Kliiniline küsimus nr 6

Kas kõigil bensodiasepiine ja alkoholi segatarvitavatel 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

Soovituse koostamiseks vaadati läbi 10 alkoholisõltuvuse ja liigkasutamise ravijuhendit. Teemakohast infot leiti neist 6-s (NICE 2011, Austraalia 2009, Soome 2010, BAP 2012, WFSBP 2008, APA 2006).

Üheski materjalis ei käsitletud bensodiasepiine ja alkoholi segatarvitavatel patsientidel võõrutussümptomite leevendamist mittefarmakoloogiliste meetoditega (sotsiaalne detoksikatsioon).

Alkoholi võõrutusseisundis olevatel patsientidel soovitatakse farmakoloogilist ravi **sõltumata sellest, kas tegemist on isoleeritud alkoholi kuritarvitamise/sõltuvusega või häirega millega seondub bensodiasepiinide kasutamine**.

Reeglina kasutatakse võõrutusseisundi korral medikamentoosset ravi, sest:

1) on keeruline ennustada, kellel tekivad rasked võõrutussümptomid (deliirium, hallutsinatsioonid, krambid);

2) ravimata võõrutusseisundi korral esineb suur haigestumus ja suremus võõrutussümptomite komplikatsioonidesse (deliiriumisse, hallutsinatsioonidesse ja krampidesse);

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.

Kui kaasuvad teised haigused (sh psühhiaatrilised) haigused, on medikamentoosset ravi soovitatud kasutada ka kergete ja mõõdukate võõrutussümptomite korral nendel patsientidel kellel esinevad

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 ($p < 0.001$).

NB! Saitz et al uuringust jäid välja patsiendid, kel esines tüsistusi (varasemad rasked võõrutused), st nende tulemusi ei saa laiendada patsientidele, kes kasutavad bensodiasepiine psühhiaatrilisel näidustusel.

Ravijuhistes on soovitatud bensodiasepiine kasutavatel alkoholivõõrutusega patsientidel kasutada bensodiasepiine fikseeritud annustes.

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

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.

Suhteliselt uudseks ravilühenemiseks on bensodiasepiinide algne suurtes kogustest manustamine (frontal loading), nt diasepaam 20 mg iga 1 tunni järel või diasepaam 20 mg iv iga 10 minuti järel kuni võõrutusnähtude kadumise või kerge sedatsiooni tekkeni (Gold et al, 2007). Seda soovitatakse kasutada raskete võõrutusnähtudega patsientidel.

Ravijuhendite soovituste tekstid (inglise keeles):

SIGN 2003:

This guideline pertains to patients with alcohol dependence, hazardous or harmful drinking, in primary care (general practice and community nursing) and among those attending, but not admitted from, A&E Departments

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.

Hospital detoxification is advised if the patient:
ß is confused or has hallucinations
ß has a history of previous complicated withdrawal
ß has epilepsy or a history of fits
ß is undernourished
ß has severe vomiting or diarrhoea
ß is at risk of suicide
ß has severe dependence and is unwilling to be seen daily
ß has a previously failed home-assisted withdrawal

ß has uncontrollable withdrawal symptoms
ß has an acute physical or psychiatric illness
*ß **has multiple substance misuse***
ß has a home environment unsupportive of abstinence.

NICE 2011:
Comorbid alcohol and benzodiazepine dependence Benzodiazepine use is more common in patients with alcohol misuse than in the general population, with surveys reporting prevalence of around 10 to 20% (Ciraulo et al. , 1988; Busto et al. , 1983). In more complex patients it can be as high as 40%, which is similar to that seen in psychiatric patients. A proportion of alcohol misusers who take benzodiazepines will be benzodiazepine dependent. For some individuals, their growing dependence on benzodiazepines began when a prescription for with-drawal from alcohol was extended and then repeatedly renewed. For others the prescription may have been initiated as a treatment for anxiety or insomnia, but then was not discontinued in line with current guidelines.

When undertaking assisted withdrawal, the patient is required to stop alcohol intake abruptly, and the ensuing withdrawal symptoms are treated with medication, usually benzodiazepines. Once the withdrawal symptoms are controlled, the medication can be gradually reduced and stopped at a rate that prevents withdrawal symptoms re-emerging but without creating over-sedation. Key elements of the process are to provide a large enough initial dose to prevent severe withdrawal symptoms including seizures, DTs, severe anxiety or autonomic instability, but to withdraw the medication at a rate which prevents re-emergence of symptoms or serious complications such as DTs or seizures. Special populations with indications for specific dosing regimens are discussed in Section 5.30.7

5.31.1.5 Consider inpatient or residential assisted withdrawal if a service user meets one or more of the following criteria. They:
•drink over 30 units of alcohol per day
• have a score of more than 30 on the SADQ
•have a history of epilepsy, or experience of withdrawal-related seizures or delirium tremens during previous assisted withdrawal programmes
• need concurrent withdrawal from alcohol and benzodiazepines

5.31.1.14 When managing withdrawal from co-existing benzodiazepine and alcohol dependence increase the dose of benzodiazepine medication used for withdrawal.
Inpatient withdrawal regimens should last for 2–3 weeks or longer, depending on the severity of co-existing benzodiazepine dependence.

Austraalia 2009:

Patients with heavy or regular use of other substances (such as benzodiazepines, stimulants, opiates) may experience more severe withdrawal features. In particular, withdrawal from both alcohol and benzodiazepines may increase the risk of withdrawal complications (Saitz 1998; Soyka et al. 1989).

Some patients wish to attempt ambulatory withdrawal despite multiple failed prior attempts. Further attempts at outpatient withdrawal may be appropriate, however clinicians should identify how this attempt will be different to previous attempts (e.g. increased home supports and monitoring), and negotiate with the patient mutually agreed criteria to be met in order to continue with the withdrawal attempt (e.g. no alcohol use in first 2 days).
Patients on waiting-lists for residential withdrawal units may require support in maintaining motivation and avoiding high risk activities until admission.
Prescribing benzodiazepines in an attempt to alleviate withdrawal prior to admission is not recommended, and may increase the risk of adverse events from the combination of alcohol and benzodiazepines.

Diazepam should be administered in a fixed dose regimen in ambulatory settings, or for those with concomitant medical, psychiatric or substance use disorders.
Diazepam should be administered in a loading regimen (20 mg 2 hourly until 60 to 80 mg or light sedation) in patients with a history of severe withdrawal complications (seizures, delirium); in patients presenting in severe alcohol withdrawal and/or with severe withdrawal complications (for example, delirium, hallucinations, following withdrawal seizure).

Patients dependent on alcohol and benzodiazepines or opioids should be stabilised on substitution medications while undergoing alcohol withdrawal.

Soome 2010:

Of intoxicant abusers seeking treatment in 1999, 22% were abusing legal drugs.
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.
– 10–20 mg of liquid diazepam is given every 1–2 hours (supervised and ntravenously, as necessary), until the patient calms down or the saturation dose (200 mg) is reached [209]. In users of mixed benzodiazepines the dose should be carefully considered: these patients may need considerably higher doses, particularly if dependent on high doses.
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 recommended.
Prevention of polysubstance use
– Drugs causing dependence should preferably not be prescribed for alcohol abusers. In emergency care, benzodiazepines should not normally be prescribed. However, should this be done, their use should be limited to the duration of withdrawal symptoms [206, 207, 290].
– Long-term use of benzodiazepines is indicated only exceptionally, when other treatment does not alleviate mental symptoms and it is possible to arr
ange frequent long-term treatment contacts.
– If benzodiazepines are considered necessary for an alcohol abuser, it must be ensured that they are appropriately taken.
Treatment of polysubstance users – Benzodiazepine intoxication (where the patient is unconscious) should be treated by flumazenil (0.25 mg i.v. repeatedly up to 2 mg, then 0.1–0.4 mg/h by infusion) [293, 294]
– The treatment of polysubstance abuse must be based on correct diagnosis and assessment of the severity of the state. Polysubstance use should be suspected if a heavy drinker or alcohol dependent person shows drug-seeking behaviour, if tolerance to benzodiazepines is observed during detoxification or if withdrawal symptoms appear when medication is reduced or withdrawn. An aggressive patient demanding a prescription, one obtaining prescriptions from various physicians or guilty of forging prescriptions may be a polysubstance user.
– At the clinic, a patient suspected of being a polysubstance user (intoxicated and lethargic, with incoordination or memory lapses, reduced inhibition, unpredictable or aggressive behaviour) should be given the required first aid. The patient should
be assessed and referred to the emergency room, detoxification or sobering-up station. Further treatment should be ensured.
– Polysubstance users have a tendency to convulsions due to alcohol and benzodiazepine withdrawal reactions. This risk needs to be considered in detoxification.
– Detoxification and rehabilitation of mixed users of alcohol and benzodiazepine should be possible under close surveillance in outpatient care, if the
patient is sufficiently motivated [298, 299].
Around 25% of motivated patients are capable of stopping the use of benzodiazepines at the first treatment attempt.
– In motivated patients dependent on alcohol and benzodiazepines, cognitive behavioural therapy will probably not improve on efficacy of the standard methods used at A-Clinics [298, 299].
– If the patient uses high doses of benzodiazepines, if the use is uncontrolled or previous attempts at detoxification and rehabilitation in outpatient care have been unsuccessful, detoxification and rehabilitation should be carried out on a detoxification ward. The severity of withdrawal symptoms can be monitored using the CIWA-B form [300].
– If detoxification is repeatedly unsuccessful, an attempt should be made to commit the patient to supervised treatment instead of "street medication", for example by making a pharmacy contract.
– Use of carbamazepine support may improve the chances of success of benzodiazepine detoxification, and so may the use of valproate but there is no reliable evidence for this. Relevant studies have been performed on patients dependent on benzodiazepines only.
– Carbamazepine can also be used to prevent withdrawal convulsions [301].

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.
The use of anticonvulsants continues to receive attention, since reducing glutamate overactivity is now thought to be key in reducing risk of brain toxicity during withdrawal.
NICE, CG100, (2010c) (Ia) recommended using carbamazepine or benzodiazepines, although in the UK there is less clinical experience in using anticonvulsants. NICE, CG115, (2011a) (Ia) guidelines did not comment on use of carbamazepine.
... the finding that using carbamazepine during withdrawal was followed by longer time to eventual return to drinking than with using the benzodiazepine, lorazepam (Malcolm et al., 2002) (Ib), raises the question of whether benzodiazepine withdrawal leaves the brain vulnerable to relapse.
Seizures
xBenzodiazepines, particularly diazepam, prevent de novo seizures (A)
x Anticonvulsants are equally as efficacious as benzodiazepines in seizure prevention, but there is no advantage when combined (A)

WFSBP 2008:
Few controlled treatment studies have been conducted in patients with co-existing psychiatric disorders, a topic that has received more attention in recent years. The limited research database indicates that in these patients treatment of alcohol dependence should be integrated with treatment of the comorbid psychiatric disorder (Berglund et al. 2003).

NICE 2010a:
Severe withdrawal (requirement for 600 mg or more, total, cumulative benzodiazepine (expressed in chlordiazepoxide equivalents) was significantly associated with participation in two or more prior alcohol treatment programs (OR 2.6 [95%CI 1.3 to 5.6]; p=0.01) (ref 21. Kraemer KL, Mayo SM, Calkins DR. Independent clinical correlates of severe alcohol withdrawal. Substance Abuse. 2003; 24(4):197-209.)

Sealsamast:
cohort) had severe withdrawal. We identified six independent correlates of severe withdrawal: use of a morning eye-opener (adjusted odds ratio [OR], 5.6; 95% confidence interval [CI], 1.2–25.9), an initial CIWA-Ar score ≥ 10 (OR, 5.1; 95% CI, 2.4–10.6), a serum aspartate aminotransferase ≥ 80 U/L (OR, 4.2; 95% CI, 2.0–8.8), past benzodiazepine use (OR, 3.6; 95% CI, 1.3–9.9), self-reported history of "delirium tremens"

APA 2006*:*
Not all individuals who are intoxicated or using substances will develop withdrawal symptoms. Withdrawal syndromes usually occur in physically dependent individuals who discontinue or reduce their substance use after a period of heavy and regular use.
Factors that predict the severity of a withdrawal syndrome include 1) type of substance used, 2) time elapsed since last use, 3) metabolic rates of the substance, 4) dissociation rates of the substance from receptor sites, 5) synergistic effects or drug-drug interactions from the concomitant use of other prescribed or nonprescribed medications, 6) the presence or absence of concurrent general medical or psychiatric disorders, and 7) past withdrawal experiences (especially for alcohol).
The high prevalence of co-occurring psychiatric disorders in substance-dependent patients implies that many such patients will require specific pharmacotherapy for a co-occurring disorder.
The presence of a substance use disorder will have an impact on psychiatric issues, such as the risk of suicide or other self-injurious behaviors and the risk of aggressive behaviors, including homicide. In addition, the presence of co-occurring psychiatric symptoms or disorders affects the patient's treatment adherence as well as the onset, course, and prognosis of the substance use disorder (170, 288–292). These factors need to be taken into consideration when arriving at a treatment plan for an individual patient.

Although the presence of multiple substance use disorders is the norm, there is limited re-

search to guide clinicians on adapting the usual evidence-based clinical interventions to the treatment of individuals using more than one substance, including medication and psychosocial treatments. The best recommendation is for the clinician to do a comprehensive assessment of the patient and integrate the evidence-based treatment approaches, including pharmacological and psychosocial treatments, for each specific substance use disorder.
Use of multiple substances and co-occurring psychiatric and substance use disorders are now so common in treatment settings that these combinations should be expected.
Once clinical stability is achieved, the tapering of benzodiazepines and other medications should be carried out as necessary, and the patient should be observed for the reemergence of withdrawal symptoms and the emergence of signs and symptoms suggestive of co-occurring psychiatric disorders.

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	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**

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 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	Williams D, McBride AJ. The drug treatment of alcohol withdrawal symptoms: a systematic review. Alcohol Alcohol 1998;33(2):103-15. **Systematic review**

be the drug of first choice.	
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 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.	Saitz R, Mayo-Smith MF, Roberts MS, Redmond HA, Bernard DR, Calkins DR. Individualized treatment for 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	Polycarpou A, Papanikolaou P, Ioannidis J, Contopoulos-Ioannidis D: Anticonvulsants for alcohol withdrawal. Cochrane Database Syst Rev 2005; CD005064

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 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.	**Systematic review**
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	Minozzi S, Amato L, Vecchi S, et al. (2010) Anticonvulsants for alcohol withdrawal. Cochrane Database Syst Rev3: CD005064

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 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.	**Systematic review**
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**

Medinfokeskuse lisaotsingud:

Lähteandmed	Otsingu kirjeldus
Milliseid publikatsioone ja millisel teemal otsitakse: *Alkoholi ja bensodiasepiine segakasutavate patsientide alkoholivõõrutussündroomi ravi erinevused võrreldes ainult alkoholi kasutavate patsientidega kirjeldatuna 2010 ja hiljem avaldatud publikatsioonides.*	*Alkoholi ja bensodiasepiine segakasutavate patsientide alkoholivõõrutussündroomi ravi erinevused võrreldes ainult alkoholi kasutavate patsientidega.* *Comorbid alcohol and benzodiazepine dependence OR co-existing benzodiazepine and alcohol dependence OR alcohol and benzodiazepine withdrawal AND systematic review OR meta-analysis OR randomized controlled trial*
 K6_tulemused_pubmed.xls **Tulemused**	Antud märksõnu kasutades leiti 73 publikatsiooni, millest relevantseimat on refereeritud allpool.
BACKGROUND:Alcohol abuse and dependence represents a serious health problem worldwide with social, interpersonal and legal interpolations. Benzodiazepines have been widely used for the treatment of alcohol withdrawal symptoms. Moreover it is unknown whether different benzodiazepines and different regimens of administration may have the same merits. OBJECTIVES:To evaluate the effectiveness and safety of benzodiazepines in the treatment of alcohol withdrawal. SEARCH STRATEGY:Cochrane Drugs and Alcohol Group' Register of Trials (December 2009), PubMed, EMBASE, CINAHL (January 1966 to December 2009), EconLIT (1969 to December 2009). Parallel searches on web sites of health technology assessment and related agencies, and their databases. SELECTION CRITERIA:Randomized controlled trials examining effectiveness, safety and risk-benefit of benzodiazepines in comparison with placebo or other pharmacological treatment and between themselves. All patients were included regardless of age, gender, nationality, and outpatient or inpatient therapy. DATA COLLECTION AND ANALYSIS:Two authors independently screened and extracted data from studies. 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,	Amato L, Minozzi S, Vecchi S, Davoli M. Benzodiazepines for alcohol withdrawal. Cochrane Database Syst Rev. 2010;(3):CD005063.

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 andthe assessment of outcomes. ---------- Selles meta-analüüsis kasutatud uuringuid hnnati eraldi (oublikatsioonis toodud sisse- ja väljalülitamiskriteeriumite alusel) selgitamaks, kas alkoholvõõrutuse kliinilisesse uuringutesse kaasati ka patsiente, kes kasutasid bensodiasepiine Enamikes uuringutes ei lubatud osaleda neil patsientidel, kes kasutasid teisi illegaalseid narkootikume (polydryg users), psühhotroopseid ravimeid, antikonvulsante, uinuteid, bensodiasepiine 5 päeva enne uuringut, kes kasutasid mingeid teisi ravimeid, kelle uriinitest oli positiivne BDZ.le – nt. Addolorato 1999; Addolorato 2006. Addinoff 1994, Ansoms 1991, Anton 1997, Baumgartner 1987, Baumgartner 1991; Brown 1972; Burroughs 1985ab; Day 2004; Favre 2005; Kolin 1981; Kramp 1978; Kumar 2009; Lapierre 1983; Longo 2002; Lucht 2003; ;Malcolm 1989; 2002; 2007; McLendon 1980; Mendels 1985; Mielke 1976; Miller 1984; Mukherjee 1983; Nava 2007; O'Brien 1983; Palestine 1976; Pena Ramos 1977; 1979; Radouco-Thomas 1989; Ritson 1986; Saitz 1994; Saletu 1983; Solomon 1983; Spies 1996; 2003; Stuppaeck 1992; Tubridy 1988; Worner 1994;	

Kokkuvõtte (abstract või kokkuvõtlikum info)	**Viide kirjandusallikale**
ABSTRACT: Complex patterns of multiple substance use pose clinical and methodological challenges for substance abuse clinical trials research. To increase measurement precision and internal validity, the modal approach has been to target both treatment interventions and outcome assessment to a single class of abused substance. This strategy warrants reconsideration because it entails limitations in recruitment feasibility and generalization of study findings. This report reviews pros and cons of single versus multiple targeted drugs, suggests guidelines for choosing between these strategies and outlines methods for broadening the scope of substance abuse clinical trails to take abuse of multiple substances into account. We recommend that investigators consider moving away from a single drug focus in three ways. First, include systematic assessment of a wide range of psychoactive substance use throughout the trial and evaluate the impact of study treatments on use of all classes of drugs. Second, except where contraindicated, include patients who use and abuse multiple classes of substances even in trials evaluating treatment of a single targeted drug. Third, consider inclusion of polysubstance abusers or those who primarily abuse multiple classes of substances in the same clinical trial. Although many treatment	Rounsaville et al (2003) Single versus multiple drug focus in substance abuse clinical trials Research. Drug and Alcohol Dependence 70:117-125.

efficacy questions can best be answered by single focus studies, we recommend that such designs be adopted only after less restrictive designs are first considered.	
Clinical Manual of Addiction Psychopharmacology is a comprehensive guide to the pharmacology of drugs of abuse and the medications used to treat dependence on those substances. This new, second edition provides a thorough update on a broad range of addictive substances, along with enhanced coverage in areas where significant advances have been made since publication of the first edition. Clinicians, including psychiatrists, psychiatric residents and fellows, and other mental health practitioners who encounter individuals with substance-related disorders in the course of their clinical work, will find the manual to be well-organized, exhaustively referenced, and current.	Clinical Manual of Addiction Psychopharmacology, Second Edition, Sedatives, Hypnotics and Anxiolytics, American Psychiatric Publishing, 2014.