Kliiniline küsimus nr 11

Kas kõigil alkoholi kuritarvitamise ja alkoholisõltuvusega patsientidel kasutada raviks aversiivseid ravimeid vs alkoholihimu vähendavaid ravimeid vs muid psühhotroopseid ravimeid?

Kriitilised tulemusnäitajad: *abstinents, tagasilangus, alkoholi tarvitamise vähenemine, patsiendi rahulolu, patsiendi elukvaliteet, kvaliteetselt elatud eluaastate lisandumine, haiguse/vaegurluse tõttu kaotatud päevade arv, ravisoostumus, ravi katkestamine mistahes põhjusel, ravi katkestamine ravimite kõrvaltoimete tõttu, juhuslik alkoholi tarvitamine*

Ravijuhendid

Kokkuvõte tõendusmaterjali kvaliteedist

Akamprosaat ja naltreksoon

3 meta-analüüsi (Kanzler et al 2001, Rosner et al 2008, Mann et al 2004) ja 2 süstemaatilist ülevaadet (Bouza et al 2004, Rösner et al 2010a) soovitavad alkoholisõltuvuse ravis kasutada akamprosaati.

3 meta-analüüsi (Kanzler et al 2001, Rosner et al 2008, Streeton et al 2001) ja 4 süstemaatilist ülevaadet (Roozen et al 2006, Srisurapanont et al 2005, Bouza et al 2004, Rösner et al 2010b) soovitavad alkoholisõltuvuse ravis kasutada naltreksooni.

1 kirjanduse ülevaade (Hulse 2013) väidab, et naltreksooni efektiivsus võib olla piiratud tingituna patsientide halvast kooperaabelsusest.

Meta-analüüs Mann et al 2004 koosnes 17 randomiseeritud kontrollitud uuringust. Püsiva abstinentsi säilitamine oli tunduvalt suurem akamprosaadi ravirühmas kui platseebo ravirühmas (akamprosaat 36.1%, platseebo 23.4%; RR 1.47; 95% CI 1.29 – 1.69; p<0.001).

1 Cochrane'i süstemaatiline ülevaade (Rösner et al 2010a) koosnes 24 RCT-st. Võrreldes platseeboga vähendas akamprosaat märgatavalt alkoholi tarbimist: RR 0.86 (95% CI 0.81-0.91); NNT 9.09 (95% CI 6.66-14.28). Kõige sagedasem kõrvaltoime oli akamprosaadil diarröa.

1 meta-analüüs (Streeton et al 2001) väidab, et naltreksoon on tunduvalt efektiivsem kui platseebo. Hinnati 7 RCT-d, mis kõik eelistasid naltreksooni platseebole: keskmine tagasilanguse määr oli 14% madalam; keskmine päevade arv, millal joodi oli 3% madalam; keskmine abstinentsi suurus oli 10% suurem.

1 süstemaatiline ülevaade (Srisurapanont et al 2005) koosnes 29 RCT-st (2 neist hindas nalmefeeni, 27 naltreksooni). Võrreldes platseeboga vähenes naltreksooni kasutajatel tunduvalt relapside hulk: RR 0.64 (95% CI 0.51-0.82). Naltreksooni kasutamine vähendab relapside hulka 36% (NNT 7) ning vähendab võimalust joomise taasalustamiseks 13% (NNT 12). Nalmefeeni kohta on kirjanduses liialt vähe infot ja selle põhjal ei saa teda alkoholisõltvuse ravis soovitada.

1 Cocharne'i süstemaatiline ülevaade (Rösner et al 2010b) koosnes 50 RCT-st ning näitas, et naltreksoon vähendab raske alkoholi tarvitamise hulka 83% võrreldes platseeboga: RR 0.83 (95% CI 0.76-0.90). Naltreksoon vähendas alkoholi tarvitamise päevade arvu 4%; MD -3.89 (95% CI -5.75 kuni -2.04). Sagedasemateks kõrvaltoimeteks olid gastrointestinaalsed kaebused ja uimasus. Ülevaade leiab, et uuringute vähesuse tõttu ei saa soovitada alkoholisõltuvuse ravis süstitavat pikatoimelist naltreksooni ja nalmefeeni.

1 meta-analüüs (Kanzler et al 2001) väidab, et akamprosaadi ja naltreksooni efektiivsuses pole statistilist erinevust alkoholisõltuvuse ravis.

1 meta-analüüs (Rosner et al 2008) ja 1 süstemaatiline ülevaade (Bouza et al 2004) võrdlesid omavahel akamprosaati ja naltreksooni. Meta-analüüs väidab, et akamprosaat sobib eelkõige abstinentsi säilitamiseks, naltreksoon aga nii abstientsi säilitamiseks kui ka joomasööstude ennetamiseks. Akamprosaat ei mõjutanud peale ühe dringi joomist alkoholi tarvitamist. Mõlemad ravimid on alkoholisõltuvuse ravis efektiivsed ja ravimi valik sõltub terapeutlistest eesmärkidest. Süstemaatilise ülevaate kohaselt on mõlemad ravimid efektiivsed, kuid akamprosaadil on parem ravisoostumus: akamprosaat OR = 1.29; 95% CI 1.13-1.47; p<0.001; naltreksoon OR = 0.94; 95% CI 0.80 – 1.1; p=0.5.

Nalmefeen

1 artikkel (Gual et al 2014) on näidanud, et nalmefeeni kasutamine 6 kuu jooksul on efektiivne eriti kõrge või väga kõrge riskiga patsientite hulgas võrreldes platseeboga. Vähenes tarbitava alkoholi kogus: -7.6 g/päevas (95% CI: -11.6 kuni -3.5); p= 0.0003). vähenes päevade arv, millal alkoholi tarbiti: -2.00 päevi/kuus (95% CI: -3.00 kuni -1.00); p=0.000001). Teisesed tulemusnäitajad, nagu GGT, ALAT, CGI (Clinical Global Impression), paranesid samuti. Nalmefeen on reeglina hästi talutav.

1 RCT (Mann et al 2013) väidab, et nalmefeen on efektiivsem kui platseebo. 6 kuu kasutamise järel vähenes nalmefeeni kasutajatel päevade arv, millal alkoholi tarbiti enam kui platseebo kasutajatel: -2.3 päeva (95% CI: -3.8 kuni -8); p=0.0021). Vähenes ka alkoholi tarvitamise hulk: (-1.0 g/päevas (95% CI: -16.8 kuni -5.1); p=0.0003).

1 ülevaate artikkel (Niciu et al 2013) väidab, et nalmefeen on Euroopas alkoholi sõltuvuse ravis lubatud kasutada. Üldine raviefekt on siiski väike (päevade arv, mil alkoholi tarbiti ja alkoholi kogus), kuid võib olla oluline teatud populatsioonis. Naltreksooni raviefekt on suurem kui nalmefeenil. Kuna olemasolevaid uuringuid nalmefeeni kohta on liialt vähe ei saa tugevaid soovitusi nalmefeeni kasutamise kohta anda.

1 artikkel (Keating 2013) hindas nalmefeeni kasutamist vastavalt vajadusele kõrge riskiga patsientidel. 2 RCT uuirngut väidavad, et nalmefeeni kasutamine vastavalt vajadusele vähendas tunduvalt päevade arvu, millal alkoholi tarvitati. Vähenes ka alkoholi tarbitav kogus. 1 RCT aga väitis, et efekt on nähtav 13 kuu möödudes, kuid mitte 6 kuu möödudes.

1 eksepertarvamus (Soyka 2010) leiab, et nalmefeen võib olla efektiivne alkoholismi ravis, kuid vajalikud on täiendavad uuringuid, kuna tõendusmaterjali on liialt vähe. Nalmefeeni ja naltreksooni toimemehhanismid on sarnased, kuid pole ühtegi uuirngut, mis võrdleks omavahel neid kahte ravimit ja näitaks, et nalmefeen on efektiivsem kui naltreksoon.

1 süstemaatiline ülevaade (Rösner et al 2010b) ütleb, et nalmefeeni kohta on andmebaasis liialt vähe infot, et teha lõplikke järeldusi. Nalmefeenil on sarnane keemiline struktuur kui naltreksoonil, kuid tal kirjeldatakse rohkem positiivseid eeliseid: nalmefeen seostub suurema efektiivsusega tsentraalsete opioidretseptoritega, tal on suurem biosaadavus, puudub annusest sõltuv maksatoksilisus. Ülevaade koosnes 50 RCT (naltreksoon: n=47, nalmefeen: n=3); 3881 patsienti said naltreksooni, 286 nalmefeeni: Nalmefeen vs platseebo: nalmefeen langetas riski taasalustada joomist 85% (RR = 0.85; 95% CI 0.67 - 1.08) ja vähendas riski taasalustada joomist pärast detoksifikatsiooni 92% (RR = 0.92; 95% CI 0.70 - 1.20). sagedasemad kõrvaltoimed olid iiveldus (RD = 0.20; 95% CI 0.14- 0.26), unetus (RD = 0.12; 95% CI 0.05 - 0.19) ja pearinglus (RD = 0.15; 95% CI 0.05 - 0.25). ükski efektiivsuse tulemusnäitaja ei saavutanud statistilist olulisust.

Disulfiraam

1 süstemaatiline ülevaade (Alharbi et al 2013) hindas disulfiraami ohutust ning leiti, et disulfiraami manustamine on ohutu ja mõistliku riskiprofiiliga.

1 randomiseeritud kontrollitud uuirng (Chick et al 1992) hindas disulfiraami efektiivsust alkoholisõltuvuse ravis, kus patsiendid olid hästi jälgitud. Võrreldi omavahel dilsufiraami ja c-vitamiini manustamist. Disulfiraam suurendas abstinentsi 100 päeva, C-vitamiini manustamine aga 69 päeva. Nädalane alkoholi kogus vähenes disulfiraami grupis 162 ühikut, C-vitamiini grupis 105 ühikut. Tõsiseid kõrvaltoimeid ei täheldatud.

1 randomiseeritud kontrollitud uuring (Laaksonen et al 2008) võrdles omavahel disulfiraami, akamprosaati ja naltreksooni koos psühhoteraapiaga. Disulfiraam koos superviseeritud kasutamisega osutus efektiivsemaks kui akamprosaat või naltreksoon. Disulfiraam vähendas nädala jooksul tarvitavate drinkide arvu, pikendas aega esimese dringini ning pikendas abstinentsi. Akamprosaadi ja naltreksooni korral raviefektiitsuses erinevusi ei olnud.

1 randomiseeritud kontrollitud uuring (De Sousa et al 2005) võrdles omavahel akamprosaati ja disulfiraami. De Sousa et al 2005 uuring näitas, et disulfiraam on võrreldes akamprosaadiga efektiivsem neil, kellel on hea tugisüsteem. Relaps kestis disulfiraami ravigrupis keskmiselt 123 päev ja akamprosaadi ravigrupis 71 päeva (p=0.0001). 88% patsientidest jäid disulfiraami grupis abstinentsi, akamprosaadi grupis aga 46% (p=0.0002).

Baklofeen

1 süstemaatiline ülevaade (Liu et al 2011) koosnes 1 RCT-st ja hindas balkofeeni kasutamist alkoholisõltuvuse ravis. Kirjanduses on liialt vähe infot, et soovitada baklofeeni alkoholisõltuvse ravis.

1 süstemaatiline ülevaade (Agabio et al 2013) koosnes 11 RCT-st, mis hindasid baklofeeni efektiivsust alkoholisõltuvuse ravis. 5 RCT-d leidsid, et baklofeen on efektiivne, 5 RCT-d et pole efektiivne. Antud tulemuste alusel ei saa baklofeeni alkoholisõltuvuse raviks soovitada.

Antidepressandid

1 meta-analüüs (Torrens et al 2005) hindas antidepressantide kasutamist alkoholisõltuvuse ravis. Antidepressante (eelkõige SSRI) pole soovitatav kasutada. Ilma depressioonita esinevat alkoholisõltuvust ei soovitata antidepressntidega ravida.

Antikonvulsandid

1 süstemaatiline ülevaade (Pani et al 2014) koosnes 25 RCT-st ja hindas antikonvulsantide kasutamist alkoholisõltuvushäire ravis. Kirjanduses on liialt vähe infot, et soovitada antikonvulsante alkoholisõltuvusehäire raviks. Uuringute tulemused on heterogeensed ja uuringud väikesed. Keskmise kvaliteediga tõendusmaterjal väidab, et antikonvulsandid vähendavad drinkide arvu ja joomasööste. Võrreldes naltreksooniga olid ravikatkestajate hulk, relapside arv ning abstinentsi pikkus samad.

Antipsühhootikumid

1 meta-analüüs (Kishi et al 2013) koosnes 13 RCT-st ja hindas antipsühhootikumide efektiivsust alkoholisõltuvushäire ravis. Antipsühhootikumid ei suurendanud abstinentsi ega vähendanud alkoholi tarbimist, seega ei soovitata neid kasutada.

Tabel 1. SAMHSA 2009 ravijuhendist

Exhibit 6-4
AUD Medication Decision Grid

Pretreatment Indicators	Medications			
	Acamprosate (Campral®)	Disulfiram (Antabuse®)	Oral Naltrexone (ReVia®, Depade®)	Injectable Naltrexone (Vivitrol®)
Renal failure	X	A	A	A
Significant liver disease	A	C	C	C
Coronary artery disease	A	C	A	A
Chronic pain	A	A	C	C
Current opioid use	A	A	X	X
Psychosis	A	C	A	A
Unwilling or unable to sustain total abstinence	A	X	A	A
Risk factors for poor medication adherence	C	C	C	A
Diabetes	A	C	A	A
Obesity that precludes IM injection	A	A	A	X
Family history of AUDs	A	A	+	+
Bleeding/other coagulation disorders	A	A	A	C
High level of craving	A	A	+	+
Opioid dependence in remission	A	A	+	+
History of postacute withdrawal syndrome	+	A	A	A
Cognitive impairment	A	X	A	A

A = Appropriate to use C = Use with caution
X = Contraindicated + = Particularly appropriate

Kokkuvõte ravijuhendites leiduvatest soovitustest

Kümnest ravijuhendist üheksas (SIGN 2003, NICE 2011, Austraalia 2009, Soome 2010, BAP 2012, WFSBP 2008, NSW 2008, APA 2006, SAMHSA 2009) leidus infot käesoleva küsimuse kohta. Kõik ravijuhendid soovitavad medikamentoosset ravi kasutada ainult koos psühhosotsiaalse teraapiaga. Austraalia 2009 ravijuhend soovitab farmakoteraapiat kasutada kõigil patsientidel. NICE 2011, BAP 2012 ravijuhendid soovitavad farmakoteraapiat kasutada nendel patsientidel, kes pole abi saanud ainult psühhoteraapiast või soovivad ise medikamentoosset ravi. Ülejäänud ravijuhendid ei täpsusta, millal konkreetselt tuleks medikamentoosse raviga alustada.

8 ravijuhendit (NICE 2011, Austraalia 2009, Soome 2010, BAP 2012, WFSBP 2008, NSW 2008, APA 2006, SAMHSA 2009) soovitavad medikamentoosseks raviks akamprosaati, naltreksooni või disulfiraami. Üks ravijuhend (SIGN 2003) naltreksooni ei soovita, kuna UKs pole see alkoholisõltuvuse ravis litsenseeritud.

8 ravijuhendit (NICE 2011, Austraalia 2009, Soome 2010, BAP 2012, WFSBP 2008, NSW 2008, APA 2006, SAMHSA 2009) soovitavad esmavaliku preparaadiks akamprosaati või naltreksooni; disulfiraam on teisevaliku preparaat.

7 ravijuhendit (SIGN 2003, NICE 2011, Austraalia 2009, Soome 2010, BAP 2012, APA 2006, SAMHSA 2009) soovitavad enne disulfiraamiga ravi alustamist küsida patsiendilt nõusolekut, teavitama teda ohtudest ning ravi peab olema hästi kontrollitud.

4 ravijuhendit (NICE 2011, Austraalia 2009, BAP 2012, APA 2006) soovitavad antidepressante ja bensodiasepiine alkoholisõltuvuse raviks mitte kasutada.

5 ravijuhendit (NICE 2011, Austraalia 2009, Soome 2010, BAP 2012, SAMHSA 2009) andsid soovitusi kas süstitava pikatoimelise naltreksooni, nalmefeeni, baklofeeni, topiramaadi, gabapentiini, pregabaliini, olansapiini või aripiprsaooli kohta. Antud ravimid on paljulubavad alkoholisõltuvuse ravis, kuid liialt väheste uuringute tõttu neid esmavaliku preparaatidena ei soovitata.

Töörühma poolt palutud täiendused küsimustele:

1. Kas nalmefeeni kohta on tehtud ka meta-analüüse?

Teostatud medinfokeskuses päring 27.08.2014 andmebaasist pubmed järgmiste otsisõnadega:

nalmefene and alcohol dependence OR nalmefene and alcohol misuse OR nalmefene and harmful alcohol use AND systematic review OR meta-analysis OR randomized controlled trial (vt. Lisa 1.)

2. Töörühm soovib teada, millised on tulemusnäitajad abstinentsi säilitamises ja alkoholikoguste vähendamises nalmefeenil ja naltreksoonil.

3. Alkoholihimu vähendavate preparaatide (nalktreksoon ja nalmefeen) efektiivsuse uuringutes palun täpsustada study population, kas oli uuringusse kaasatud ka ALKOHOLI KURITARVITAMISE diagnoosiga pt-e? Seda on vaja, et vastata K11 küsimusele, mis puudutab ka kuritarivtajaid (ehk et kui uuringud on kõik tehtud alkoholi sõltuvatel patsientidel, siis on raske kuritarvitajatele naltreksooni või nalmefeeni soovitada, kui uuringuid sellel populatsioonil ei ole tehtud.)

1. ja 2. Punkt vt tabel 2

2. Rösner 2010b üheks esmaseks tulemusnäitajaks on taaspöördumine alkoholi tarvitamisele *(return to any drinking. Return to any drinking with its complementary event "continuous abstinence" is a binary variable containing the information whether a patient returned to drinking after detoxification, or whether a patient remained completely abstinent throughout the entire course of the study*).

Taaspöördumine alkoholi tarvitamisele hõlmab mõistet, kus patsient taasalustab joomist, pärast detoksifikatsiooni, või kui patsient oli abstinentsis kogu uuringu aja.

Naltreksoon vs platseebo

Outcome	**No. of studies**	**No. of participants**	**Statistical method**	**Effect size**
Return to drinking	27	4693	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.92, 1.00]

3. Läbiviidud uuringud naltreksooni ja nalmefeeniga hõlmavad alkoholisõltuvusega patsiente. NICE 2011 ravijuhendi koostajad püüdsid teostada meta-analüüsi alkoholi kuritarvitajate farmakoteraapia kohta, kuid kuna sellel populatsioonil puudusid sellised uuringud, siis piirduti narratiivse sünteesiga uuringutest, mis saadaval oli. Kokkuvõte tõendusmaterjalist alkoholi kuritarvitajatele:

Evidence summary NICE 2011:

In general, psychosocial approaches should be offered to all individuals who misuse alcohol. For those for whom such approaches have not worked or who are mildly dependent, medication may be a treatment option. However the only medication that has been studied in this population is naltrexone. Whilst the majority of participants included in the trials in the meta-analyses were abstinent prior to starting naltrexone, in some of these studies people were still drinking with the aim that naltrexone would

help to reduce consumption.

Heinala and colleagues (2001) investigated naltrexone (50 mg) started without assisted withdrawal in people who were dependent and treatment-seeking. They showed that in combination with coping skills but not supportive therapy, naltrexone reduced risk of relapse to heavy drinking but did not improve abstinence or time to first drink. In this study, abstinence was not emphasised as part of coping skills, but was in supportive therapy.

In those less severely dependent and non-dependent, naltrexone (50 mg per day) has been shown to reduce the likelihood of any drinking (Kranzler et al. , 2003). Interestingly, if they were taking medication (naltrexone or placebo) in a targeted manner (that is, when anticipating a high-risk situation), greater reductions in heavy drinking days were seen compared with taking medication daily. A follow-up trial confirmed 'targeted' naltrex-one reduced drinks per day, but only in men (Kranzler et al. , 2009). Notably both trials excluded people who had an unsuccessful attempt to reduce their drinking. Leeman and colleagues (2008) reported in a pilot open study of heavy-drinking young adults (18 to 25 years old) that targeted naltrexone as an adjunct to counselling was well tolerated and reduced drinking, suggesting that this might be a way forward to improve outcomes beyond counselling alone.

Karhuvaara and colleagues (2007) reported that in harmful drinkers experiencing problems controlling their drinking (some may have been dependent), nalmefene (20 mg per day) similarly reduced the number of heavy drinking days.

Clinical summary (NICE 2011):

The evidence is limited but does support the use of medication (naltrexone) to reduce drinking in non-dependence or mild dependence and does not demonstrate equiva-lence with psychological interventions for this group. There was no direct evidence for the use of acamprosate in this group.

Tabel 2. Uuringud nalmefeeni kohta

Study	Design	Sample size/group distribution	Outcomes	Effect size
Karhuvaara et al 2007 Targeted nalmefene with simple medical management in the treatment of heavy drinkers: a randomized double-blind placebo-controlled multicenter study.	Prospective, multi-site double blind, parallel group, randomized controlled trial over 28 weeks (with 24 week randomized withdrawal extension) of nalmefene vs placebo	403 subjects whom 242 took nalmefene (10 to 40 mg) and 161 took placebo	The mean monthly number of heavy drinking days after 28 weeks	Mean monthly no. of heavy drinking days at 28 weeks: Cohen's d=0,15 (95 % CI -0,11 to 0,41). During treatment, the mean numbers of HDDs were 8.6 to 9.3 in the nalmefene group and 10.6 to 12.0 in the placebo group (p=0.0065)
Mann et al 2013 Extending the Treatment Options in Alcohol Dependence: A Randomized Controlled Study of As-Needed Nalmefene	Prospective, multi-site (Europe), double blind, parallel group, randomized controlled trial over 6 months	Patients taking placebo (n=289) and patients taking nalmefene (n=290)	Change from baseline in heavy drinking days and total alcohol consumption (grams/day) at Month 6	At Month 6, nalmefene compared with placebo in reducing the number of heavy drinking days (-2.3 days [95% confidence interval:-3.8 to-0.8]; p=0.0021) and total alcohol consumption (-11.0 g/day [95% confidence interval:-16.8 to -5.1]; p = 0.0003).
Gual et al. 2013 A randomised, double-blind, placebo-controlled, efficacy study of nalmefene, as-needed use, in patients with alcohol dependence.	Prospective, multi-site (Europe), double blind, parallel group, randomized controlled trial over 6 months	718 patients (placebo=360; nalmefene=358). Nalmefene dose was 18 mg/day	Change from baseline to month 6 in heavy drinking days Reducing total alcohol consumption	Nalmefene compared to placebo in the change from baseline to month 6 in heavy drinking days (group difference: -1.7 days/month [95% CI -3.1; -0.4]; p=0.012). Reducing total alcohol consumption (group difference: -5.0 g/day last month [95% CI -10.6; 0.7]; p=0.088).
Van den Brink et al 2014. Long-term efficacy, tolerability and safety of nalmefene as-needed in patients	Prospective, multi-site (Europe), double blind, parallel group, randomized (3:1) controlled trial over 1 year	675 alcohol-dependent patients; A total of 166 patients (68%) in the placebo group and 509 in the nalmefene group (18 mg/day) completed the	Reduction of the number of heavy drinking days (HDDs) Reduction of total alcohol consumption	Nalmefene vs placebo, in the reduction of the number of heavy drinking days (HDDs) (- 1.6 days/month (95% CI - 2.9; - 0.3); p = 0.017)

with alcohol dependence: A 1-year, randomised controlled study.		study.		in the reduction of total alcohol consumption (TAC) (- 6.5 g/day last month (95% CI - 12.5; - 0.4); p = 0.036)
Anton et al 2004. Multi-site dose ranging study of nalmefene in the treatment of alcohol dependence.	Double-blind comparison to placebo multisite trial	3 doses of nalmefene (5, 20, or 40 mg) in a double-blind comparison to placebo over a 12-week treatment period in 270 recently abstinent outpatient alcohol-dependent individuals	The time to first heavy drinking day	The time to first heavy drinking day was also not significantly different between the placebo and the active treatment groups. Possibly because of variation among the sites or the comparatively small sample size, there was no evidence of superior efficacy outcomes with nalmefene treatment.
Mason 1994 A double-blind, placebo-controlled pilot study to evaluate the efficacy and safety of oral nalmefene HCl for alcohol dependence.	A double-blind pilot study	21 alcohol-dependent subjects were randomly assigned to 12 weeks of double-blind treatment with 40 mg nalmefene, 10 mg nalmefene, or placebo, resulting in 7 patients/treatment group	Relapse rate Number of abstinent days/week Decrease in the number of drinks/drinking day	The 40 mg group had a significantly lower rate of relapse (p < or = 0.05), and a greater increase in the number of abstinent days/week (p < or = 0.09). A significant decrease in the number of drinks/drinking day was noted for both nalmefene groups (p < or = 0.04), but not for placebo.
Mason 1999 A double-blind, placebo-controlled study of oral nalmefene for alcohol dependence.	A double-blind, placebo-controlled study	The 105 outpatient volunteers were abstinent for a mean of 2 weeks prior to random assignment to the placebo or 20- or 80-mg/d dose nalmefene groups for 12 weeks.	Relapse to heavy drinking	Fewer patients treated with nalmefene relapsed to heavy drinking through 12 weeks of treatment (P<0.02). The odds ratio of relapsing to heavy drinking was 2.4 times greater with placebo compared with nalmefene (95% confidence interval, 1.05-5.59).

Ravijuhendite soovituste tekstid (inglise keeles):

SIGN 2003

Acamprosate is recommended in newly detoxified dependent patients as an adjunct to psychosocial interventions.

Acamprosate will usually be initiated by a specialist service within a few days of successful detoxification. If a specialist service is not available, the GP should offer acamprosate, monitor its efficacy and provide links to local support organisations.

Supervised oral disulfiram may be used to prevent relapse but patients must be informed that this is a treatment requiring complete abstinence and be clear about the dangers of taking alcohol with it.

Disulfiram supervision may be undertaken by the spouse, healthcare or support worker, or the workplace representative if appropriate. Naltrexone, although supported by the above reports, and used by specialists in Scotland, is not licensed in the UK for the treatment of alcohol dependence.

NICE 2011

For harmful drinkers and people with mild alcohol dependence who have not responded to psychological interventions alone, or who have specifically requested a pharmacological intervention, consider offering acamprosate or oral naltrexone in combination with an individual psychological intervention (cognitive behavioural therapies, behavioural therapies or social network and environment-based therapies) or behavioural couples therapy.

After a successful withdrawal for people with moderate and severe alcohol dependence, consider offering acamprosate or oral naltrexone in combination with an individual psychological intervention (cognitive behavioural therapies, behavioural therapies or social network and environment-based therapies) focused specifically on alcohol misuse.

After a successful withdrawal for people with moderate and severe alcohol dependence, consider offering acamprosate or oral naltrexone in combination with behavioural couples therapy to service users who have a regular partner and whose partner is willing to participate in treatment.

After a successful withdrawal for people with moderate and severe alcohol dependence, consider offering disulfiram in combination with a psychological intervention to service users who:

1) *have a goal of abstinence but for whom acamprosate and oral naltrexone are not suitable, or*
2) *prefer disulfiram and understand the relative risks of taking the drug.*

Do not use antidepressants (including selective serotonin reuptake inhibitors [SSRIs]) routinely for the treatment of alcohol misuse alone.

Do not use gammahydroxybutyrate (GHB) for the treatment of alcohol misuse.

Benzodiazepines should only be used for managing alcohol withdrawal and not as ongoing treatment for alcohol dependence.

If using acamprosate, start treatment as soon as possible after assisted withdrawal. Usually prescribe at a dose of 1,998 mg (666 mg three times a day) unless the service user weighs less than 60 kg, and then a maximum of 1,332 mg should be prescribed per day. Acamprosate should:

1) *usually be prescribed for up to 6 months, or longer for those benefiting from the drug who want to continue with it*
2) *be stopped if drinking persists 4–6 weeks after starting the drug.*

Service users taking acamprosate should stay under supervision, at least monthly, for 6 months, and at reduced but regular intervals if the drug is continued after 6 months. Do not use blood tests routinely, but consider them to monitor for recovery of liver function and as a motivational aid for service users to show improvement.

If using oral naltrexone, start treatment after assisted withdrawal. Start prescribing at a dose of 25 mg per day and aim for a maintenance dose of 50 mg per day. Draw the service user's attention to the information card that is issued with oral naltrexone about its impact on opioid-based analgesics. Oral naltrexone should:

1) *usually be prescribed for up to 6 months, or longer for those benefiting from the drug who want to continue with it*
2) *be stopped if drinking persists 4–6 weeks after starting the drug.*

Service users taking oral naltrexone should stay under supervision, at least monthly, for 6 months, and at reduced but regular intervals if the drug is continued after 6 months. Do not use blood tests routinely, but consider them for older people, for people with obesity, for monitoring recovery of liver function and as a motivational aid for service users to show improvement. If the service user feels unwell advise them to stop the oral naltrexone immediately.

If using disulfiram, start treatment at least 24 hours after the last alcoholic drink consumed. Usually prescribe at a dose of 200 mg per day. For service users who continue to drink, if a dose of 200 mg (taken regularly for at least 1 week) does not cause a sufficiently unpleasant reaction to deter drinking, consider increasing the dose in consultation with the service user.

Before starting treatment with disulfiram, test liver function, urea and electrolytes to assess for liver or renal impairment. Check the SPC for warnings and contraindications in pregnancy and in the following conditions: a history of severe mental illness, stroke, heart disease or hypertension.

Make sure that service users taking disulfiram:

1) *stay under supervision, at least every 2 weeks for the first 2 months, then monthly for the following 4 months*
2) *if possible, have a family member or carer, who is properly informed about the use of disulfiram, oversee the administration of the drug*
3) *are medically monitored at least every 6 months after the initial 6 months of treatment and monitoring.*

Warn service users taking disulfiram, and their families and carers, about:

1) *the interaction between disulfiram and alcohol (which may also be found in food, perfume, aerosol sprays and so on), the symptoms of which may include flushing, nausea, palpitations and, more seriously, arrhythmias, hypotension and collapse*
2) *the rapid and unpredictable onset of the rare complication of hepatotoxicity; advise service users that if they feel unwell or develop a fever or jaundice that they should stop taking disulfiram and seek urgent medical attention.*

Austraalia 2009

Pharmacotherapy should be considered for all alcohol-dependent patients, in association with psychosocial supports.
Naltrexone is recommended as relapse prevention for alcohol-dependent patients.
Naltrexone is not suitable for people who are opioid dependent or who have pain disorders needing opioid analgesia.
Naltrexone should be started as soon as possible after completion of withdrawal (usually 3 to 7 days after last drink).
Acamprosate is recommended as relapse prevention for alcohol-dependent patients.
Acamprosate should be started as soon as possible after completion of withdrawal (usually 3 to 7 days after last drink).
Disulfiram is recommended in closely supervised alcohol-dependent patients motivated for abstinence and with no contraindication.
A range of medications appear promising agents in reducing alcohol relapse (such as topiramate, gabapentin, baclofen, aripiprazole); however, need further research and are not recommended as first-line options at this stage.
Benzodiazepines and antidepressants are not recommended as relapse prevention agents in alcohol dependence.

Soome 2010

Psychosocial therapies form the cornerstone of treatment in alcohol dependence, but the results may be significantly enhanced (by 15-25%, on an average) with drug therapies.
Unsupervised, patients may take disulfiram irregularly and often without achieving results. Supervised disulfiram medication (400 mg twice a week or 200 mg/day) has significantly improved the results achieved with psychosocial therapies alone in the treatment of alcohol dependence.
With disulfiram implants inadequate blood levels are achieved, and the effect is therefore no greater than that of a placebo.
Opioid antagonists (naltrexone and nalmefene) are thought to reduce the pleasure associated with intoxication, making drinking less rewarding and therefore likely to reduce craving and relapses.
Naltrexone (50 mg daily) increases the number of non-drinking days and reduces relapses compared with placebo. Concomitant behavioural or motivational therapy greatly improves the treatment results.
A long-acting naltrexone injection evidently increases the number of non-drinking days and reduces drinking when combined with motivational or cognitive therapy.
Naltrexone or nalmefene taken in situations associated with imminent relapse (targeted medication) evidently reduces alcohol consumption and increases the number of non-drinking days.
Acamprosate, a calcium salt of taurine available on special licence in Finland, affects the excitatory glutaminergic pathway in the brain and acts as a GABA receptor agonist. Its mechanism of action in reducing craving for alcohol is unknown. Compared with placebo, acamprosate has improved the treatment results achieved with pscyhosocial therapy alone.
Ondansetron (antiemetic) is a serotonin 5-HT_3 receptor blocker. It evidently reduces alcohol consumption and appears to be effective particularly in the treatment of early-onset alcoholism.
Baclofen (reducing skeletal muscle spasticity) is a GABA(B) receptor agonist inhibiting the transmission of spinal reflex impulses, probably by stimulating GABA(B) receptors. It has no effect on neuromuscular transmission. Baclofen may extend the period of sobriety achieved by psychosocial therapy in cirrhotic alcoholics.
Three studies, two of them controlled, have been performed with quetiapine in the treatment of alcoholic patients with personality disorder or young patients with bipolar affective disorder. Quetiapine may decrease alcohol consumption among patients with bipolar affective disorder and early-onset alcoholism.
The antiepileptic topiramate apparently decreases the release of dopamine in the mesolimbic brain area, enhances the action of gamma-aminobutyric acid and acts as a glutamate antagonist. Topiramate may improve the results achieved with psychosocial therapy.

BAP 2012
Pharmacotherapy should be the default position, such that the decision not to prescribe is made actively for those patients presenting with harmful alcohol use or abuse that have not benefited from psychosocial interventions and for everyone with dependence, rather than only thinking of medication for more complex patients.
Acamprosate can be used to improve abstinence rates (A). It should be continued if the person starts drinking, since there is evidence that acamprosate reduces alcohol consumption (A), at least for a period to assess whether there is overall patient benefit attributable to acamprosate.
Naltrexone can be used to reduce risk of lapse becoming a relapse, but there is less evidence to support its use in maintaining abstinence (A). Naltrexone may therefore be a better choice if someone is 'sampling' alcohol regularly but wishes to be abstinent.
For acamprosate and naltrexone there is no consistent evidence to suggest which types of patient will respond, and relapse prevention medication should be offered to/considered for everyone who is alcohol dependent wanting to be abstinent (A).
Disulfiram is effective if intake is witnessed. Disulfiram can be offered as a treatment option for patients who intend to maintain abstinence, and for whom there are no contraindications (B).
Baclofen should be considered if a patient wants tobe abstinent, has high levels of anxiety and has not benefited from or is unable to take acamprosate, naltrexone or disulfiram (C).
SSRIs should be avoided, or used with caution in type 2 alcoholism (B)

WFSBP 2008
In conclusion, there is abundant evidence supporting the use of naltrexone for treatment of alcohol dependence (Level A).
For example, in a meta-analysis of data from 11 European clinical trials that included more than 3,000 patients, acamprosate nearly doubled the likelihood of preventing relapse to drinking [odds ratio (OR)=1.88, 95% confidence interval (CI) =1.57 - 2.25, P<0.001] and increased the likelihood that patients would remain in treatment by nearly one-third (OR=1.29, 95% CI =1.13 - 1.47, P<0.001).
Disulfiram is best considered a second-line medication in relapse prevention, which can be combined with either acamprosate or naltrexone.
Nalmefene was significantly better than placebo in reducing heavy drinking days, very heavy drinking days, and drinks per drinking day and in increasing abstinent days.

NSW 2008
A number of pharmacotherapies are available to assist a client in working toward abstinence, manage withdrawal symptoms and to prevent cravings. In particular, naltrexone, acamprosate and disulfiram have shown benefits in treating alcohol use problems over the short-term, if combined with a psychological intervention. Naltrexone in particular, if combined with coping skills training, is useful in preventing relapse to alcohol use.

APA 2006
Naltrexone may attenuate some of the reinforcing effects of alcohol.
Acamprosate, a γ-aminobutyric acid (GABA) analog that may decrease alcohol craving in abstinent individuals, may also be an effective adjunctive medication in motivated patients who are concomitantly receiving psychosocial treatment.
Disulfiram is an effective adjunct to a comprehensive treatment program for reliable, motivated patients whose drinking may be triggered by events that suddenly increase alcohol craving.
Disulfiram should never be used without the patient's knowledge and consent.
However, subsequent studies in patients diagnosed with alcohol dependence have been less consistent and suggest that SSRIs may worsen drinking behaviors in some individuals.

SAMHSA 2009
Disulfiram should never be administered to a patient who is in a state of alcohol intoxication or without the patient's full knowledge. The physician should instruct relatives accordingly.
Disulfiram appears to have modest clinical efficacy in maintaining alcohol abstinence in patients with AUDs, particularly when administered under supervision.
Disulfiram may work as an adjunct to psychosocial treatment to eliminate alcohol consumption for patients who can achieve initial abstinence of at least 12 hours, are committed to maintaining abstinence, agree to take the medication, and do not have contraindications to disulfiram. The consensus panel concludes that disulfiram is most effective for patients who have undergone detoxification or are in the initiation stage of abstinence, especially when they are committed to abstinence and receive adequate, ongoing supervision. Disulfiram may not reduce the urge to

drink alcohol.
Acamprosate is typically initiated 5 days following drinking cessation. Acamprosate reaches full effectiveness in 5 to 8 days. However, evidence exists that acamprosate is most effective for patients who, at treatment onset, are motivated for complete abstinence rather than decreased drinking
Naltrexone appears to be effective for attenuating craving in people who are alcohol dependent.
Naltrexone has the capacity to cause hepatocellular injury when given in excessive doses. Naltrexone is contraindicated in acute hepatitis or liver failure, and its use in patients with active liver disease must be carefully considered in light of its hepatotoxic effects. The margin of separation between the apparently safe dose of naltrexone and the dose causing hepatic injury appears to be only fivefold or less. Naltrexone does not appear to be a hepatotoxin at the recommended doses. Patients should be warned of the risk of hepatic injury and advised to stop the use of naltrexone and seek medical attention if they experience symptoms of acute hepatitis.
The FDA Center for Drug Evaluation and Research (CDER) analysis of the study data concluded that injectable naltrexone is effective only in those who were abstinent at baseline. This medication should be considered for individuals with alcohol dependence who have not responded to other pharmacological and behavioral treatments, in particular those who have problems with treatment adherence. Physicians may be concerned that the decreased frequency of required medical visits that comes with monthly medication will result in decreased use of medical and psychosocial services, making patients less likely to attend counseling, 12-Step, or mutual-help group meetings.

Viited

Ravijuhendid

The management of harmful drinking and alcohol dependence in primary care, a national clinical guideline, Scottish Intercollegiate Guidelines Network, 2003	SIGN 2003
Treatment of Alcohol Abuse, Current Care Guideline**,** The Finnish Medical Society Duodecim and the Finnish Society of Addiction Medicine,2010	Soome 2010
NSW Health Drug and Alcohol Psychosocial Interventions Professional Practice Guidelines, 2008	NSW 2008
Guidelines for the Treatment of Alcohol Problems, Australian Government Department of Health and Ageing, 2009	Austraalia 2009
Incorporating Alcohol Pharmacotherapies Into Medical Practice . Treatment Improvement Protocol (TIP) Series, Substance Abuse and Mental Health Services Administration, 2009.	SAMHSA 2009
Practice Guideline For The Treatment of Patients With Substance Use Disorders, 2nd Edition, American Psychiatric Association, 2006	APA 2006
Alcohol-Use Disorders: Diagnosis, Assessment and Management of Harmful Drinking and Alcohol Dependence, National Institute for Health & Clinical Excellence, 2011	NICE 2011
World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Substance Use and Related Disorders, Part 1: Alcoholism, 2008	WFSBP 2008
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

Süstemaatilised ülevaated ja ristläbilõikelised uuringud

Kokkuvõtte (abstract või kokkuvõtlikum info)	**Viide kirjandusallikale**
SIGN 2003, Austraalia 2009, Soome 2010, BAP 2012, WFSBP 2008, APA 2006, SAMHSA 2009	
RESULTS: Both antidipsotropics exerted significant, but modest, effects on treatment retention and/or drinking outcomes. There was significant variability among the studies for the measure on which the largest effect was exerted by each of these medications. Based on limited comparisons of the two medications, there appears to be no statistical difference in their efficacy in the treatment of alcohol dependence. In contrast, there was a consistent effect of selective serotonin reuptake inhibitors on depressive symptoms in major depression, which was significantly greater than the effects observed for the antidipsotropics. **CONCLUSIONS:** Both naltrexone and acamprosate are efficacious in reducing alcohol consumption in alcoholics. However, their specific role in alcoholism treatment remains to be more clearly defined. New approaches to the use of these medications and development of new medications are needed if pharmacotherapy is to play a substantial role in the treatment of alcoholism.	Kranzler HR, Van Kirk J. Efficacy of naltrexone and acamprosate for alcoholism treatment: a meta-analysis. Alc Clin Exp Res 2001;25(9):1335-41 **Meta-analysis**
NICE 2011, Austraalia 2009, BAP 2012, WFSBP 2008	
Abstract: Two pharmacological agents have repeatedly been shown to be efficacious for relapse prevention in alcohol dependence: The putative glutamate-antagonist *acamprosate* and the opioid-antagonist *naltrexone*. Clinical evidence for both drugs is based on various outcome criteria. Whereas for acamprosate primarily abstinence maintenance has been demonstrated, studies with naltrexone have mostly emphasised the prevention of heavy drinking. The remaining effects of both drugs are not always reported; accordingly the corresponding database is fragmentary. Thus, the primary objective of the present meta-analysis was to complete the efficacy profiles for acamprosate and naltrexone and to compare them with each other. Unreported results, requested from the study investigators and the drug manufacturers, were integrated in the computation of effect sizes. For the meta-analysis, emphasis was placed on the conceptual distinction between having a first drink and returning to heavy drinking. Naltrexone was found to have a significant effect on the maintenance of abstinence as well as the prevention of heavy drinking. Acamprosate was shown only to support abstinence; it did not influence alcohol consumption after the first drink. When the efficacy profiles of the two drugs were compared, acamprosate was found to be more effective in preventing a lapse, whereas naltrexone was better in preventing a lapse from becoming a relapse. The superiority of either one drug or over the other one cannot be determined as a general rule, it rather depends on the therapeutic target. Benefits in the treatment of alcohol dependence might be optimized by matching the efficacy profiles of specific antidipsotropics with the motivational status of alcohol-dependent patients.	Rosner, S., Leucht, S., Lehert, P., et al.(2008) Acamprosate supports abstinence, naltrexone prevents excessive drinking: evidence from a meta-analysis with unreported outcomes. Journal of Psychopharmacology, 22, 11–23. **Meta-analysis**
NICE 2011, Austraalia 2009, BAP 2012, WFSBP 2008, APA 2006	
Abstract: Antidepressants are commonly used in substance abusers due to the potential effect on some underlying mechanisms involved in drug use disorders and to treat comorbid depression. A systematic review of the literature of the efficacy of antidepressant drugs in subjects with drug abuse disorders, including alcohol, cocaine, nicotine and opioid, with and without comorbid depression was performed. Only randomised, double-	Torrens, M., Fonseca, F., Mateu, G., et al. (2005) Efficacy of antidepressants in substance use disorders with and without comorbid depression: a systematic review and meta-analysis. Drug and Alcohol DependenceDrug and Alcohol

blind, controlled trials have been evaluated. A meta-analysis was done with the included studies that used common evaluation procedures in alcohol, cocaine and opioid dependence. Based on the present review some recommendations may be proposed. The prescription of antidepressants for drug abuse seems only clear for nicotine dependence with or without previous comorbid depression (bupropion and nortryptiline). In alcohol dependence without comorbid depression, the use of any antidepressant seems not justified, while in cocaine dependence has to be clarified. The use of antidepressants in alcohol, cocaine or opioid dependence with comorbid depression needs more studies in well-defined samples, adequate doses and duration of treatment to be really conclusive. Interestingly, SSRIs do not seem to offer significant advantages compared with tricyclic drugs in substance abuse disorders. Differences both related to individual characteristics and specific antidepressant drugs need to be clarified in future studies.	Dependence, 78, 1–22. **Meta-analysis**
Austraalia 2009, BAP 2012, WFSBP 2008, APA 2006, SAMHSA 2009	
RESULTS: A total of 19 published 1 unpublished RCTs were identified that fulfilled the selection criteria; 3 were excluded because the documentation available was insufficient to allow adequate assessment. The remaining 17 studies, which included 4087 individuals, 53% of whom received active drug, were of good quality and were otherwise reasonably comparable. There was no evidence of publication bias. Continuous abstinence rates at 6 months were significantly higher in the acamprosate-treated patients (acamprosate, 36.1%; placebo, 23.4%; RB, 1.47; [95% confidence intervals (CI): 1.29-1.69]; $p < 0.001$). This effect was observed independently of the method used for assigning missing data. The effect sizes in abstinent rates at 3, 6, and 12 months were 1.33, 1.50, and 1.95, respectively. At 12 months, the overall pooled difference in success rates between acamprosate and placebo was 13.3% (95% CI, 7.8-18.7%; number needed to treat, 7.5). Acamprosate also had a modest but significant beneficial effect on retention (6.01%; [95% CI, 2.90-8.82]; $p = 0.0106$). **CONCLUSION:** Acamprosate has a significant beneficial effect in enhancing abstinence in recently detoxified, alcohol-dependent individuals.	Mann, K, P Lehert and MY Morgan 2004, The efficacy of acamprosate in the maintenance of abstinence in alcohol-dependent individuals: Results of a meta-analysis. Alcohol Clin Exp Res28: 51–63. **Meta-analysis**
Austraalia 2009, WFSBP 2008, APA 2006, SAMHSA 2009	
RESULTS: The meta-analysis of benefit indicates that naltrexone is superior to placebo. Subjects treated with naltrexone experience significantly fewer episodes of relapse, and significantly more remain abstinent when compared to placebo-treated subjects [risk difference of relapse rates = -14% [95% confidence interval (CI): -23%, -5%]; and risk difference of abstinence rates = 10% (95% CI: 4%, 16%)] after 12 weeks of treatment. The naltrexone-treated subjects also consume significantly less alcohol over the study period than do placebo-treated subjects. There is no significant difference between naltrexone and placebo in terms of the number of subjects with at least one adverse event or the number of subjects who discontinued the trial due to an adverse event. Seven trials were reviewed. All outcomes favored the naltrexone	Streeton, C and G Whelan 2001 Naltrexone, a relapse prevention maintenance treatment of alcohol dependence: a meta-analysis of randomized controlled trials. Alcohol Alcohol36(6): 544-552. **Meta-analysis**

subjects over those receiving placebo: the average relapse rate was 14 percent lower; the average days of drinking was 3 percent lower; and the average abstinence rate was 10 percent greater. There were no differences in the incidence of reporting at least one adverse event or the incidence of discontinuation because of adverse events between the naltrexone and placebo subject groups. **CONCLUSION:** Naltrexone is superior to placebo for the treatment of alcohol dependence.	
Austraalia 2009, SAMHSA 2009	
Abstract: This systematic review summarises evidence of the effectiveness of naltrexone (NTX) and the added value of psychosocial treatment in the maintenance treatment of opioid and alcohol dependence. Studies were selected through a literature search conducted in March 2004. Seven opioid and seventeen alcohol studies were identified. When possible, meta-(regression) analyses were performed. There is lack of evidence about the effectiveness of NTX in the maintenance treatment of opioid dependence. There is evidence for the effectiveness and applicability of NTX in the management of alcohol dependence. The opioid studies combined NTX with a variety of psychosocial interventions, which plagued the evaluation of their value. Concomitant psychosocial interventions used in the alcohol studies were mainly cognitive behavioural, which seems to be more effective than NTX combined with supportive therapy. Available data do not allow firm conclusions regarding the added effect of psychosocial interventions. However, the data suggest that a combination of naltrexone with cognitive behavioural relapse prevention therapy is beneficial in alcohol dependent patients.	Roozen, H, de Waart R, van der Windt DA et al. 2006, A systematic review of the effetiveness of nalterxone on the maintenance treatment of opioid and alcohol dependence. Eur Neuropsychopharmacol16: 311-323. **Systematic review**
Austraalia 2009, Soome 2010, WFSBP 2008, APA 2006, SAMHSA 2009	
MAIN RESULTS: The review included 29 RCTs presented in 36 articles. Except two RCTs of nalmefene, all others investigated NTX. In comparison to placebo, a short-term treatment of NTX significantly decreased the relapse [RR (95% CI) = 0.64 (0.51 to 0.82)] and was likely to decrease the return to drinking [RR (95% CI) = 0.87 (0.76 to 1.00). In the respect of acceptability, NTX treatment significantly diminished treatment withdrawal [RR (95% CI) = 0.82 (0.70 to 0.97). While a medium-term treatment of NTX gave no benefit in the respect of relapse prevention, it was found to be beneficial on two of four secondary outcomes by increasing time to first drink and diminishing craving. A medium-term treatment of NTX was superior to acamprosate in reducing relapses, standard drinks and craving. NTX plus an intensive psychosocial treatment (PST) was not superior to NTX plus a simple PST on any primary and secondary short-term outcomes. For a medium-term treatment, NTX plus an intensive PST was superior to NTX plus a simple PST in increasing time to first drink and decreasing craving. **AUTHORS' CONCLUSIONS:** The review findings support that short-term treatment of NTX decreases the chance of alcohol relapses for 36% (number-needed-to-treat or NNT = 7) and likely to reduce the chance of returning to drinking for 13% (NNT = 12). In comparison to placebo group, NTX treatment can lower the risk of treatment withdrawal in alcohol-dependent patients for 28% (NNT = 13). Some major limitations of the available evidence include short study duration in many trials,	Srisurapanont, M and N Jarusuraisin 2005, Opioid antagonists for alcohol dependence. Cochrane Database of Systematic Reviews (2). **Systematic review**

small sample sizes in most trials and lack of data on psychosocial benefits. In conclusion, NTX should be accepted as a short-term treatment for alcoholism. Strategies to improve adherence to NTX treatment, eg, PSTs and management of adverse effects, should be concomitantly given. We have not yet known so far how long alcohol-dependent patients who respond to NTX treatment should continue their treatment. Due to too little evidence, NMF should have no role for the treatment of alcohol dependence.	
Austraalia 2009, BAP 2012, WFSBP 2008, APA 2006, SAMHSA 2009	
MEASUREMENTS: Relapse and abstinence rates, cumulative abstinence duration and treatment compliance were considered as primary outcomes. Findings Thirty-three studies met the inclusion criteria. Acamprosate was associated with a significant improvement in abstinence rate [odds ratio (OR): 1.88 (1.57, 2.25), P < 0.001] and days of cumulative abstinence [WMD: 26.55 (17.56, 36.54]. Short-term administration of naltrexone reduced the relapse rate significantly [OR: 0.62 (0.52, 0.75), P < 0.001], but was not associated with a significant modification in the abstinence rate [OR: 1.26 (0.97,1.64), P = 0.08]. There were insufficient data to ascertain naltrexone's efficacy over more prolonged periods. Acamprosate had a good safety pattern and was associated with a significant improvement in treatment compliance [OR: 1.29 (1.13,1.47), P < 0.001]. Naltrexone's side effects were more numerous, yet the drug was nevertheless tolerated acceptably without being associated with a lower adherence to treatment (OR: 0.94 (0.80, 1.1), P = 0.5). However, overall compliance was relatively low with both medications. **CONCLUSIONS**: Both acamprosate and naltrexone are effective as adjuvant therapies for alcohol dependence in adults. Acamprosate appears to be especially useful in a therapeutic approach targeted at achieving abstinence, whereas naltrexone seems more indicated in programmes geared to controlled consumption. Both drugs are safe and acceptably tolerated but issues of compliance need to be addressed adequately to assure their usefulness in clinical practice.	Bouza, C, Angeles M, Magro A et al. 2004, Efficacy and safety of naltrexone and acamprosate in the treatment of alcohol dependence: a systematic review. Addiction99(7): 811-828. **Systematic review**
BAP 2012	
MAIN RESULTS: We identified a total of 82 references from all electronic databases searched excluding duplicate. After screening of titles and abstracts, full papers of 7 studies were obtained and assessed for eligibility. Finally, only one study met the inclusion criteria, with 37 participants. **AUTHORS' CONCLUSIONS:** The evidence of recommending baclofen for AWS is insufficient. More well designed RCTs are demanded to further prove its efficacy and safety.	Liu J and Wang L (2011) Baclofen for alcohol withdrawal. Cochrane Database Syst Rev1: CD008502. **Systematic review**
BAP 2012	
MAIN RESULTS: 24 RCTs with 6915 participants fulfilled the criteria of inclusion and were included in the review. Compared to placebo, acamprosate was shown to significantly reduce the risk of any drinking RR 0.86 (95% CI 0.81 to 0.91); NNT 9.09 (95% CI 6.66 to 14.28) and to significantly increase the cumulative abstinence duration MD 10.94 (95% CI 5.08 to 16.81), while secondary outcomes (gamma-glutamyltransferase, heavy drinking) did not reach statistical significance. Diarrhea was the only side effect that was more frequently reported under acamprosate than placebo RD 0.11 (95% 0.09 to 0.13); NNTB 9.09 (95% CI 7.69 to 11.11). Effects of industry-sponsored trials RR 0.88 (95% 0.80 to 0.97) did not significantly	Rösner S, Hackl-Herrwerth A, Leucht S, et al. (2010a) Acamprosate for alcohol dependence. Cochrane Database Syst Rev9: CD004332. **Systematic review**

differ from those of non-profit funded trials RR 0.88 (95% CI 0.81 to 0.96). In addition, the linear regression test did not indicate a significant risk of publication bias (p = 0.861). **AUTHORS' CONCLUSIONS:** Acamprosate appears to be an effective and safe treatment strategy for supporting continuous abstinence after detoxification in alcohol dependent patients. Even though the sizes of treatment effects appear to be rather moderate in their magnitude, they should be valued against the background of the relapsing nature of alcoholism and the limited therapeutic options currently available for its treatment.	
BAP 2012	
MAIN RESULTS: Based on a total of 50 RCTs with 7793 patients, naltrexone reduced the risk of heavy drinking to 83% of the risk in the placebo group RR 0.83 (95% CI 0.76 to 0.90) and decreased drinking days by about 4%, MD -3.89 (95% CI -5.75 to -2.04). Significant effects were also demonstrated for the secondary outcomes of the review including heavy drinking days, MD - 3.25 (95% CI -5.51 to -0.99), consumed amount of alcohol, MD - 10.83 (95% CI -19.69 to -1.97) and gamma-glutamyltransferase, MD - 10.37 (95% CI -18.99 to -1.75), while effects on return to any drinking, RR 0.96 (95 CI 0.92 to 1.00) missed statistical significance. Side effects of naltrexone were mainly gastrointestinal problems (e.g. nausea: RD 0.10; 95% CI 0.07 to 0.13) and sedative effects (e.g. daytime sleepiness: RD 0.09; 95% CI 0.05 to 0.14). Based on a limited study sample, effects of injectable naltrexone and nalmefene missed statistical significance. Effects of industry-sponsored studies, RR 0.90 (95% CI 0.78 to 1.05) did not significantly differ from those of non-profit funded trials, RR 0.84 (95% CI 0.77 to 0.91) and the linear regression test did not indicate publication bias (P = 0.765). **AUTHORS' CONCLUSIONS:** Naltrexone appears to be an effective and safe strategy in alcoholism treatment. Even though the sizes of treatment effects might appear moderate in their magnitudes, these should be valued against the background of the relapsing nature of alcoholism and the limited therapeutic options currently available for its treatment.	Rösner S, Hackl-Herrwerth A, Leucht S, et al. (2010b) Opioid antagonists for alcohol dependence. Cochrane Database Syst Rev12: CD001867. **Systematic review**
NICE 2011, Austraalia 2009, BAP 2012, WFSBP 2008, SAMHSA 2009	
Abstract: To assess the efficacy of supervised disulfiram as an adjunct to out-patient treatment of alcoholics, a randomised, partially blind, six-month follow-up study was conducted in which 126 patients received 200 mg disulfiram or 100 mg vitamin C under the supervision of a nominated informant. In the opinion of the (blinded) independent assessor, patients on disulfiram increased average total abstinent days by 100 and patients on vitamin C by 69, thus enhancing by one-third this measure of treatment outcome. Mean weekly alcohol consumption was reduced by 162 units with disulfiram, compared with 105 units with vitamin C, and the disulfiram patients reduced their total six-month alcohol consumption by 2572 units compared with an average reduction of 1448 units in the vitamin C group. Serum gamma-GT showed a mean fall of 21 IU/I in patients on disulfiram but rose by a mean of 13 IU/I	Chick, J., Gough, K., Falkowski, W., et al.(1992) Disulfiram treatment of alcoholism. British Journal of Psychiatry, 161, 84–89 **RCT**

with vitamin C. Unwanted effects in the disulfiram group led to a dose reduction in seven patients and to treatment withdrawal in four (and in one vitamin C patient). Two-thirds of the disulfiram group asked to continue the treatment at the end of the study. There were no medically serious adverse reactions.	
NICE 2011, BAP 2012, WFSBP 2008	
Results: At the end of the trial, 93 patients were still in contact. Relapse (the consumption of >5 drinks/40 g of alcohol) occurred at a mean of 123 days with DSF compared to 71 days with ACP (P= 0.0001). Eighty-eight per cent of patients on DSF remained abstinent compared to 46% with ACP (P = 0.0002). However, patients allocated to ACP had lower craving than those on DSF (P = 0.002). **Conclusion:** DSF is superior to ACP for preventing relapse in alcohol-dependent men with good family support. Further comparisons between these two drugs in different treatment settings and populations are warranted.	De Sousa, A. & De Sousa, A. (2005) An open randomized study comparing disulfiram and acamprosate in the treatment of alcohol dependence. Alcohol and Alcoholism, 40, 545–548. **RCT**
NICE 2011, Austraalia 2009, Soome 2010, BAP 2012, SAMHSA 2009	
RESULTS: All three study groups showed marked reduction in drinking, from baseline to the end of the study. During the continuous medication phase, treatment with DIS was more effective in reducing HDDs and average weekly alcohol consumption, and increasing time to the first drink, as well as the number of abstinent days. During the TM period, there were no significant differences between the groups in time to first HDD and days to first drinking, but the abstinence days were significantly more frequent in the DIS group than ACA and NTX. There were no differences between the NTX and ACA groups in either phase of the study of drinking outcomes. However, SADD scores improved more in the NTX group than the ACA group. **CONCLUSIONS:** Patients allocated to ACA, NTX and DIS combined with brief manual-based cognitive behavioural intervention significantly reduce their alcohol consumption and report improved QL. Supervised DIS appeared superior, especially during the continuous medication period, to NTX and ACA.	Laaksonen, E., Koski-Jannes, A., Salapuro, M., et al. (2008) A randomized, multicentre, open-label, comparative trial of disulfiram, naltrexone and acamprosate in the treatment of alcohol dependence. Alcohol and Alcoholism, 43, 53–61. **RCT**

Medinfokeskuse lisaotsingud

Kokkuvõtte (abstract või kokkuvõtlikum info)	**Viide kirjandusallikale**
Result: Within the specified period, there have been 30 case reports and 8 clinical trials regarding DSF's side effects. One was a longer trial of DSF spanning >50 weeks. The case reports were related to neurological, hepatic, cardiac, dermatological, psychiatric adverse events, neuroimaging findings, and drug-drug interaction. Because of exclusion criteria, adverse events in DSF randomized double-blind clinical trials seem to be less serious and less frequent than adverse events reported postmarketing. **Conclusions:** With the safety recommendations in place, we consider the administration of DSF to be safe practice and within	Alharbi F.F., El-Guebaly N. The relative safety of disulfiram. Addictive Disorders and their Treatment. 2013;12(3):140-147. **Systematic review**

an acceptable risk profile.	
Abstract: Despite being a relatively effective and safe treatment, the clinical management of alcohol abuse/dependence by oral naltrexone can be compromised due to the patient's non-compliance with daily use of this medication. Over the past decade an increasing body of research has suggested that the use of sustained release depot naltrexone preparations can overcome this issue and deliver improved clinical outcomes. However, at the same time, research findings from diverse areas of pharmacogenetics, neurobiology and behavioural psychology have also been converging to identify variables including genetic markers, patient psychosocial characteristics and drug use history differences, or clusters of these variables that play a major role in mediating the response of alcohol abuse/dependent persons to treatment by naltrexone. While this article does not attempt to review all available data pertaining to an individual alcohol dependent patient's response to treatment by naltrexone, it does identify relevant research areas and highlights the importance of data arising from them. The characterization of clinical markers, to identify those patients who are most likely to benefit from naltrexone and to tailor a more individual naltrexone treatment, will ultimately provide significant benefit to both patients and clinicians by optimizing treatment outcome.	Hulse G.K. Improving clinical outcomes for naltrexone as a management of problem alcohol use. British Journal of Clinical Pharmacology. 2013;76(5):632-641. **Review**
RESULTS: Across 13 double-blind studies, 1,593 patients were randomly assigned to one of the following: amisulpride (1 study, n = 37), aripiprazole (2 studies, n = 163), flupenthixol decanoate (1 study, n = 142), olanzapine (2 studies, n = 62), quetiapine (4 studies, n = 174), tiapride (3 studies, n = 212), or placebo (13 studies, n = 803). Neither pooled nor individual antipsychotics outperformed placebo regarding relapse prevention (pooled RR = 1.05 [95% CI, 0.95 to 1.16], P = .38, 9 studies, n = 1,405). Antipsychotics were similar to placebo regarding heavy drinking days (P = .15), craving (P = .82), and first alcohol consumption time (P = .94). Placebo outperformed pooled antipsychotics regarding number or percentage of abstinent days/lack of drinking days (SMD = 0.17 [95% CI, 0.01 to 0.33], P = .04, 5 studies, n = 918), without significant group differences after removal of 1 outlying flupenthixol decanoate study (P = .24). Individually, flupenthixol decanoate (1 study, n = 281) was inferior to placebo regarding abstinence/drinking days (P = .004), whereas aripiprazole (1 study, n = 30) was superior regarding heavy drinking days (P < .00001). Antipsychotics caused greater all-cause discontinuation than placebo (RR = 1.24 [95% CI, 1.07 to 1.45], P = .005, NNH = 14), especially aripiprazole (P = .01) and flupenthixol decanoate (P = .001). Discontinuation due to intolerability was similar between antipsychotics and placebo (P = .12), but aripiprazole's risk was higher (P = .003). Drowsiness/sedation (P < .0001, NNH = 9), increased appetite (P = .02, NNH = 14), and dry mouth (P < .0001, NNH = 7) occurred more frequently with pooled antipsychotics. **CONCLUSIONS:** Except for 1 isolated outcome, the studied antipsychotics did not improve abstinence or reduce drinking or craving in patients with primary alcohol dependence.	Kishi T, Sevy S, Chekuri R, Correll CU. Antipsychotics for primary alcohol dependence: a systematic review and meta-analysis of placebo-controlled trials. J Clin Psychiatry. 2013 Jul;74(7):e642-54. **Meta-analysis**
MAIN RESULTS: A total of 25 studies were included in the review (2641 participants). Most participants were male, with an average age of 44 years. Anticonvulsants were compared with placebo (17 studies), other medications (seven studies) and no medication (two studies). The mean duration of the trials was 17 weeks (range four to 52 weeks). The studies took place in the USA, Europe, South America, India and Thailand. Variation was	Pani PP, Trogu E, Pacini M, Maremmani I. Anticonvulsants for alcohol dependence. Cochrane Database Syst Rev. 2014;2:CD008544. **Systematic review**

reported in the characteristics of the studies, including their design and the rating instruments used. For many key outcomes, the risk of bias associated with unclear or unconcealed allocation and lack of blinding affected the quality of the evidence.Anticonvulsants versus placebo: For dropouts (16 studies, 1675 participants, risk ratio (RR) 0.94, 95% confidence interval (CI) 0.74 to 1.19, moderate-quality evidence) and continuous abstinence (eight studies, 634 participants, RR 1.21, 95% CI 95% 0.97 to 1.52, moderate-quality evidence), results showed no evidence of differences. Moderate-quality evidence suggested that anticonvulsants reduced drinks/drinking days (11 studies, 1126 participants, mean difference (MD) -1.49, 95% CI -2.32 to -0.65) and heavy drinking (12 studies, 1129 participants, standardised mean difference (SMD) -0.35, 95% CI -0.51 to -0.19). Moreover, withdrawal for medical reasons (12 studies, 1410 participants, RR 1.22, 95% CI 0.58 to 2.56, moderate-quality evidence) showed no evidence of difference, but for specific adverse effects (nine studies, 1164 participants), two of 18 adverse event outcomes favoured placebo. The direction of results was confirmed by subgroup analyses for topiramate and partially for gabapentin and valproate.Anticonvulsants versus naltrexone: No evidence of difference was shown in dropout rates (five studies, 528 participants, RR 0.74, 95% CI 0.52 to 1.06), severe relapse rates (four studies, 427 participants, RR 0.69, 95% CI 0.44 to 1.07) and continuous abstinence rates (five studies, 528 participants, RR 1.21, 95% CI 0.99 to 1.49); anticonvulsants were associated with fewer heavy drinking days (three studies, 308 participants, MD -5.21, 95% CI -8.58 to -1.83), more days to severe relapse (three studies, 244 participants, MD 11.88, 95% CI 3.29 to 20.46) and lower withdrawal for medical reasons (three studies, 245 participants, RR 0.13, 95% CI 0.03 to 0.58). **AUTHORS' CONCLUSIONS:** At the current stage of research, randomised evidence supporting the clinical use of anticonvulsants to treat alcohol dependence is insufficient. Results are conditioned by heterogeneity and by the low number and quality of studies comparing anticonvulsants with other medications. The uncertainty associated with these results leaves to clinicians the need to balance possible benefits/risks of treatment with anticonvulsants versus other medications as supported by evidence of efficacy.	
RESULTS: Baclofen tolerability is generally considered to be good. Eleven RCTs investigated its effectiveness in the treatment of SUDs. Of these, 5 RCTs found that baclofen is effective, 5 RCTs found that it is ineffective and the results of 1 RCT were not appreciable because it did not achieve the preplanned level of participation. **CONCLUSIONS:** The number of RCTs on baclofen and SUDs is still low, and their results are divergent. Further RCTs should be undertaken, particularly with higher doses of baclofen. Its administration may be suggested in patients who fail to respond	Agabio R., Preti A., Gessa G.L. Efficacy and tolerability of baclofen in substance use disorders: A systematic review. European Addiction Research. 2013;19(6):325-345. **Systematic review**

to other approved drugs or who are affected by liver disease that prevents their administration, or in patients affected by SUDs for which no approved drugs are available. Treatment should be conducted under strict medical supervision.	
RESULTS: patients taking placebo (n=289) and patients taking nalmefene (n=290) were included in the efficacy analyses. At month 6, there was a significant effect of nalmefene compared with placebo in reducing the number of heavy drinking days (-2.3 days [95% confidence interval: -3.8 kuni -8]; p=0.0021) and total alcohol consumption (-1.0 g/day [95% confidence interval:-16.8 kuni -5.1]; p=0.0003). Improvements in clinical global impression and liver enzymes were larger in the nalmefene group compared with placebo at week 24. Adverse events (most mild or moderate) and dropouts due to adverse events were more common with nalmefene than placebo. The number of patients with serious adverse events was similar in the two groups. **CONCLUSIONS:** Nalmefene provides clinical benefit, constitutes a potential new pharmacological treatment paradigm in terms of the treatment goal and dosing regimen, and provides a method to address the unmet medical need in patients with alcohol dependence that need to reduce their alcohol consumption.	Karl Mann, Anna Bladström, Lars Torup, Antoni Gual, and Wim van den Brink. Extending the Treatment Options in Alcohol Dependence: A Randomized Controlled Study of As-Needed Nalmefene. BIOL PSYCHIATRY 2013;73:706–713 **RCT**
ABSTRACT: In 1994, the US Food and Drug Administration approved the μ-opioid receptor antagonist naltrexone to treat alcohol dependence. However, treatments requiring daily administration, such as naltrexone, are inconsistently adhered to in substance abusing populations, and constant medication exposure can increase risk of adverse outcomes, e.g., hepatotoxicity. This has fostered a 'targeted' or 'as needed' approach to opioid receptor antagonist treatment, in which medications are used only in anticipation of or during high-risk situations, including times of intense cravings. Initial studies of the ability of targeted naltrexone to reduce drinking-related outcomes were conducted in problem drinkers and have been extended into larger, multi-site, placebo-controlled investigations with positive results. Another l-opioid receptor antagonist, nalmefene, has been studied on an 'as-needed' basis to reduce heavy drinking in alcohol-dependent individuals. These studies include three large multi-site trials in Europe of up to 1 year in duration, and serve as the basis for the recent approval of nalmefene by the European Medicines Agency as an 'as-needed' adjunctive treatment for alcohol dependence. We review potential moderators of opioid receptor antagonist treatment response including subjective assessments, objective clinical measures and genetic variants. In sum, the targeted or 'as-needed' approach to treatment with opioid antagonists is an efficacious harmreduction strategy for problem drinking and	Mark J. Niciu, Albert J. Arias. Targeted Opioid Receptor Antagonists in the Treatment of Alcohol Use Disorders. CNS Drugs (2013) 27:777–787 **Review**

alcohol dependence. **CONCLUSION:** Targeted nalmefene is now approved for the treatment of alcohol dependence in Europe. The overall effects size on HDDs (heavy drinking days) and TAC (total alcohol consumption) appears small but may be clinically significant in this often chronic, non-adherent, and treatment-resistant population. Though the effect size for targeted naltrexone appears to be more robust than for targeted nalmefene, it is difficult to draw any firm conclusions because of the relatively few number of studies overall and the smaller size of the targeted naltrexone samples. There are also differences in psychosocial/behavioral regimens between the published naltrexone and nalmefene studies that may have contributed to effect size differences, possibly via interaction between cognitive-behavioral therapy (CBT)-based skills as opposed to the modified BRENDA in most targeted naltrexone versus targeted nalmefene studies, respectively. The type or minimal required 'dose' of psychosocial treatment is an interesting area for future study with targeted opioid receptor antagonists.	
Nalmefene is the first available drug approved in the E.U. to reduce alcohol use in alcohol-dependent patients. Reduction in alcohol use in heavy drinkers diminishes mortality risk and socio-economic burden. Nalmefene has shown efficacy at 6 months in alcohol-dependent patients with high or very high drinking risk levels in reducing total alcohol consumption (-7.6 g/day [95% confidence interval (CI): -11.6 to -3.5]; P = 0.0003), heavy drinking days (-2.00 days/month [95% CI: -3.00 to -1.00]; P ⟨ 0.00001) and other secondary outcome measures such as γ-glutamyl transferase, alanine aminotransferase, drinking risk level and Clinical Global Impression. It is generally well tolerated and has limited contraindications and interactions. As-needed dosage is a novel concept in the addictions field, which may overcome limitations of traditional regimens. In the pivotal trials, nalmefene was taken 52% of the days and compliance with the as-needed treatment regimen was good (above 80% of the days) in 68% of the nalmefene-treated patients. A new pharmacological approach combined with a brief psychosocial intervention for alcoholism is available and appears to be feasible, safe and efficacious.	Gual A, Bruguera P, López-Pelayo H. Nalmefene and its use in alcohol dependence. Drugs Today (Barc). 2014 May;50(5):347-55. **Article**
The opioid system modulator nalmefene (Selincro®) is approved in the EU for as-needed use to reduce alcohol consumption in alcohol-dependent adults with a high drinking risk level. This article reviews the efficacy and tolerability of as-needed oral nalmefene in the treatment of alcohol dependence, as well as summarizing its pharmacological properties. In two randomized, double-blind, multinational trials (ESENSE 1 and ESENSE 2), as-needed nalmefene significantly reduced the number of heavy drinking days (in both trials) and total alcohol consumption (in ESENSE 1) at month 6. In the randomized, double-blind,	Keating GM. Nalmefene: a review of its use in the treatment of alcohol dependence. CNS Drugs. 2013 Sep;27(9):761-72. **Article**

multinational SENSE trial, as-needed nalmefene significantly improved both of these endpoints at month 13, but not at month 6. As-needed nalmefene had a greater beneficial effect in the target population (i.e. alcohol-dependent patients with at least a high drinking risk level at screening and randomization), with post hoc analyses revealing significant reductions in both the number of heavy drinking days and total alcohol consumption at month 6 (in ESENSE 1 and ESENSE 2) and at month 13 (in SENSE). Oral nalmefene was generally well tolerated in patients with alcohol dependence, with the most commonly occurring adverse events including nausea, insomnia and dizziness. In conclusion, as-needed nalmefene provides an important new option for use in the treatment of alcohol dependence.	
There is a sound rationale for the use of opioid antagonists in alcoholism. Nalmefene half-life and mode of application are similar to those of naltrexone. Some but not many preclinical studies have been performed and indicate a therapeutic effect of nalmefene; to date results from four randomized clinical trials on a total of some 600 patients have been published and indicate a significant effect on outcome criteria in alcohol dependence. Some clinical trials essential for the drug approval process are ongoing. These results are needed to allow definite conclusions to be drawn about nalmefene's efficacy in alcohol dependence. The central question is whether nalmefene has substantial advantages over naltrexone in treatment of alcohol dependence. Since no studies have directly compared the two drugs it remains unclear whether nalmefene offers advantages over naltrexone in efficacy or side-effect profile.	Soyka M, Rösner S. Nalmefene for treatment of alcohol dependence. Expert. Opin. Investig. Drugs (2010) 19(11):1451-1459 **Expert opinion**
METHODS: This multisite, randomized double-blind study investigated targeted nalmefene in reducing heavy drinking. Specialized alcohol treatment centers and private general practices enrolled 403 subjects (328 men, 75 women). Subjects were instructed to take nalmefene 10 to 40 mg (n=242) or placebo (n=161) when they believed drinking to be imminent. After 28 weeks, 57 subjects from the nalmefene group continued into a 24-week randomized withdrawal extension. Concomitant psychosocial intervention was minimal and no treatment goals were imposed. Alcohol consumption was recorded using the time-line follow-back method. Biochemical indicators of alcohol use were also measured. **RESULTS:** The mean monthly number of heavy drinking days (HDDs) during the 12-week period before inclusion was 15.5 (SD 6.9) in the nalmefene group and 16.2 (SD 6.9) in the placebo group. During treatment, the mean numbers of HDDs were 8.6 to 9.3 in the nalmefene group and 10.6 to 12.0 in the placebo group (p=0.0065). The levels of serum alanine aminotransferase and gamma-glutamyl transferase decreased in the nalmefene group compared with the placebo group (p=0.0088 and 0.0023). During the randomized withdrawal period, subjects randomized	Karhuvaara S et al. Targeted nalmefene with simple medical management in the treatment of heavy drinkers: a randomized double-blind placebo-controlled multicenter study. Alcohol Clin Exp Res. 2007 Jul;31(7):1179-87. **RCT**

to placebo apparently returned to heavier drinking. Subjects receiving nalmefene reported more nausea, insomnia, fatigue, dizziness, and malaise than subjects on placebo. **CONCLUSIONS:** Nalmefene appears to be effective and safe in reducing heavy drinking, even when accompanied by minimal psychosocial support	
Abstract This study evaluated the long-term efficacy and safety of nalmefene treatment in reducing alcohol consumption. We randomised (1:3) 675 alcohol-dependent patients ≥ 18 years of age to 52 weeks of as-needed treatment with placebo or nalmefene 18 mg/day: A total of 112 patients (68%) in the placebo group and 310 (62%) in the nalmefene group completed the study. At month 6, the co-primary outcome variables showed no statistically-significant differences between the treatment groups; but at month 13, nalmefene was more effective than placebo, both in the reduction of the number of heavy drinking days (HDDs) (- 1.6 days/month (95% CI - 2.9; - 0.3); p = 0.017) and the reduction of total alcohol consumption (TAC) (- 6.5 g/day last month (95% CI - 12.5; - 0.4); p = 0.036). In a subgroup analysis of patients with high/very high drinking risk levels at screening and at randomisation (the target population), there was a significant effect in favour of nalmefene on TAC at month 6, and on both HDD and TAC at month 13. Improvements in Clinical Global Impression and liver enzymes were greater with nalmefene, compared to placebo. Most adverse events were mild or moderate, and transient; adverse events, including those leading to dropout, were more common with nalmefene. This study provides evidence for the long-term safety and efficacy of nalmefene as-needed in alcohol-dependent patients whom continue to drink heavily, following a brief intervention.	Van den Brink W et al. Long-term efficacy, tolerability and safety of nalmefene as-needed in patients with alcohol dependence: A 1-year, randomised controlled study. J Psychopharmacol. 2014 Mar 26;28(8):733-744. **RCT**
Abstract The opiate antagonist nalmefene has been shown in 2 single-site studies to reduce alcohol consumption and relapse drinking in alcohol-dependent individuals. This safety and preliminary multisite efficacy study evaluated 3 doses of nalmefene (5, 20, or 40 mg) in a double-blind comparison to placebo over a 12-week treatment period in 270 recently abstinent outpatient alcohol-dependent individuals. Participants concomitantly received 4 sessions of a motivational enhancement therapy (with a medication compliance component) delivered from trained counselors. Although more subjects in the active medication groups terminated the study early secondary to adverse events, the rates did not differ significantly from that of placebo. The 20-mg/d group experienced more insomnia, dizziness, and confusion, while the 5-mg group also had more dizziness and the 40-mg group had more nausea than the placebo group. Most of these symptoms were mild and improved over time. Although all subjects had a reduction in heavy drinking days, craving, gamma-glutamyl transferase, and carbohydrate-deficient	Anton RF, Pettinati H, Zweben A, Kranzler HR, Johnson B, Bohn MJ, et al. A multi-site dose ranging study of nalmefene in the treatment of alcohol dependence. Journal of Clinical Psychopharmacology 2004;24(4):421–28 **A multi-site dose ranging study**

transferrin concentrations over the course of the study, there was no difference between the active medication and placebo groups on these measures. The time to first heavy drinking day was also not significantly different between the placebo and the active treatment groups. This relatively small multisite trial showed that nalmefene was reasonably well tolerated in recently abstinent alcoholics. However, possibly because of variation among the sites or the comparatively small sample size, there was no evidence of superior efficacy outcomes with nalmefene treatment.	
Abstract A dozen studies have been published showing that opiate antagonists suppress alcohol drinking in animals, and two independent placebo-controlled, double-blind clinical trials of naltrexone found this agent was associated with decreased alcohol craving and consumption in alcohol-dependent patients. Nalmefene is a newer opiate antagonist that has a number of potential advantages over naltrexone in the treatment of alcoholism, including no dose-dependent association with liver toxicity and more effective binding to central opiate receptors. Consequently, a double-blind pilot study was conducted to gather preliminary data on the safety and efficacy of nalmefene for reducing alcohol consumption in alcohol-dependent subjects. Twenty-one alcohol-dependent subjects meeting admission criteria were randomly assigned to 12 weeks of double-blind treatment with 40 mg nalmefene, 10 mg nalmefene, or placebo, resulting in 7 patients/treatment group. Nalmefene was well tolerated, with no serious adverse drug reactions. The 40 mg group had a significantly lower rate of relapse ($p < or = 0.05$), and a greater increase in the number of abstinent days/week ($p < or = 0.09$), than the other treatment groups. A significant decrease in the number of drinks/drinking day was noted for both nalmefene groups ($p < or = 0.04$), but not for placebo. These results were supported by parallel decreases in ALT. These pilot data provide preliminary support for the hypotheses that nalmefene can be safely given to alcoholics, and that nalmefene may have a role in reducing alcohol consumption and preventing relapse, particularly at the 40 mg level. A full-scale study is underway to confirm these preliminary findings.	Mason BJ, Ritvo EC, Morgan RO, Salvato FR, Goldberg G, Welch B, et al. A double-blind, placebo-controlled pilot study to evaluate the efficacy and safety of oral nalmefene HCl for alcohol dependence. Alcoholism: Clinical and Experimental Research 1994; 18(5):1162–7 **A double-blind, placebo-controlled pilot study**
METHODS: A double-blind, placebo-controlled trial was conducted to evaluate the safety and efficacy of 2 doses of oral nalmefene for alcohol dependence. The 105 outpatient volunteers were abstinent for a mean of 2 weeks prior to random assignment to the placebo or 20- or 80-mg/d dose nalmefene groups for 12 weeks. Cognitive behavioral therapy was provided weekly during treatment. Self-reported drinking or abstinence was confirmed by determinations of breath alcohol concentration and by collateral informant reports. **RESULTS:** Outcomes did not differ between the 20- and 80-mg dose nalmefene groups. Significantly fewer patients treated with nalmefene than patients given placebo relapsed to heavy drinking through 12 weeks of treatment (P<.02), with a	Mason BJ, Salvato FR, Williams LD, Ritvo EC, Cutler RB. A double-blind, placebo-controlled study of oral nalmefene for alcohol dependence. Archives of General Psychiatry 1999;56(8): 719–24 **A double-blind, placebo-controlled study**

significant treatment effect at the first weekly study visit (P<.02). The odds ratio of relapsing to heavy drinking was 2.4 times greater with placebo compared with nalmefene (95% confidence interval, 1.05-5.59). Patients treated with nalmefene also had fewer subsequent relapses (P<.03) than patients given placebo. **CONCLUSIONS:** Treatment with nalmefene was effective in preventing relapse to heavy drinking relative to placebo in alcohol-dependent outpatients and was accompanied by acceptable side effects.	

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Search	Query	Items found
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#7	Search **(((aversive) OR aversion) OR "Aversive Therapy"[Mesh]) OR "Disulfiram"[Mesh]**	17733
#6	Search **"Disulfiram"[Mesh]**	3077
#4	Search **"Aversive Therapy"[Mesh]**	793
#2	Search **aversion**	6562
#1	Search **aversive**	9527