidel farmakoloogilist ravi. 2 ravijuhist (SIGN 2003, BAP 2012) soovitavad medikamentoosset ravi kasutada ainult patsientidel, kellel esinevad võõrutussümptomid. SIGN 2003 ravijuhis soovitab medikamentoosset ravi mitte kasutada järgnevatel juhtudel:

1) kui alkoholi tarbimine meestel on <15 ühikut/päevas ja naistel <10 ühikut/päevas ning ei esine võõrutussümptomeid

2) kui patsiendi väljahingatavas õhus ei leidu alkoholi ning ei esine võõrutussümptomeid

<u>Bensodiasepiinid</u>

Kõik ravijuhendid soovitavad esmaseks ravivalikuks bensodiasepiine. Kõik ravijuhised soovitavad kasutada pikatoimelisi bensodiasepiine: diasepaami ja kloordiasepoksiidi (pole Eestis registreeritud). 5 ravijuhist (SIGN 2003, NICE 2011, Austraalia 2009, WFSBP 2008, APA 2006) soovitavad maksapuudulikkuse korral, eakatel, KOKi ja hingamispuudulikkuse korral ning rasvunutel kasutada lühitoimelisi bensodiasepiine: oksasepaam, lorasepaam.

<u>Antikonvulsandid (karbamasepiin)</u>

2 ravijuhist (Soome 2010, BAP 2012) soovitavad kasutada karbamasepiini, kuid ei täpsusta, kas seda tuleb manustada kombinatsioonis bensodiasepiinidega.

2 ravijuhist (WFSBP 2008, NICE 2010a) lubavad kasutada karbamasepiini ka monoteraapiana.

2 ravijuhist (SIGN 2003, APA 2006) soovitavad karbamasepiini kasutada ainult koos bensodiasepiinidega. SIGN 2003 ravijuhis soovitab antikonvulsante esmatasandi meditsiinis mitte määrata. Kui tekib vajadus antikonvulsantide (anamneesis krambid) manustamiseks, siis tuleb patsient suunata spetsialisti juurde.

Austraalia 2009 ravijuhis ütleb, et karbamasepiini ja bensodiasepiinide koosmanustamisel lisaefekti ei esine ja soovitab antikonvulsante mitte kasutada.

1 ravijuhendis (NICE 2011) ei leidu infot antikonvulsantide kasutamise kohta võõrutussümptomite korral.

Antipsühhootikumid

3 ravijuhist (SIGN 2003, Austraalia 2009, APA 2012) soovitavad antipsühhootikume kasutada ainult koos bensodiasepiinidega kui patsiendil esinevad hallutsinatsioonid. SIGN 2003 ravijuhis soovitab antipsühhootikume esmatasandi meditsiinis mitte määrata. Kui tekib vajadus antipsühhotikumide (esinevad hallutsinatsioonid) manustamiseks, siis tuleb patsient suunata spetsialisti juurde.

5 ravijuhist (NICE 2011, Soome 2010, BAP 2012, WFSBP 2008, NICE 2010a) ei sisalda infot antipsühhootikumide manustamise kohta võõrtussümptomite korral.

8 ravijuhist (SIGN 2003, NICE 2011, Austraalia 2009, Soome 2010, BAP 2012, WFSBP 2008, NICE 2010a, APA 2012,) soovitavad alkoholi võõrutusseisundis olevatel patsientidel kasutada lisaks tiamiini.

Bensodiasepiinide manustamine

Fikseeritud annus või annustamine vastavalt sümptomitele

6 ravijuhist (SIGN 2003, NICE 2011, Austraalia 2009, BAP 2012, WFSBP 2008, NICE 2010a) soovitavad ambulatoorsetel patsientidel kasutada fikseeritud bensodiasepiinide annuseid. NICE 2011 ravijuhis soovitab ravi lõpetamisel bensodiasepiinide annust vähendada 7-10 päeva jooksul. Austraalia 2009 ravijuhis soovitab ravi lõpetamisel bensodiasepiinide annust vähendada 3-6 päeva jooksul.

6 ravijuhist (SIGN 2003, NICE 2011, Austraalia 2009, BAP 2012, WFSBP 2008, NICE 2010a) soovitavad sümptomite põhist manustamist kasutada statsionaaris olevatel patsientidel, kuna on näidatud, et sümptomite põhisel manustamisel kulus vähem ravimeid, hospitaliseerimine võõrutussümptomite tõttu oli väiksem ning ravikestvus oli lühem.

1 ravijuhis (APA 2012) soovitab ka ambulatoorsetel patsientidel kasutada bensodiasepiine vastavalt sümptomitele.

Soome 2010 ravijuhendis ei leidu infot, kuidas tuleb bensodiasepiine võõrutussümptomite korral manustada.

Statsionaarne vs ambulatoorne ravi

5 ravijuhendis (SIGN 2003, NICE 2011, Austraalia 2009, APA 2006, WFSBP 2008) leidub infot ambulatoorse ja statsionaarse ravi kasutamise kohta. Kõik 4 ravijuhendit soovitavad raskete sümptomite esinemise korral kasutada statsionaarset ravi. Statsionaarsed ravi tuleb kindlasti kasutada järgnevatel juhtudel: esineb segasusseisund või hallutsinatsioonid; anamneesis rasked võõrutusseisundid; anamneesis epilepsia; alatoitunud; raske oksendamine või diarröoa; suitsiidirisk; pole koostöövõimeline käima igapäevaselt arsti vastuvõtul; varem on ambulatoorne ravi ebaõnnestunud; rasked võõrutussümptomid; anamneesis psühhiaatriline haigus; mitmete ainete koos kuritarvitamine; pole toetavat kodukeskkonda või patsient on kodutu; rasedad, lapsed, eakad

Ravijuhendite soovituste tekstid (inglise keeles):

SIGN 2003: *Medication may not be necessary if:*
1) the patient reports consumption is less than 15 units/day in men / 10 units/day in women and reports neither recent withdrawal symptoms nor recent drinking to prevent withdrawal symptoms
2) the patient has no alcohol on breath test, and no withdrawal signs or symptoms. When

medication to manage withdrawal is not needed, patients should be informed that at the start of detoxification they may feel nervous or anxious for several days, with difficulty in going to sleep for several nights.

Benzodiazepines should be used in primary care to manage withdrawal symptoms in alcohol detoxification, but for a maximum period of seven days.
For patients managed in the community, chlordiazepoxide is the preferred benzodiazepine.
Antiepileptic medication should not be used as the sole medication for alcohol detoxification in primary care.
People with a history of alcohol related seizures should be referred to specialist services for detoxification management.
Antipsychotic drugs should not be used as first line treatment for alcohol detoxification.
Delusions and hallucinations due to alcohol withdrawal, which would indicate the need for antipsychotic drugs, should be managed by specialist services.
Tapered fixed dose regimen of a benzodiazepine is recommended for primary care alcohol detoxification, with daily monitoring whenever possible.
Patients who have a chronic alcohol problem and whose diet may be deficient should be given oral thiamine indefinitely.
Where community detoxification is offered, it should be delivered using protocols specifying daily monitoring of breath alcohol level and withdrawal symptoms, and dosage adjustment.
Every GP practice (and out-of-hours service) would benefit from access to a breathalyser for use in the acute situation and for follow up.
Intoxicated patients presenting in GP practices, out-of-hours services and A&E, requesting detoxification should be advised to make a primary care appointment and be given written information about available community agencies.

NICE 2011: *When conducting community-based assisted withdrawal programmes, use fixed-dose medication regimens.*
Fixed-dose or symptom-triggered medication regimens can be used in assisted withdrawal programmes in inpatient or residential settings. If a symptom-triggered regimen is used, all staff should be competent in monitoring symptoms effectively and the unit should have sufficient resources to allow them to do so frequently and safely.
Prescribe and administer medication for assisted withdrawal within a standard clinical protocol. The preferred medication for assisted withdrawal is a benzodiazepine (chlordiazepoxide or diazepam).
In a fixed-dose regimen, titrate the initial dose of medication to the severity of alcohol dependence and/or regular daily level of alcohol consumption. In severe alcohol dependence higher doses will be required to adequately control withdrawal and should be prescribed according to the Summary of Product Characteristics (SPC). Make sure there is adequate supervision if high doses are administered. Gradually reduce the dose of the benzodiazepine over 7–10 days to avoid alcohol withdrawal recurring.
If benzodiazepines are used for people with liver impairment, consider one requiring limited liver metabolism (for example, lorazepam); start with a reduced dose and monitor liver function carefully. Avoid using benzodiazepines for people with severe liver impairment.
When managing alcohol withdrawal in the community, avoid giving people who misuse alcohol large quantities of medication to take home to prevent overdose or diversion. Prescribe for installment dispensing, with no more than 2 days' medication supplied at any time.
In a community-based assisted withdrawal programme, monitor the service user every other day during assisted withdrawal. A family member or carer should preferably oversee the administration of medication. Adjust the dose if severe withdrawal symptoms or over-sedation occur.
Offer parenteral thiamine followed by oral thiamine to prevent Wernicke-Korsakoff syndrome in people who are entering planned assisted alcohol withdrawal in specialist inpatient alcohol services or prison settings and who are malnourished or at risk of malnourishment (for example, people who are homeless) or have decompensated liver disease.
For service users who typically drink over 15 units of alcohol per day and/or who score 20 or more on the AUDIT, consider offering: an assessment for and delivery of a community-based assisted withdrawal; assessment and management in specialist alcohol services if there are safety concerns about a community-based assisted withdrawal.
Service users who need assisted withdrawal should usually be offered a community-based programme, which should vary in intensity according to the severity of the dependence, available social support and the presence of comorbidities. For people with mild to moderate

dependence, offer an outpatientbased withdrawal programme in which contact between staff and the service user averages 2–4 meetings per week over the first week. For people with mild to moderate dependence and complex needs, or severe dependence, offer an intensive community programme following assisted withdrawal in which the service user may attend a day programme lasting between 4 and 7 days per week over a 3-week period.

Austraalia 2009: *Benzodiazepines are the recommended medication in managing alcohol withdrawal. In Australia, diazepam is recommended as first-line treatment because of its rapid onset of action, long half-life and evidence for effectiveness.*
Shorter-acting benzodiazepines (lorazepam, oxazepam, midazolam) may be indicated where the clinician is concerned about accumulation and over sedation from diazepam, such as in the elderly, severe liver disease, recent head injury, respiratory failure, in obese patients, or where the diagnosis is unclear.
Benzodiazepines should not be continued beyond the first week for managing alcohol withdrawal due to the risk of rebound phenomenon and dependence.
Diazepam should be administered in a symptom-triggered regimen in residential withdrawal settings for people with no concomitant medical, psychiatric or substance use disorders.
Diazepam should be administered in a fixed dose regimen in ambulatory settings, or for those with concomitant medical, psychiatric or substance use disorders.
Carbamazepine is safe and effective as an alternative to benzodiazepines, although it is not effective in preventing further seizures in the same withdrawal episode.
Phenytoin and valproate are not effective in preventing alcohol withdrawal seizures and are not recommended.
Newer anticonvulsant agents (such as gabapentin) are not recommended at this stage due to limited clinical evidence.
There is no benefit in adding anticonvulsants to benzodiazepines to manage alcohol withdrawal.
Anticonvulsant medications should be continued in patients who take them regularly (such as for epilepsy not related to withdrawal).
Antipsychotic medications should only be used as an adjunct to adequate benzodiazepine therapy for hallucinations or agitated delirium. They should not be used as stand-alone medication for withdrawal.
Thiamine should be provided to all patients undergoing alcohol withdrawal to prevent Wernicke's encephalopathy.
Ambulatory withdrawal is appropriate for those with mild to moderate predicted withdrawal severity, a safe 'home' environment and social supports, no history of severe withdrawal complications, and no severe concomitant medical, psychiatric or other substance use disorders. Community residential withdrawal is appropriate for those with predicted moderate to severe withdrawal, a history of severe withdrawal complications, withdrawing from multiple substances, no safe environment or social supports, repeated failed ambulatory withdrawal attempts, and with no severe medical or psychiatric comorbidity. Inpatient hospital treatment is appropriate for those with severe withdrawal complications (such as delirium or seizures of unknown cause), and/or severe medical or psychiatric comorbidity. Hospital addiction medicine consultation liaison services should be accessible in hospitals to aid assessment, management and discharge planning.

Soome 2010: *Benzodiazepines are most effective in treating withdrawal symptoms and delirium tremens; there are no significant differences between various benzodiazepines.*
Carbamazepine is not a first-line drug for alcohol withdrawal. However, it is evidently effective in preventing convulsions and can probably be used in patients with a history of withdrawal convulsions. Withdrawal treatment is often started with 250 mg thiamine intramuscularly or intravenously on three days. As thiamine may prevent Wernicke's encephalopathy, this can probably be recommende.

BAP 2012: *Although many alcohol-withdrawal episodes take place without any pharmacological support, particularly in those patients with a mild level of alcohol dependence, in the presence of symptoms medication should be given. Detoxification should be planned as part of a treatment programme to increase the likelihood of patients successfully altering their subsequent drinking behaviour. Early identification and treatment of alcohol dependence can reduce the level of complications.*
Benzodiazepines are efficacious in reducing signs and symptoms of withdrawal; fixed-dose regimens are recommended for routine use with symptom-triggered dosing reserved for use only

with adequate monitoring.
Carbamazepine has also been shown to be equally efficacious to benzodiazepines. In healthy uncomplicated alcohol-dependent/heavy drinkers (i.e. those at low risk), oral thiamine >300 mg/day should be given during detoxification

WFSBP 2008: *Vitamin deficiencies are very common in patients with heavy alcoholic intake. Supplementation, especially of B vitamins including thiamine to prevent the development of Wernicke-Korsakoff syndrome, is recommended.*
Worldwide, benzodiazepines (BZDs) are the drugs of first choice in the treatment of AWS. They are also superior to many other drugs for this indication.
The most commonly used BZDs are diazepam, chlordiazepoxide, oxazepam, lorazepam and alprazolam. It is a matter of debate whether short-acting or long-acting BZDs are preferable.
While many clinicians favour a symptom-triggered approach and an individualized dosage, Sellers et al. (1983) proposed a fixed dosage scheme with diazepam 'loading,' involving administration of 20 mg every hour until the patient's symptoms subside. Other possible dosage regimens are diazepam 10 mg every 6 h, or lorazepam 2 mg or chlordiazepoxide 50 mg.
A number of studies demonstrating the efficacy and safety of anticonvulsants such as carbamazepine and valproate suggest that they provide safe alternatives to benzodiazepines for the treatment of alcohol withdrawal. They are considered to be relatively safe, free from abuse liability, and usually do not potentiate the psychomotor or cognitive effects of alcohol. Controlled studies have shown CBZ to be superior to placebo and as effective as BZDs or clomethiazole for the treatment of the symptoms of AWS. In addition to reducing symptoms ofAWS, carbamazepine reduced drinks per drinking day and time to first drink in abstinent alcoholics.
Patients with severe symptoms, extremely high alcohol intake, significant somatic or psychiatric symptoms, or delirium tremens should be treated as inpatients.

NICE 2010a: *Offer pharmacotherapy to treat the symptoms of acute alcohol withdrawal as follows: Consider offering a benzodiazepine or carbamazepine; Clomethiazole may be offered as an alternative to a benzodiazepine or carbamazepine. However, it should be used with caution, in inpatient settings only and according to the summary of product characteristics.*
Follow a symptom-triggered regimen for drug treatment for people in acute alcohol withdrawal who are: in hospital or; in other settings where 24-hour assessment and monitoring are available.
Overall, symptom-triggered dosing was associated with significantly lower doses of benzodiazepines than fixed-dosing (31) and with a shorter treatment duration and importantly without an increase in the incidence of seizures or delirium tremens.
Offer thiamine to people at high risk of developing, or with suspected, Wernicke's encephalopathy. It should be given orally or parenterally. Offer prophylactic oral thiamine to harmful or dependent drinkers: if they are malnourished or at risk of malnourishment; if they have decompensated liver disease; if they are in acute withdrawal;before and during a planned medically assisted alcohol withdrawal.

APA 2006*: The treatment of patients in moderate to severe withdrawal includes efforts to reduce central nervous system (CNS) irritability and restore physiological homeostasis and generally requires the use of thiamine and fluids, benzodiazepines, and, in some patients, other medications such as anticonvulsants, clonidine, or antipsychotic agents.*
Consensus does suggest that thiamine be given routinely to all patients receiving treatment for a moderate to severe alcohol use disorder to treat or prevent common neurological sequelae of chronic alcohol use (983–986). In addition, patients in more severe withdrawal and those who develop hallucinations require pharmacological treatment.
The use of benzodiazepines to control withdrawal symptoms takes advantage of the crosstolerance between alcohol and this class of medication. For patients who have severe hepatic disease, are elderly, or have delirium, dementia, or another cognitive disorder, short-acting benzodiazepines such as oxazepam or lorazepam (1004) are preferred by some clinicians and appear to be efficacious.
Anticonvulsants and benzodiazepines appear to have comparable efficacy in preventing seizures during alcohol withdrawal.
For patients manifesting delirium, delusions, or hallucinations, antipsychotic agents, particularly haloperidol (0.5–2.0 mg i.m. q2h, as needed) are recommended. Because antipsychotic agents are not effective for treating the underlying withdrawal state (992), they should be used as an adjunct to benzodiazepines.
Evidence from multiple randomized, controlled trials also supports the use of symptomtriggered therapy, with symptom-triggered detoxification protocols leading to less use of medication as

well as shorter duration of treatment than fixed-dose protocols

Viited

Ravijuhendid

The management of harmful drinking and alcohol dependence in primary care, a national clinical guideline, Scottish Intercollegiate Guidelines Network, 2003	SIGN 2003
Alcohol-Use Disorders: Diagnosis, Assessment and Management of Harmful Drinking and Alcohol Dependence, National Institute for Health & Clinical Excellence, 2011	NICE 2011
Guidelines for the Treatment of Alcohol Problems, Australian Government Department of Health and Ageing, 2009	Austraalia 2009
Treatment of Alcohol Abuse, Current Care Guideline**,** The Finnish Medical Society Duodecim and the Finnish Society of Addiction Medicine,2010	Soome 2010
Evidence-based guidelines for the pharmacological management of substance abuse, harmful use, addiction and comorbidity: recommendations from The British Association for Psychopharmacology,2012	BAP 2012
World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Substance Use and Related Disorders, Part 1: Alcoholism, 2008	WFSBP 2008
Alcohol-use disorders. Diagnosis and clinical management of alcohol-related physical complications, National Institute for Health & Clinical Excellence, 2010	NICE 2010a
Practice Guideline For The Treatment of Patients With Substance Use Disorders, 2nd Edition, American Psychiatric Association, 2006	APA 2006

Süstemaatilised ülevaated ja ristläbilõikelised uuringud

Kokkuvõtte (abstract või kokkuvõtlikum info)	**Viide kirjandusallikale**
SIGN 2003, NICE 2011, Austraalia 2009, Soome 2010, WFSBP 2008, APA 2006	
DATA SYNTHESIS: Benzodiazepines reduce withdrawal severity, reduce incidence of delirium (-4.9 cases per 100 patients; 95% confidence interval, -9.0 to -0.7; P=.04), and reduce seizures (-7.7 seizures per 100 patients; 95% confidence interval, -12.0 to -3.5; P=.003). Individualizing therapy with withdrawal scales results in administration of significantly less medication and shorter treatment (P<.001). beta-Blockers, clonidine, and carbamazepine ameliorate withdrawal severity, but evidence is inadequate to determine their effect on delirium and seizures. Phenothiazines ameliorate withdrawal but are less effective than benzodiazepines in reducing delirium (P=.002) or seizures (P<.001). **CONCLUSIONS:** Benzodiazepines are suitable agents for alcohol withdrawal, with choice among different agents	Mayo-Smith, M. F. (1997) Pharmacological management of alcohol withdrawal. A meta-analysis and evidence-based practice guideline. Journal of American Medical Association, 278, 144–151. **Meta-analysis**

guided by duration of action, rapidity of onset, and cost. Dosage should be individualized, based on withdrawal severity measured by withdrawal scales, comorbid illness, and history of withdrawal seizures. beta-Blockers, clonidine, carbamazepine, and neuroleptics may be used as adjunctive therapy but are not recommended as monotherapy.	
SIGN 2003, Austraalia 2009, Soome 2010, APA 2006	
STUDY SELECTION: Articles were considered for the meta-analysis if they were RCTs involving patients experiencing acute alcohol withdrawal and comparing a benzodiazepine available in Canada with placebo or an active control drug. Of the original 23 trials identified, 11 met these criteria, representing a total of 1286 patients. **DATA SYNTHESIS:** The meta-analysis of benefit (therapeutic success within 2 days) showed that benzodiazepines were superior to placebo (common odds ratio [OR] 3.28, 95% confidence interval [CI] 1.30-8.28). Data on comparisons between benzodiazepines and other drugs, including beta-blockers, carbamazepine and clonidine, could not be pooled, but none of the alternative drugs was found to be clearly more beneficial than the benzodiazepines. The meta-analysis of harm revealed no significant difference between benzodiazepines and alternative drugs in terms of adverse events (common OR 0.67, 95% CI 0.34-1.32) or dropout rates (common OR 0.68, 95% CI 0.47-0.97). **INTERPRETATION**: Benzodiazepines should remain the drugs of choice for the treatment of acute alcohol withdrawal.	Holbrook AM, Crowther R, Lotter A, Cheng C, King D. Meta-analysis of benzodiazepine use in the treatment of acute alcohol withdrawal. CMAJ 1999;160(5):649-55. **Meta-analysis**
SIGN 2003, Soome 2010, APA 2006	
A computer-assisted and cross-reference literature search identified trials of therapy for alcohol withdrawal symptoms. Those with a randomized, double-blind placebo-controlled design were systematically assessed for quality of methodology. Fourteen studies were identified investigating 12 different drugs. The quality of methodological design, even among this highly selected group of published studies, was often poor. Study populations were generally under-defined, most studies excluded severely ill patients, control groups were poorly matched, and the use of additional medication may have confounded results in some studies. Twelve different rating scales were used to assess severity of symptoms. All 12 compounds investigated were reported to be superior to placebo, but this has only been replicated for benzodiazepines and chlormethiazole. Further research using better methods is required to allow comparison of different drugs in the treatment of alcohol withdrawal symptoms. On the evidence available, a long-acting benzodiazepine should be the drug of first choice.	Williams D, McBride AJ. The drug treatment of alcohol withdrawal symptoms: a systematic review. Alcohol Alcohol 1998;33(2):103-15. **Systematic review**
SIGN 2003, Austraalia 2009, NICE 2010a, APA 2006	
INTERVENTION: Patients were randomized to either a standard course of chlordiazepoxide four times daily with additional medication as needed (fixed-schedule therapy) or to a	Saitz R, Mayo-Smith MF, Roberts MS, Redmond HA, Bernard DR, Calkins DR. Individualized treatment for

treatment regimen that provided chlordiazepoxide only in response to the development of the signs and symptoms of alcohol withdrawal (symptom-triggered therapy). The need for administration of "as-needed" medication was determined using a validated measure of the severity of alcohol withdrawal. **RESULTS:** The median duration of treatment in the symptom-triggered group was 9 hours, compared with 68 hours in the fixed-schedule group (P < .001). The symptom-triggered group received 100 mg of chlordiazepoxide, and the fixed-schedule group received 425 mg (P < .001). There were no significant differences in the severity of withdrawal during treatment or in the incidence of seizures or delirium tremens. **CONCLUSIONS:** Symptom-triggered therapy individualizes treatment, decreases both treatment duration and the amount of benzodiazepine used, and is as efficacious as standard fixed-schedule therapy for alcohol withdrawal.	alcohol withdrawal. A randomized double-blind controlled trial. JAMA 1994;272(7):519-23. **RCT**
Austraalia 2009, Soome 2010, NICE 2010a, APA 2006	
MAIN RESULTS: Fifty-seven trials, with a total of 4,051 people were included. Despite the considerable number of randomized controlled trials, there was a very large variety of outcomes and of different rating scales and relatively limited quantitative synthesis of data was feasible. Benzodiazepines offered a large benefit against alcohol withdrawal seizures compared to placebo (relative risk [RR] 0.16; 95% confidence interval [CI] 0.04 to 0.69; p = 0.01). Benzodiazepines had similar success rates as other drugs (RR 1.02; 95% CI 0.92 to 1.12) or anticonvulsants in particular (RR 1.00; 95% CI 0.87 to 1.16) and offered a significant benefit for seizure control against non-anticonvulsants (RR 0.23; 95% CI 0.07 to 0.75; p = 0.02), but not against anticonvulsants (RR 1.99; 95% CI 0.46 to 8.65). Changes in Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar) scores at the end of treatment were similar with benzodiazepines versus other drugs, although some small studies showed isolated significant differences for other, less commonly, used scales. Data on other comparisons were very limited, thus making quantitative synthesis for various outcomes not very informative. **AUTHORS' CONCLUSIONS:** Benzodiazepines are effective against alcohol withdrawal symptoms, in particular seizures, when compared to placebo. It is not possible to draw definite conclusions about the relative effectiveness and safety of benzodiazepines against other drugs in alcohol withdrawal, because of the large heterogeneity of the trials both in interventions and assessment of outcomes but the available data do not show prominent differences between benzodiazepines and other drugs in success rates.	Ntais, C, Pakos E, Kyzas P et al. 2005, Benzodiazepines for alcohol withdrawal. Cochrane Database Syst Rev.(3):CD005063. **Systematic review**
Austraalia 2009, Soome 2010, APA 2006	
MAIN RESULTS: Forty-eight studies, involving 3610 people were included. Despite the considerable number of randomized controlled trials, there was a variety of outcomes and of different rating scales that led to a limited quantitative synthesis of data. For the anticonvulsant versus placebo comparison, therapeutic success tended to be more common among the anticonvulsant-treated patients (relative risk (RR) 1.32; 95% confidence interval (CI) 0.92 to 1.91), and anticonvulsant tended to show a protective benefit against seizures (RR 0.57; 95% CI 0.27 to 1.19), but no effect reached formal statistical significance. For the anticonvulsant versus other drug comparison, CIWA-Ar score	Polycarpou A, Papanikolaou P, Ioannidis J, Contopoulos-Ioannidis D: Anticonvulsants for alcohol withdrawal. Cochrane Database Syst Rev 2005; CD005064 **Systematic review**

showed non-significant differences for the anticonvulsants compared to the other drugs at the end of treatment (weighted mean difference (WMD) -0.73; 95% CI -1.76 to 0.31). For the subgroup analysis of carbamazepine versus benzodiazepine, a statistically significant protective effect was found for the anticonvulsant (WMD -1.04; 95% CI -1.89 to -0.20), p = 0.02), but this was based on only 260 randomized participants. There was a non-significant decreased incidence of seizures (RR 0.50; 95% CI 0.18 to 1.34) favouring the patients that were treated with anticonvulsants than other drugs, and side-effects tended to be less common in the anticonvulsant-group (RR 0.56; 95% CI 0.31 to 1.02). **AUTHORS' CONCLUSIONS:** It is not possible to draw definite conclusions about the effectiveness and safety of anticonvulsants in alcohol withdrawal, because of the heterogeneity of the trials both in interventions and the assessment of outcomes. The extremely small mortality rate in all these studies is reassuring, but data on other safety outcomes are sparse and fragmented.	
BAP 2012	
MAIN RESULTS: Sixty four studies, 4309 participants, met the inclusion criteria.- Comparing benzodiazepines versus placebo, benzodiazepines performed better for seizures, 3 studies, 324 participants, RR 0.16 (0.04 to 0.69), no statistically significant difference for the other outcomes considered.- Comparing benzodiazepines versus other drugs, there is a trend in favour of benzodiazepines for seizure and delirium control, severe life threatening side effect, dropouts, dropouts due to side effects and patient's global assessment score. A trend in favour of control group was observed for CIWA-Ar scores at 48 hours and at the end of treatment. The results reach statistical significance only in one study, with 61 participants, results on Hamilton anxiety rating scale favour control MD -1.60 (-2.59 to -0.61)- Comparing different benzodiazepines among themselves,results never reached statistical significance but chlordiazepoxide performed better- Comparing benzodiazepine plus other drug versus other drug, results never reached statistical significance.- In the comparison of fixed-schedule versus symptom-triggered regimens, results from a single study, with 159 participants, favour symptom-triggered regimens MD -1.10 [-3.27, 1.07] for CIWA-Ar scores at the end of treatment. Differences in isolated trials should be interpreted very cautiously. **AUTHORS' CONCLUSIONS**: Benzodiazepines showed a protective benefit against alcohol withdrawal symptoms, in particular seizures, when compared to placebo and a potentially protective benefit for many outcomes when compared with other drugs. Nevertheless, no definite conclusions about the effectiveness and safety of benzodiazepines was possible, because of the heterogeneity of the trials both in interventions and the assessment of outcomes.	Amato L, Minozzi S, Vecchi S, et al. (2010) Benzodiazepines for alcohol withdrawal. Cochrane Database Syst Rev3: CD005063. **Systematic review**
BAP 2012	
MAIN RESULTS: Fifty-six studies, with a total of 4076 participants, met the inclusion criteria. Comparing anticonvulsants with placebo, no statistically significant differences for the six outcomes considered.Comparing anticonvulsant versus other drug, 19 outcomes considered, results favour anticonvulsants only in the comparison carbamazepine versus benzodiazepine (oxazepam and lorazepam) for alcohol withdrawal symptoms (CIWA-Ar score): 3 studies, 262 participants, MD -1.04 (-1.89 to -0.20), none of the	Minozzi S, Amato L, Vecchi S, et al. (2010) Anticonvulsants for alcohol withdrawal. Cochrane Database Syst Rev3: CD005064 **Systematic review**

other comparisons reached statistical significance.Comparing different anticonvulsants no statistically significant differences in the two outcomes considered.Comparing anticonvulsants plus other drugs versus other drugs (3 outcomes considered), results from one study, 72 participants, favour paraldehyde plus chloral hydrate versus chlordiazepoxide, for the severe-life threatening side effects, RR 0.12 (0.03 to 0.44). **AUTHORS' CONCLUSIONS:** Results of this review do not provide sufficient evidence in favour of anticonvulsants for the treatment of AWS. There are some suggestions that carbamazepine may actually be more effective in treating some aspects of alcohol withdrawal when compared to benzodiazepines, the current first-line regimen for alcohol withdrawal syndrome. Anticonvulsants seem to have limited side effects, although adverse effects are not rigorously reported in the analysed trials.	
Austraalia 2009, NICE 2010a, APA 2006	
METHODS: We conducted a prospective, randomized, double-blind, controlled trial including 117 consecutive patients with alcohol dependence. Patients were randomized into 2 groups: (1) 56 were treated with oxazepam in response to the development of signs of alcohol withdrawal (symptom-triggered); and (2) 61 were treated with oxazepam every 6 hours with additional doses as needed (fixed-schedule). The administration of oxazepam in group 1 and additional oxazepam in group 2 was determined using a standardized measure of alcohol withdrawal. The main outcome measures were the total amount and duration of treatment with oxazepam, the incidence of complications, and the comfort level. **RESULTS:** A total of 22 patients (39%) in the symptom-triggered group were treated with oxazepam vs 100% in the fixed-schedule group (P<.001). The mean oxazepam dose administered in the symptom-triggered group was 37.5 mg compared with 231.4 mg in the fixed-schedule group (P<.001). The mean duration of oxazepam treatment was 20.0 hours in the symptom-triggered group vs 62.7 hours in the fixed-schedule group (P<.001). Withdrawal complications were limited to a single episode of seizures in the symptom-triggered group. There were no differences in the measures of comfort between the 2 groups. **CONCLUSIONS:** Symptom-triggered benzodiazepine treatment for alcohol withdrawal is safe, comfortable, and associated with a decrease in the quantity of medication and duration of treatment.	Daeppen JB, Gache P, Landry U, Sekera E, Schweizer V, Gloor S, Yersin B: Symptomtriggered vs fixed-schedule doses of benzodiazepine for alcohol withdrawal: a randomized treatment trial. Arch Intern Med 2002; 162:1117–1121 **RCT**
NICE 2011, Austraalia 2009, NICE 2010a	
Alcohol misuse and alcohol withdrawal are associated with a variety of neuropsychiatric syndromes, some of which are associated with significant morbidity and mortality. B vitamin deficiency is known to contribute to the aetiology of a number of these syndromes, and B vitamin supplementation thus plays a significant part in prophylaxis and treatment. In particular, the Wernicke Korsakoff syndrome (WKS). due to thiamine deficiency, is a common condition in association with alcohol	Cook CC, Hallwood PM, Thomson AD. B Vitamin deficiency and neuropsychiatric syndromes in alcohol misuse. Alcohol 1998: Jul-Aug;33(4):317-36 **Review article**

misuse, and is associated with high morbidity and mortality. Nicotinamide deficiency may result in a rarer condition, alcoholic pellagra encephalopathy, which often has a similar clinical presentation to WKS. This review considers the role of B vitamins in the aetiology and treatment of neuropsychiatric syndromes associated with alcohol misuse, with particular emphasis on WKS. It is clear that oral thiamine supplementation is inadequate and ineffective. Parenteral supplements are associated with an extremely low incidence of serious adverse effects.Therefore, both prophylaxis and treatment should be routinely based upon parenteral vitamin supplementation. Given the high prevalence of B vitamin deficiency in alcohol-dependent patients,the increased thiamine requirement associated with the increased metabolic demands at alcohol withdrawal, and the lack of rapid efficient laboratory tests for B vitamin deficiency, it would appear to be wise to provide prophylactic B vitamin supplementation for all patients who undergo alcohol withdrawal on an in-patient basis.	
Asutraalia 2009, BAP 2012, APA 2006	
MAIN RESULTS: Two studies were identified that met the inclusion criteria, but only one contained sufficient data for quantitative analysis. Ambrose (2001) randomized participants (n=107) to one of five doses of intramuscular thiamine and measured outcomes after 2 days of treatment. We compared the lowest dose (5mg/day) with each of the other four doses. There was a significant difference in favour of the 200mg/day compared with the 5 mg/day dose in the number of trials taken to reach criterion on a delayed alternation test (MD -17.90, 95% CI -35.4 to -0.40, p=0.04). No significant differences emerged in comparing the other doses with 5 mg/day. The pattern of results did not present a simple dose-response relationship. The study had methodological shortcomings in design and the presentation of results that limited further analysis. **REVIEWER'S CONCLUSIONS:** There is insufficient evidence from randomized controlled clinical trials to guide clinicians in the dose, frequency, route or duration of thiamine treatment for prophylaxis against or treatment of WKS due to alcohol abuse.	Day E, Bentham P, Callaghan R, Kuruvilla T, George S. Thiamine for Wernicke Korsakoff Syndrome in people at risk from alcohol abuse. Cochrane Database Syst Rev. 2013;7:CD004033. **Systematic review**
SIGN 2003, NICE 2011, Austraalia 2009, APA 2006,	
Randomised trial (Hayashida et al., 1989), conducted in a US Department of Veterans Affairs (VA) medical centre, compared the effectiveness and safety of inpatient (n=77) and outpatient (n=87) assisted withdrawal. Patients with serious medical or psychiatric symptoms, predicted DTs and a very recent history of seizures were excluded from this study. The authors reported that more inpatients than outpatients completed assisted withdrawal. However, inpatient treatment was significantly longer and more costly than outpatient treatment. Additionally, both groups had similar reductions in problems post-treatment when assessed at 1- and 6-month follow-up. Although abstinence was	Hayashida, M., Alterman, A. I., McLellan, A. T., et al. (1989) Comparative effectiveness and costs of in-patient and out-patient detoxification of patients with mild-to-moderate alcohol withdrawal syndrome. New England Journal of Medicine, 320, 358–365 **RCT**

statistically significantly higher for the inpatient group at 1-month follow-up, these differences were not observed at 6-month follow-up. The authors concluded that outpatient assisted withdrawal should be considered for people with mild-to-moderate symptoms of alcohol withdrawal.	

Medinfokeskuse lisaotsingud

Kokkuvõtte (abstract või kokkuvõtlikum info)	**Viide kirjandusallikale**
MAIN RESULTS: We identified a total of 113 references from all electronic databases searched excluding duplicates. After screening of titles and abstracts, full papers of 10 studies were obtained and assessed for eligibility. Finally, two RCTs with 81 participants were eligible according to the inclusion criteria. Regarding the efficacy, one study suggested that both baclofen and diazepam significantly decreased the Clinical Institute Withdrawal Assessment of Alcohol Scale Revised (CIWA-Ar) score, without any significant difference between the two interventions. The other study showed no significant difference in CIWA-Ar score between baclofen and placebo but a significantly decreased dependence on high-dose benzodiazepines with baclofen compared to placebo. Meanwhile, only one study reported the safety outcomes and there were no side effects in either the baclofen or diazepam groups. **AUTHORS' CONCLUSIONS:** The evidence for recommending baclofen for AWS is insufficient. More well designed RCTs are needed to prove its efficacy and safety.	Liu j, Wang LN (2013) Baclofen for alcohol withdrawal. Cochrane Database Syst Rev 2013; CD008502 **Systematic review**
MAIN RESULTS: Four trials involving 317 people met the inclusion criteria. Three trials studied oral magnesium, with doses ranging from 12.5 mmol/day to 20 mmol/day. One trial studied parenteral magnesium (16.24 mEq q6h for 24 hours). Each trial demonstrated a high risk of bias in at least one domain. There was significant clinical and methodological variation between trials.We found no study that measured all of the identified primary outcomes and met the objectives of this review. Only one trial measured clinical symptoms of seizure, delirium tremens or components of the Clinical Institute Withdrawal Assessment for Alcohol (CIWA) score. A single outcome (handgrip strength) in three trials (113 people), was amenable to meta-analysis. There was no significant increase in handgrip strength in the magnesium group (SMD 0.04; 95% CI -0.22 to 0.30). No clinically important changes in adverse events were reported. **AUTHORS' CONCLUSIONS**: There is insufficient evidence to determine whether magnesium is beneficial or harmful for the treatment or prevention of alcohol withdrawal syndrome.	Sarai M, Tejani AM et al. (2013) Magnesium for alcohol withdrawal. Cochrane Database Syst Rev 2013; CD008358 **Systematic review**