Tõendusmaterjali kokkuvõte - EvSu

Kliiniline küsimus nr 10

Kas kõigil alkoholi kuritarvitavatel ja alkoholisõltuvusega patsientidel kasutada abstinentsi või alkoholi tarvitamise vähendamise saavutamiseks akupunktuuri vs sugestsioonravi vs platseeboefektiga ravivõtteid vs mitte kasutada?

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

Soovituse koostamiseks vaadati läbi 12 alkoholisõltuvuse ja liigkasutamise ravijuhendit. Teemakohast infot sisaldus neist kolmes: SIGN2003, NICE2011, Soome2010. Lisainformatsiooni saamiseks teostati otsing PubMed andmebaasist.

Teaduslikku kirjandust ega tõendusmaterjali ei leitud teaduspublikatsioonidest ega ravijuhenditest sugestioonravi efektiivsuse või ebaefektiivsuse tõendamiseks, mistõttu sellekohast kokkuvõtet ega soovitust siinkohal tehtud ei ole.

Ravijuhendites olevad soovitused olid koostatud akupunktuuri kohta randomiseeritud-kontrollitud uuringute ja süstemaatiliste uuringute põhjal. Tõendusmaterjal oli hea kvaliteediga (väiksed valimi suurused), aga saadud tulemused konfliktsed. SIGN2003-s Sapir-Weise (1999) randomiseeritud kontrollitud uuring 72 patsiendiga ning 22 kliinilist uuringut koondav süstemaatiline ülevaade ei leidnud akupunktuuri kui ravimeetodi efektiivsust alkoholisõltuvuse ravimisel. Sarnane tulemus saadi ka Soome 2010 ravijuhendis neljas randomiseeritud-kontrollitud uuringus (Trümpler 2003; Karst 2002; Kunz 2007; Brewer 1995). Vastukäivad tulemused saadi NICE2011 ravijuhendis, kus Bullock jt vanemates (1987; 1989) randomiseeritud-kontrollitud uuringutes leiti, et akupunktuur aitab joomisepisoode vähendada ning on abiks kainuse säilitamisel. Bullocki ja kolleegide uuemas (2002) ja Worner (1992) ning Rampes (1997) poolt läbiviidud randomiseeritud-kontrollitud uuringutes aga akupunktuur positiivset efekti ei omanud.

Ravim vs platseebo võrdlust oli kajastatud Soome2010 ravijuhendis. Soovituste tegemiseks kasutati randomiseeritud-kontrollitud uuringuid, süstemaatilisi ülevaateid ja kahte metaanalüüsi. Mõlemad metaanalüüsid (Kranzler jt 2001; Adi jt 2007) leidsid, et ravim nalmefeen on efektiivsem kui platseebo. Varasemad randomiseeritud-kontrollitud uuringud ravimi ja platseebo vahelisi erinevusi ei näidanud. Uuemates süstemaatilistes ülevaadetes olid tulemused siiski ravimi kasuks.

Andmebaaside otsingul saadud artiklitest käsitlesid akupunktuuri Cho ja Wang´i (2009) süstemaatiline ülevaade ning Trümpler jt (2003) ning Kunz jt (2007) randomiseeritud kontrollitud uuring. Ühelgi juhul ei suudetud tõestada akupunktuuri efektiivsust ravimisel, v.a Kunz jt uuring, kus näidati akupunktuuri mõju paremale elukvaliteedile (enesekohaselt hinnatud ärevuse vähenemine).

Andmebaasidest tehtud ravim vs platseebo võrdlus - Del re 2013 metaanalüüsil näidati, et varasemates uuringutes on ravimi ja platseebo vaheline erinevus olemas (ravimi kasuks), kuid uuemates uuringutes on see erinevus väiksem või puudub üldse. Jorgensen 2011 metaanalüüsil oli aga kõikide kaasatud uuringute puhul selge erinevus ravimi kasuks olemas. Weiss jt 2008 metaanalüüsi autorid leidsid, et patsientidel, kes said platseeboravimit + regulaarsed visiidid meditsiinitöötajaga + käitumuslik psühhoteraapia, olid olulised paremad tulemusnäitajad kui ainult psühhoteraapiat saanutel. Platseebokontrollitud randomiseeritud uuringu (Skinner et al., 2010) autorite arvates annab antud uuring tõestust sellele, et disulfiraami tuleks näha mitte karistava ravimeetodina vaid kasuliku ravimina, mis toob olulist kergendust pidevale sisemisele konfliktile juua või mitte juua.

Kokkuvõte ravijuhendites leiduvatest soovitustest

Akupunktuur:

SIGN2003

Alternatiivsetest ravimeetoditest leidus infot vaid akupunktuuri ja transtsendetaalse meditatsiooni osas. Randomiseeritud-kontrollitud uuringud ja süstemaatilised ülevaated ei ole leidnud akupunktuuri kui ravimeetodi efektiivsust alkoholisõltuvuse ravimisel. Seega ei ole tõendusmaterjal piisav, soovitamaks akupunktuuri kui ühte võimalikku alternatiivset ravimeetodit alkoholisõltuvuse ravis (Sapir-Weise jt 1999; Ter Riet jt 1990; NIH Consensus Conference 1998).

NICE2011

Bullock ja kolleegid (1987) leidsid, et akupunktuuriga ravitud grupis esines oluliselt vähem joomisepisoode kui kontrollgrupis (p=0,007) peale teist (28 päeva) ja kolmandat (45 päeva) ravi faasi, erinevus puudus peale esimest faasi (5 päeva).

Bullock jt (1989) uuring näitas samuti, et akupunktuuri saanud grupis oli peale 3 ja 6 ravikuud joomisepisoode (3+ drinki) oluliselt vähem kui kontrollgrupis. Erinevus puudus kahe grupi vahel peale esimest ravikuud (p=0,001). Ravigrupp oli edukam ka kainuse säilitamisel ja oma eesmärkide saavutamisel alkoholi tarbimise vähendamise osas peale esimest (p=0,01), 3 ja 6 ravikuud (p=0,05) (ei ole randomiseeritud uuring!).

Worner jt (1992) uuringus võrreldi akupunktuuri, nõelteta stimulatsiooni ja kontrollgruppi ning ei leitud peale 3 ravikuud mingeid erinevusi patsientide arvu osas, kellel tekkis relaps.

Rampes jt (1997) võrdlesid sõltuvusravi spetsiifilist elektrilist akupunktuuri, mitte-spetsiifilist akupunktuuri ja kontrollgruppi. Autorid ei leidnud peale 2 ja 6 ravikuud erinevusi joomahimu vähenemises nende kolme grupi vahel.

Bullock jt (2002) uurisid sõltuvusspetsiifilist ja mitte-spetsiifilist akupunktuuri, sümptomaatilist akupunktuuri ja standardravi. Peale 3, 6 ja 12 kuulist ravi ei leitud gruppide vahel erinevusi alkoholi tarbimise vähendamises ega kainuse säilitamises.

- Kuna uuringute tulemused on konfliktsed ning uuringud ise on omavahel halvasti võrreldavad (erinevad kehaosad akupunktuuris, erinev ravikestvus, erinev jälgimisaeg, erinev uuringualuste arv), ei ole piisavalt tõendusmaterjali kinnitamaks akupunktuuri kasumlikkust kainuse säilitamisel või tarbitava alkoholi koguse vähendamisel.

Table 87: Clinical review protocol for the review of acupuncture

Electronic databases	AMED, CINAHL, EMBASE, MEDLINE, PsycINFO, Cochrane Library
Date searched	Systematic reviews from 1993 to March 2010. All other searches from database inception to March 2010
Study design	RCTs (at least ten participants per arm); systematic reviews
Population	Adults (over 18 years old) At least 80% of the sample meet the criteria for alcohol dependence or harmful alcohol use (clinical diagnosis or drinking more than 30 drinks per week)
Excluded populations	Hazardous drinkers and those drinking fewer than 30 drinks per week Pregnant women
Interventions	Acupuncture (all types)
Comparator	Control or other active intervention
Outcomes	Abstinence Amount of alcohol consumed Rates of consumption Relapse (>X number of drinks or number of participants who have relapsed) Lapse (time to first drink or number of participants who have lapsed) Attrition (leaving the study early for any reason)

Soome2010

Akupunktuur ei ole abiks alkoholismi ega alkoholi võõrutussündroomi sümptomite raviks. Kliinilise kogemuse põhjal näib akupunktuur tõstvat patsiendi pühendumust ravile, kuid teaduskirjanduses vastav tõendusmaterjal puudub (Trümpler 2003; Karst 2002; Kunz 2007; Brewer 1995).

Platseeboravi:

(Ravim vs platseebo)

Soome2010

Disulfiraami implant vs platseebo – positiivne efekt ravimi kasuks ilmnes vaid ühes uuringus (Wilson jt 1980), neljas kontrollitud uuringus platseebo ja ravimi vaheline erinevus puudus (Borg jt 1984, Johnsen jt 1991, Wilson jt 1976, Wilson jt 1978).

Naltrexone ja nalmefene vs platseebo – Naltrexooni võrreldi platseeboga kokku 21-s uuringus, nalmefeni 2-s randomiseeritud kontrollitud uuringus. 17-s uuringus oli patsientide arv suurem kui 50, nendest 12-s uuringus näidati paremaid tulemusi ravimi grupis, 5-s uuringus puudus ravaimi ja platseebo vaheline erinevus.

Viiel süstemaatilisel ülevaatel (Berglund M.; Snyder jt 2008; Adi jt 2007; Kranzler jt, 2001; Srisurapanont jt 2005) ja metaanalüüsil baseeruv uuring näitas, et opioidide antagonist suurendab kainete päevade arvu ja vähendab relapse võrreldes platseeboga.

Kaheksast uuringust koosnev metaanalüüs (Kranzler jt 2001)-ravimi erinevus platseebost oli nalmefeni võtjate kasuks12% abstinentsil ja 16% relapsil. Streeton ja Whelan´i metaanalüüsis (Adi jt 2007) olid vastavad tulemused 10% ja 14%.

Ravijuhendite inglisekeelsed tekstid:

Akupunktuur

SIGN2003

Information on outcomes following use of alternative therapies was found only for acupuncture

and transcendental meditation. RCTs and systematic reviews have not demonstrated an effect for acupuncture in the treatment of alcohol dependence.148-150

A review of transcendental meditation151 (plus the accompanying erratum152) reports that this

may be useful as an adjunctive treatment for people with an alcohol or drug dependence. The

studies included in this review were heterogeneous and patient selection criteria were not reported.

There is insufficient evidence to make any recommendations about the use of acupuncture,

transcendental meditation or other alternative therapies in treating patients with an alcohol

problem.

NICE2011

Bullock and colleagues (1987) investigated acupuncture at addiction-specific points versus non-specific points for reducing craving and maintaining abstinence. The authors reported that the treatment group had significantly fewer drinking episodes than the control group (p=0.007) after the second (28 days) and third (45 days) phase of treatment, but not after the first phase (5 days). Bullock and colleagues (1989) also investigated acupuncture at addiction-specific points versus non-specific points for craving reduction, maintaining abstinence and drinking reduction in people with chronic alcohol misuse. The study found that there was no significant difference between the treatment group and control group at 1- month follow-up in the number of drinking episodes (consumption of more than three drinks in one period). However, at both 3- and 6-month follow-up, the treatment group reported significantly fewer drinking episodes than the control group (p=0.001). Furthermore, the treatment group was significantly more effective than control at maintaining abstinence and controlled drinking goals when assessed at 1-month (p=0.01), and at 3- and 6-month follow-up (both p=0.05). This study was not randomised, therefore the results must be viewed with caution.

Worner and colleagues (1992) evaluated acupuncture at addiction-specific points versus needleless transdermal stimulation as well as a standard care group that received no acupuncture. This study found no significant difference between groups in the number of participants who relapsed or needed further withdrawal management at 3-month follow-up.

Rampes and colleagues (1997) assessed addiction-specific electro-acupuncture versus non-specific electro-acupuncture and no treatment (control). The main outcome of interest was craving reduction, which is outside the scope of this guideline. However, the authors also reported no significant difference between groups in amount of alcohol consumed at 2- and 6-month follow-up.

Bullock and colleagues (2002) investigated addiction-specific and non-specific acupuncture as well as symptom-based acupuncture and standard care (based on the Minnesota model). The authors found no significant difference in alcohol consumption at 3-, 6- and 12-month follow-up. Overall, the evidence suggests that acupuncture is not effective in drinking reduction and maintaining abstinence.

The results of these studies are conflicting and show both a benefit of addictionspecific acupuncture as well as no difference between addiction-specific acupuncture and other control

conditions. Additionally, the treatments across studies are not comparable because the studies used different body parts for acupuncture treatment, different types of control group, had different length of treatment and follow-up, and varied significantly in sample size. Although the quality of these trials are acceptable in the most part, the number of studies are limited and there is not enough evidence to confirm the benefit of acupuncture in maintaining abstinence or reducing the amount of alcohol consumed. Therefore no clinical recommendations are made but the GDG has developed a recommendation for further research.

Soome2010

– Acupuncture is not useful in the treatment of alcohol withdrawal symptoms [215–218]B. In clinical experience it would seem to improve commitment to treatment but there are no research data available to support this notion.

- Acupuncture does not improve the efficacy of the treatment of alcoholism «Akupunktuurilla ei voida tehostaa alkoholismin hoitoa.»A. In clinical experience it would seem to improve commitment to treatment but there is no research data available to support this notion.

Platseebo vs ravim

Soome2010

Grade of recommendation = A

With disulfiram implants inadequate blood levels are achieved, and the effect is therefore no greater than that of a placebo.

Currently available disulfiram implants are incapable of providing therapeutically sufficient blood levels. In one trial, only, a positive treatment result was achieved using the implant product «Wilson A, Davidson WJ, Blanchard R. Disulfiram implantation: a trial using placebo implants and two types of controls. J Stud Alcohol 1980;41:429-36»1. In four controlled studies (n = 76, 120, 12, 36) the results were negative «Borg S, Halldin J, Kuhlhorn E et al. Disulfiram implantation – en placebokontrollerad multicenter studie stödjer inte dess terapeutiska effekt. Läkartidningen 1984;81:4381-7»2, «Johnsen J, Mörland J. Disulfiram implant: a double-blind placebo-controlled follow-up on treatment outcome. Alcohol Clin Exp Res 1991;15:532-6»3, «Wilson A, Davidson WJ, White J. Disulfiram implantation: placebo, psychological deterrent, and pharmacological deterrent effects. Br J Psychiatry 1976;129:277-80»4, «Wilson A, Davidson WJ, Blanchard R, White J. Disulfiram implantation. A placebo-controlled trial with two-year followup. J Stud Alcohol 1978;39:809-19»5.

- Quality of study: acceptable
- Applicability to the Finnish population: good

Naltrexone in the treatment of alcohol dependence

Evidence summaries

25.3.2010

Hannu Alho

Grade of recommendation = A

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.

Naltrexone and nalmefene are opioid antagonists considered to reduce the feeling of pleasure associated with intoxication. Opioid antagonists affect the mesolimbic-hypothalamic pleasure system in the central nervous system regulated by, for example, endorphins, i.e. endogenous opiates. The medication is believed to make drinking less rewarding for the alcohol-dependent person. This is hoped to gradually decrease both the craving for alcohol and relapses as well as the severity of problems.

So far, naltrexone has been compared to placebo in 21 and nalmefene in two published randomized, controlled studies «Berglund M. Pharmacotherapy for alcohol dependence. In: Treating alcohol and drug abuse. An evidence based review. Berglund M, Thelander S, Jonsson E (Eds.) Wiley-VHC amp Co. KgaA, Weinheim, Germ»1, «Gastpar M, Bonnet U, Boning J et al. Lack

of efficacy of naltrexone in the prevention of alcohol relapse: results from a German multicenter study. J Clin Psychopharmacol 2002;22:592-8»2, «Rubio G, Manzanares J, Lopez-Munoz F et al. Naltrexone improves outcome of a controlled drinking program. J Subst Abuse Treat 2002;23:361-6»3, «Karhuvaara S, Simojoki K, Virta A et al. Targeted nalmefene with simple medical management in the treatment of heavy drinkers: a randomized double-blind placebo-controlled multicenter study. Alcohol Clin»4, «Guardia J, Caso C, Arias F et al. A double-blind, placebo-controlled study of naltrexone in the treatment of alcohol-dependence disorder: results from a multicenter clinical trial. Alcohol Clin Exp Res 2»5, «Heinälä P, Alho H, Kiianmaa K, Lönnqvist J, Kuoppasalmi K, Sinclair JD. Targeted use of naltrexone without prior detoxification in the treatment of alcohol dependence: a factorial double-blind, placeb»10. In 17 studies, the number of patients was higher than 50. Of these, 12 showed better therapeutic results with an opioid antagonist than with placebo. In three studies, the originally positive therapeutic result was lost in ITT (intention to treat) analysis. In five studies, there was no significant difference between the treatment groups.

Based on five systematic reviews and a meta-analysis «Berglund M. Pharmacotherapy for alcohol dependence. In: Treating alcohol and drug abuse. An evidence based review. Berglund M, Thelander S, Jonsson E (Eds.) Wiley-VHC & Co. KgaA, Weinheim, Germ»1, «Snyder JL, Bowers TG. The efficacy of acamprosate and naltrexone in the treatment of alcohol dependence: a relative benefits analysis of randomized controlled trials. Am J Drug Alcohol Abuse 2008;34:4»6, «Adi Y, Juarez-Garcia A, Wang D et al. Oral naltrexone as a treatment for relapse prevention in formerly opioid-dependent drug users: a systematic review and economic evaluation. Health Technol Assess 200»7, «Kranzler HR, van Kirk J. Efficacy of naltrexone and acamprosate for alcoholism treatment: a meta-analysis. Alcohol Clin Exp Res 2001;25:1335-41»8, «Srisurapanont M, Jarusuraisin N. Opioid antagonists for alcohol-dependence. Cochrane Database Syst Rev 2005;1:CD001867»9 opioid antagonists increase the number of non-drinking days significantly and reduce relapses compared to placebo. Based on a meta-analysis of eight studies «Kranzler HR, van Kirk J. Efficacy of naltrexone and acamprosate for alcoholism treatment: a meta-analysis. Alcohol Clin Exp Res 2001;25:1335-41»8 the difference in favour of those taking nalmefene was 12% for complete abstinence and 16% for the number of relapses. In a meta-analysis performed by Streeton and Whelan «Adi Y, Juarez-Garcia A, Wang D et al. Oral naltrexone as a treatment for relapse prevention in formerly opioid-dependent drug users: a systematic review and economic evaluation. Health Technol Assess 200»7 the respective figures were 10% and 14%. When pharmacotherapy is combined with psychosocial therapy based on cognitive behavioural therapy and relapse is taken as the parameter of treatment outcome, NNT values in various studies range from 10 to 4.

In most of these studies, subjects taking either the opioid antagonist or placebo were also given some psychosocial therapy. In six of seven studies, the opioid antagonist clearly improved the therapeutic outcome compared to placebo if the patients were given concomitant cognitive behavioural or motivational therapy «Berglund M. Pharmacotherapy for alcohol dependence. In: Treating alcohol and drug abuse. An evidence based review. Berglund M, Thelander S, Jonsson E (Eds.) Wiley-VHC amp Co. KgaA, Weinheim, Germ»1, «Rubio G, Manzanares J, Lopez-Munoz F et al. Naltrexone improves outcome of a controlled drinking program. J Subst Abuse Treat 2002;23:361-6»3, «Kranzler HR, van Kirk J. Efficacy of naltrexone and acamprosate for alcoholism treatment: a meta-analysis. Alcohol Clin Exp Res 2001;25:1335-41»8. In cases where basic treatment consisted of psychosocial support alone, naltrexone improved the therapeutic results in only two of seven studies. The significance of opioid antagonists for improving therapeutic results obtained with various forms of psychosocial therapy will require further research because the forms of psychosocial therapy used in the studies published to date have varied substantially.

Süstemaatilised ülevaated

Medinfokeskuse poolt teostatud lisaotsing 25.08.2014 otsisõnadega:

Acupuncture and alcohol dependence OR suggestion therapy and alcohol dependence OR placebo effect and alcohol dependence AND systematic review OR meta-analysis OR randomized controlled trial

Search	Query	Items found
#19	Search **(((((((acupuncture) OR acupuncture therapy)) AND alcohol dependence)) OR ((suggestion therapy) AND alcohol dependence)) OR ((placebo effect) AND alcohol dependence))) AND (((systematic review) OR meta-analysis) OR randomized controlled trial)** **Filters: Publication date from 2003/01/01; English; Estonian**	247
#16	Search **(((((((acupuncture) OR acupuncture therapy)) AND alcohol dependence)) OR ((suggestion therapy) AND alcohol dependence)) OR ((placebo effect) AND alcohol dependence))) AND (((systematic review) OR meta-analysis) OR randomized controlled trial)**	417
#15	Search **((systematic review) OR meta-analysis) OR randomized controlled trial**	2365086
#14	Search **randomized controlled trial**	468638
#13	Search **meta-analysis**	80748
#12	Search **systematic review**	1909992
#11	Search **((((((acupuncture) OR acupuncture therapy)) AND alcohol dependence)) OR ((suggestion therapy) AND alcohol dependence)) OR ((placebo effect) AND alcohol dependence)**	674
#10	Search **(placebo effect) AND alcohol dependence**	527
#9	Search **placebo effect**	67365
#8	Search **(suggestion therapy) AND alcohol dependence**	75
#7	Search **suggestion therapy**	8752
#6	Search **(((acupuncture) OR acupuncture therapy)) AND alcohol dependence**	75
#5	Search **alcohol dependence**	83837
#4	Search **(acupuncture) OR acupuncture therapy**	21136
#3	Search **acupuncture therapy**	18620
#2	Search **acupuncture**	21136

Leitud kirjetest sobivateks osutusid 9 süstemaatilist ülevaadet (vt. viited).

Akupunktuur

Formatted: English (United Kingdom)

Cho ja Wang poolt läbi viidud süstemaatiline ülevaade leidis, et akupunktuuri on randomiseeritud-kontrollitud uuringutega uuritud liialt vähe (väiksed valimid). Üheteistkümnes uuringus osales kokku vaid 1110 patsienti. Üheteistkümne randomiseeritud kontrollitud uuringuga ei leitud mingit erinevust simuleeritud ravi ja akupunktuuri vahel (Risk Ratio = 1.07, 95% confidence interval, CI = 0.91 to 1.25) või akupunktuuri tegemise ja mitte-tegemise vahel (Risk Ratio = 1.15, 95% CI = 0.79 to 1.67)

Trümpler 2003 – randomiseeritud uuring, kus vaadati kõrvalesta laser- ja nõelakupunktuuri mõju alkoholi võõrutusnähtude kadumisele ja kõrvutati seda võlts laserakupunktuuriga. Uuring teostati psühhiaatriahaiglasse ravile tulnud patsientidel ja gruppidesse kuulusid

laserakupunktuuril 17, nõelakupunktuuril 15 ja võlts laserakupunktuuril 16 patsienti. Esmase väljundina mõõdeti ja võrreldi õdede poolt hinnatud võõrutusnähtude pikkust päevades. Teisesena hinnati rahustite kasutamise aega päevades. Mõlema laserravi puhul oli võõrutusnähtude aja pikkuseks neli päeva – nõelravi puhul vastavalt kolm päeva (p=0.019 vs võlts laseraukupunktuur). Lühemat rahustite kasutusaega ei suudetud tõestada, kui arvesse võeti baastasemete erinevused. Kokkuvõttes väidab uuring, et kõrvalesta akupunktuuri efektiivsust alkoholismist võõrutusele kaasaaitamisel ei suudetud tõestada. Peamiselt mitteadekvaatse kontrollgruppi puudumise tõttu.

Kunz 2007 – randomiseeritud kontrollitud uuring. Uuringu eesmärk oli leida kinnitust akupunktuuri positiivsele mõjule alkoholismi leevendamiseks. Varemalt on näidatud positiivset mõju muudest sõltuvusainetest vabanemise ravil. Uuringus võrreldi akupunktuuri (55 osalejat) ja aroomiteraapia (54 osalejat) mõju alkoholi joomisest loobumise kärvalnähtude vähendamisele ja leevendamisele. Hindamiseks kasutati alkoholist loobumise sündroomi (AWS) skaalat ja teiseste mõõdikutena subjektiivset visuaalset joomahimu hindamist ning SAM-i (self assesment manikin). AWS-i ja joomahimu hindamisel ei suudetud leida erinevusi gruppide vahel. Enda hinnatud ärevuse määr mõlemas gruppis langes - p-väärtus <0.001.

Ravim vs Platseebo

Litten 2013 koos kaasautoritega analüüsisid 51 randomiseeritud platseebokontrollitud naltreksooni ja akamprosaadi uuringut, et hinnata platseeboefekti alkoholisõltuvuse ravi uuringutes. Uuritavateks olid täiskasvanud, üle 18 aastased alkoholisõltuvad patsiendid. Kui tulemusnäitajateks olid abstinentsis veedetud päevade arv (%) ja totaalne abstinents, siis platseeboefekt korreleerus negatiivselt naltreksooni või akamprosaadi ravi efektiivsusega. Ehk, et mida suurem oli platseeboefekt, seda väiksem oli uuritava ravimi (naltreksoon või akamprosaat) efekti suurus. Samuti täheldati, et nooremate patsientide seas oli platseeboefekt suurem kui vanemate patsientide hulgas. Akamprosaadi uuringutes leiti, et platseeboefekt oli suurem, mida nooremad on uuringud aastaarvu poolest. Sama trendi on märgatud ka depressiooniuuringutega ning selle põhjuseks võib olla, et uuritavateks on kaasatud kergemate sümptomitega patsiendid kui vanemate uuringute puhul. Akamprosaadi hilisemad uuringud on võrreldes vanemate uuringutega lühema kestusega (nooremad keskmiselt 20 nädalat, varasemad 35 nädalat), mis võib samuti suurenenud platseeboefektiga seotud olla.

Weiss et 2008 koostas uurimuse COMBINE 2006 uuringu põhjal, kus vaatles platseeboravimi efekti patsientidel, kes lisaks said ka psühhoteraapiat. Autorid leidsid, et patsientidel, kes said platseeboravimit + regulaarsed visiidid meditsiinitöötajaga + käitumuslik psühhoteraapia, olid olulised paremad tulemusnäitajad kui ainult psühhoteraapiat saanutel. Patsiendid grupist platseeboravi+ regulaarsed visiidid meditsiinitöötajaga omasid oluliselt rohkem abstinentsis veedetud päevi kui ainult käitumuslikku psühhoteraapiat saanud patsiendid. Autorid oletavad platseeboefektiks siinses uuringus asjaolu, et platseeboravimi võtmine iga päev 3 korda päevas oli kinnitus patsiendile endale, et ta soovib muuta oma joomiskäitumist. Teiseks, platseeboravimi saajad kohtusid regulaarselt meditsiinitöötajaga, kes instrueeris neid ravimi võtmise osas, uuris kõrvaltoimete kohta ja haris patsiente alkoholisõltuvuse häirest üldiselt, mis samuti võis tõsta platseeboravi efekti. Samuti soovitas meditsiinitöötaja platseeboravimi võtjat korduvalt osa võtma AA tugirühmadest, milles osalemine viib parematele alkoholi tarvitamise tulemusnäitajatele.

Platseebokontrollitud randomiseeritud uuringus (Skinner et al., 2010), kus osales 38 alkoholisõltuvat patsienti, hinnati uuritavate füsioloogilisi ja psühholoogilisi reaktsioone neutraalses ja ähvardavas (threat) olukorras. Neutraalseks olukorraks oli, kui patsient oli teadlik, et talle manustati ravimit, millel ei ole alkoholi tarvitamisele negatiivset reaktsiooni ning ähvardavaks olukorras teadis patsient, et talle manustati 500mg disulfiraami, millega võib alkoholi juues kaasneda ebameeldivad sümptomid. Patsientidel ei muutunud psühholoogilsed näitajad erinevas grupis, küll aga füsioloogilistest näitajatest oli ähvardavas situatsioonis diastoolne vererõhk madalam võrreldes neutraalse situatsiooniga. Uuringu autorid seostavad seda psühhofüsioloogilise mehhanismiga, mis vähendab negatiivset mõju ja on seotud suurenenud kontrolli, tähelepanu ja pühendumisega. Patiendid, keda raviti disulfiraamiga ja kes soovisid hoiduda disulfiraam-alkohol koostoimest, pidid endale meelde tuletama võimalikke negatiivseid tagajärgi kui nad alkoholi tarbivad. Pingutus olla pidevalt valvas, hoolimata tungist alkoholi järele, võib neid kõrvale juhtida kalduvusest läheneda alkoholile. See võib seletada, miks disulfiraam vähendab oluliselt joomispäevi paljude patsientide hulgas. Autorite arvates

annab antud uuring tõestust sellele, et disulfiraami tuleks näha mitte karistava ravimeetodina vaid kasuliku ravimina, mis toob olulist kergendust pidevale sisemisele konfliktile juua või mitte juua.

Del re 2013 – Naltrexone vs platseebo. Metaanalüüs – aastatel 2004-2009 tehtud uuringud, kuhu valitud uuringud olid kõik topelt-pime, platseebokontrollitud, randomized. Kaasati uuringud, kus oli vähemalt 5 ravi ja 5 platseebogruppis. Varemalt on näidatud, et ravim on efektiivne. Samas on näidatud, et hiljutistes uuringutes on ravimi efekti suurus väiksem tagasipöördumisele tugevale alkoholi pruukimisele ja joomise päevadele protsentides. Samuti on leitud, et mitut meditsiiniasutust hõlmavad uuringud annavad ravimile võrreldes platseeboga väiksema efekti. Antud töö metaanalüüs kinnitas, et statistiliselt oluliselt erines ravimi vs platseebo puhul kainete päevade arv ja tagasipöördumine tugevale alkoholi pruukimisele – ravimi kasuks. Hiljutiste uuringute puhul oli efekti suurus kahele eelnevale tulemusele vähenenud ehk ravim ei omanud nii suurt mõju. Ei suudetud tuvastada multikeskus vs ühe keskuse põhist erinevust naltrexone efektile.

Jorgensen 2011 – metaanalüüs randomiseeritud kliinilistele uuringutele. Kaasamise kriteeriumiteks olid uuringud, kus võrreldi ravimi disulfiram efektiivsust platseebo, mitteravimise, mõne teise ravimi või käitumusliku raviviisiga. Võrdlemise kriteeriumiteks olid pidev tarbimine alla 20 ja 30 gr/päevas vastavalt meestel ja naistel, kainus jätku-uuringul, päevade arv kuni uuesti alkoholi pruukimiseni, vähenenud alkoholi tarbimine ja joomispäevade arv. Kokku kaasati 11 uuringut, kus osalenud patsientide arv varieerus 26-605ni. Keskmisega 139 patsienti uuringus.

· Disulfiram vs muu ravim. 6st uuringust neljal oli disulfiram efektiivsem, kui muu alternatiivne ravim kainuse mõõtmisel – kõigil juhul p-väärtus <0,0002. Sarnast tulemust andis ka teine mõõdetav väärtus – päevade arv kuni uuesti jooma hakkamiseni

· Disulfiram vs platseebo. Ühe kaasatud uuringu puhul näitas disulfiram oluliselt suuremat efektiivsust kainena püsimise suhtes – p-väärtus 0.0063

· Disulfiram vs mitteravimine. Kahest kaasatud uuringust ühe puhul oli disulfiram efektiivsem, kui mitte ravimine kainuse säilitamiseks – p-väärtus <0,001. Teise uuringu puhul ei olnud kahe gruppi erinevused statistiliselt tõestatud.

<u>Platseebo (Finniss 2010)</u>

Platseebo mehanismid – Psühholoogilised mehanismid – mitmed mehanismid mõjutavad platseebo efekti, näiteks ootused, tingimine, õppimine, mälu, motivatsioon, somaatiline fookus, tasu, ärevuse vähendamine ja tähendus. Enim tõestust on leidnud kaks mehanismi: ootused ja klassikaline tingimine. Ootused võivad nii vahendada kui muuta platseeboefekti. Näiteks kui valu vaigistamiseks antakse patsiendile kreemi ühel juhul öeldes, et kreem tegelikult efekti ei oma ja teisel juhul öeldes, et tegemist on tugeva valuvaigistiga. Teiseks peamiseks mehanismiks on klassikaline tingimine, kus korduv assotsiatsioon neutraalse stiimuli ja aktiivse ravimi vahel võib viia selleni, et neutraalne stiimul omandab iseseisvalt aktiivse ravimi tulemi.

Neurobioloogilised mehanismid – Mitmed uuringud on näidanud, et platseebo efekti saab osaliselt või täielikult ümber pöörata opioidide antagonisti naloxoni poolt, toetades ideed, et endogeensed opioidid osalevad platseebo „valu vaigistavas" (toime) efektis. Toime efekti arvatakse omakorda inhibeerivat valgu CCK poolt (cholecystokinin). Uuringud näitavd, et mõned platseebo mehanismid töötavad, muutes nii CCK kui endogeensete opioidide aktiivsust. Platseebo poolt tingitud muutused ajus on näidatud olevat samad, mis tekivad opioidsete ravimite manustamisel. Opioidide vahendatud platseebo efektid esinevad ka mujal peale valusignaali radade. Näiteks platseebo indutseeritud respiratoorne depressioon, kiirenenud südametöö ja *β-adrenergic* aktiivsus on ümberpööratavad naoloxoni poolt, mis tõestab opioidide mehanismi osalust ka teistes füsioloogilistes protsessides (nt respiratoorne ja kardiovaskulaarne). Lisaks opioidide vahendatud platseebo efektile vahendavad neid efekte ka erinevate neurotransmitterite ja neuromodulaatorite vabanemine.

Platseeboefekt kliinilises praktikas – Kliinilises praktikas on oluline mõista, kuidas töötab platseeboefekt. Tõelise platseeboefekti tajumiseks peab uuringusse olema kaasatud ilma igasuguse sekkumiseta grupp, mida aga uuemates uuringutes kasutatakse vähe. On proovitud teha metaanalüüse, selgitamaks välja tõelist platseebo efekti, kasutades lisaks ka sekkumiseta gruppi. Nende uuringute alusel on aga platseeboefekt väike. Seevastu uuringutes, kus vaadeldakse platseebo mehanisme on platseeboefekt vastupidiselt suur. See tulem on aga loogiline, kuna mehanisme vaatlevates uuringud kasutavad kontrollitud manipulatsioone (verbaalsed instruktsioonid, kontekst jne). Seetõttu tuleks platseeboefekti uurida baasteaduse tasemel. Mitmed randomiseeritud-kontrollitud uuringud on võrrelnud erinevate platseebo protseduuridega kaasnevaid efekte. Näiteks kui platseebo manustamisel (tablet või akupunktuur) teavitatakse patsienti võimalikest kaasuvatest notseebo efektidest, siis esines neid

30%-il patsientidest mõlemas platseebo grupis. Samas oli kõikidel juhtudel tegemist väga erinevate kõrvalmõjudega, mis jäljendasid tervishoiutöötaja poolt loetletud kõrvalmõjusid. On näidatud, et need alternatiivsed ravimeetodid, mis on väga põhjalikult ette valmistatud ja läbi mõeldud ning toimuvad spetsiifilistes tingimustes, omavad kliiniliselt olulist platseebo efekti. Näiteks akupunktuur. Läbi viidud randoimiseeritud-kontrollitud uuringutes ei olnud erinevust võlts-akupunktuuri ja traditsioonilist akupunktuuri saanud rühmade vahel, küll aga oli nendes gruppides oluliselt parem sümptomite vähenemine (paranemine), võrrelduna sekkumiseta ja tavalist kontrollgruppi. Viimane tõestab akupunktuuri kui platseebo efekti ravis. Sellise platseeboefekti kasu kestab kuni aasta. Platseebo efekt võib olla olemas isegi juhul, kui platseebot ei manustata. Uuringud, kus kasutatakse ravimi manustamist patsiendile avalikult ja salaja, on näidanud, et sama ravim salajasel manustamisel soovitud efekti ei oma.
Ravi efektiivsust saab parandada mõjutades ootusi. Viidi läbi eksperiment, kus püüti kindlaks teha platseebo efekti mõju sõltuvust oodatavast tulemusest. Selleks manustati kahele katsegruppile (operatsioonijärgsed indiviidid) intravenoosselt soolalahust, kuid ühtedel öeldi, et tegemist on rehüdreeriva toimega ja teistele, et tegemist on ülitugeva valuvaigistiga. Mõlemale gruppile manustati samaaegselt ka rutiinset valuvaigistit. See grupp, kus usuti, et saadakse lisaks ülitugevat valuvaigistit vajas 33% vähem aktiivset valuvaigistit. See tõestab, et platseebo ravi lisaks aktiivsele ravile võimaldab manustada vähem ravimit.
Sarnane uuring viidi läbi ka ärritunud soole sündroomiga patsientidel, kellel rakendati valuliku protseduuri. Uuringus, kus patsientidele anti mõista, et antav ravim võib, kuid ei pruugi valu vähendada, oli platseebole reageerimine tunduvalt väiksem sellest, kui instruktiooniks ole, et ravimil on suur valuvaigistav toime mõnedel patsientidel. Kokkuvõtvalt on oluline sõnum, mida uuringus osalevatele edastatakse. Positiivne ootus suurendab platseebo efekti tunduvalt.

Viited (Ravijuhendid)

Kokkuvõtte (abstract või kokkuvõtlikum info)	**Viide kirjandusallikale**
Seventy-two alcoholics were treated with acupuncture to the ear in a randomized single-blind controlled design over 10 weeks. Orthodox points and incorrect points 3–5 mm from orthodox points were used. No initial differences were found regarding social characteristics, the responses to the Swedish version of the Alcohol Use Inventory and the Three-dimensional Personality Questionnaire, indicating a successful randomization. There were non-significant tendencies towards gender differential response after acupuncture treatment (P = 0.07). There was no difference in the number of drinking days or level of craving between treatment and control patients. Among females, those in the treatment group reported reduction of anxiety after 1 month, more often than those in the control group (P < 0.05). Response to acupuncture was not related to personality or drinking pattern. Patients' experience of needle placement was similar in the study and control groups. The effects of acupuncture were less pronounced than those previously reported.	Sapir-Weise R, Berglund M, Frank A, Kristenson H. Acupuncture in alcoholism treatment: a randomized out-patient study. Alcohol Alcohol 1999;34(4):629-35.
A literature search revealed 22 controlled clinical studies on the efficacy of acupuncture in three fields of addiction: cigarette smoking (15), heroin (five), and alcohol (two). These studies were reviewed using a list of 18 predefined criteria of good methodology. A maximum of 100 points for study design could be earned, divided over four categories: comparability of prognosis; adequate intervention; adequate effect measurement; and good data presentation. The study design was generally poor. No study earned more than 75 points and 12 studies (55%) earned less than 50 points. For smoking cessation, the number of studies with negative outcomes exceeded by far the number with positive outcomes. Taking the quality of the studies into account this negative picture becomes even stronger. For heroin and alcohol addiction controlled clinical research is both scarce and of low quality. Claims that acupuncture is efficacious as a therapy for these addictions are thus not supported by results from sound clinical research.	Ter Riet G, Kleijnen J, Knipschild P. A meta-analysis of studies into the effect of acupuncture on addiction. Br J Gen Pract 1990;40(338):379-82.

Abstract NA	NIH Consensus Conference. Acupuncture. JAMA 1998;280(17):1518-24.
We performed a randomized trial of acupuncture on a group of 54 hardcore alcoholic recidivists to determine if sobriety could be achieved and episodes of drinking and/or Detox Center admissions be decreased by this mode of therapy. Patients in the treatment group received acupuncture points specific for the treatment of substance abuse; control patients received nonspecific points. Significant differences in the two groups were noted at the end of the study. Patients in the treatment group expressed less need for alcohol ($p < 0.003$), and had fewer drinking episodes ($p < 0.0076$) and admissions to the Detox Center ($p < 0.03$) during the study than did control patients. THe majority of treated patients felt that acupuncture had a definite impact on their desire to drink, whereas only a few control patients noted this effect ($p < 0.015$). The results of this study suggest that acupuncture may be able to interdict the cycle of alcoholic recidivism. Further investigation is needed to define the role of acupuncture in the treatment of alcoholism more precisely. The authors wish to express their appreciation to Dr. Michael O. Smith for his encouragement and consultation during the course of this study, and to Drs. Alvin L. Schultz and Nicole Lurie for their critical review of the manuscript. Mary Kay Messner provided expert secretarial assistance.	Milton L Bullock MD*, Andrew J Umen MS, Patricia D Culliton MA andRobert T Olander MA Volume 11, Issue 3, pages 292–295, June 1987 published online: 11 APR 2006 Acupuncture treatment of alcoholic recidivism: a pilot study
In a placebo-controlled study, 80 severe recidivist alcoholics received acupuncture either at points specific for the treatment of substance abuse (treatment group) or at nonspecific points (control group). 21 of 40 patients in the treatment group completed the programme compared with 1 of 40 controls. Significant treatment effects persisted at the end of the six-month follow-up: by comparison with treatment patients more control patients expressed a moderate to strong need for alcohol, and had more than twice the number of both drinking episodes and admissions to a detoxification centre.	MiltonL. Bullock, PatriciaD. Culliton a, RobertT. Olander The Lancet, Volume 333, Issue 8652, Pages 1435 - 1439, 24 June 1989 doi:10.1016/S0140-6736(89)90135-9 Controlled trial of acupuncture for severe recidivist alcoholism
We report clinical data on the efficacy of acupuncture for alcohol dependence. 503 patients whose primary substance of abuse was alcohol participated in this randomized, single blind, placebo controlled trial. Patients were assigned to either specific acupuncture, nonspecific acupuncture, symptom based acupuncture or convention treatment alone. Alcohol use was assessed, along with depression, anxiety, functional status, and preference for therapy. This article will focus on results pertaining to alcohol use. Significant improvement was shown on nearly all measures. There were few differences associated with treatment assignment and there were no treatment differences on alcohol use measures, although 49% of subjects reported acupuncture reduced their desire for alcohol. The placebo and preference for treatment measures did not materially effect the results. Generally, acupuncture was not found to make a significant contribution over and above that achieved by conventional treatment alone in reduction of alcohol use.	Milton L Bullock, Thomas J Kiresuk, Robert E Sherman, Scott K Lenz, Patricia D Culliton, Tacey A Boucher, Christopher J Nolana Journal of Substance Abuse Treatment Volume 22, Issue 2, March 2002, Pages 71–77 A large randomized placebo controlled study of auricular acupuncture for alcohol dependence
We conducted a randomized single-blind controlled study to determine whether auricular electroacupuncture reduces craving for alcohol. Patients who met Diagnostic and Statistical Manual of Mental Disorders IIIR criteria for alcohol-dependence or -abuse were randomized to specific electroacupuncture plus treatment as usual (group 1, n = 23), non-specific electroacupuncture plus treatment as usual (group 2, n = 20) or treatment as usual (group 3, n = 16). Electroacupuncture was carried out weekly for six weeks, each treatment lasting 30 min. Our main outcome measure was craving for alcohol, measured by a visual analogue scale. Assessments were done by blind investigators, at baseline, week 8 and week 24. There	H. Rampes, S. Pereira, , A. Mortimer, S. Manoharan M. Knowles Complementary Therapies in Medicine Volume 5, Issue 1, March 1997, Pages 19–26 Does electroacupuncture reduce craving for alcohol? A randomized controlled study

was a significant change in the craving for alcohol scores in all three groups at week 8. A 59.8% and 54% reduction in mean craving scores was noted in electroacupuncture groups 1 and 2 respectively. There was a 44.1% increase in craving in the control group at week 8. Craving was low in all three groups by week 24 and not significantly different between them at wee 8. Craving was correlated significantly with units of alcohol consumed (r = 0.38, P = 0.004), breathalyser level (r = 0.34, P = 0.009) and anxiety (r = 0.29, P = 0.024) at baseline. We did not find any major advantage in treating auricular acupuncture points regraded as specific for addiction.	
Fifty-six alcoholics (49 male, 7 female) of lower socioeconomic class attending an outpatient treatment program in Brooklyn, New York were prospectively randomized to one of three treatment groups: point-specific acupuncture, sham transdermal stimulation or standard care (control). One third of the subjects reported a history of drug use in addition to alcohol. Results in this small sample showed no significant differences in attendance at Alcoholics Anonymous meetings, number of outpatients sessions attended, number of weeks in either the study or in the outpatient program, number of persons completing treatment or in the number of relapses. It is therefore concluded that in this small racially mixed sample of urban outpatient alcoholics, fixed point-specific standardized acupuncture did not improve outcome. We caution against the routine use of this treatment until more randomized controlled trials demonstrate a beneficial effect.	T.M. Worner, B. Zeller, H. Schwarz, F. Zwas, D. Lyon Drug and Alcohol Dependence Volume 30, Issue 2, June 1992, Pages 169–173 Acupuncture fails to improve treatment outcome in alcoholics
Background and Aims: Previous trials on acupuncture in alcohol addiction were in outpatients and focused on relapse prevention. Rates of dropout were high and interpretation of results difficult. We compared auricular laser and needle acupuncture with sham laser stimulation in reducing the duration of alcohol withdrawal. Methods: Inpatients undergoing alcohol withdrawal were randomly allocated to laser acupuncture (n = 17), needle acupuncture (n = 15) or sham laser stimulation (n = 16). Attempts were made to blind patients, therapists and outcome assessors, but this was not feasible for needle acupuncture. The duration of withdrawal symptoms (as assessed using a nurse-rated scale) was the primary outcome; the duration of sedative prescription was the secondary outcome. Results: Patients randomized to laser and sham laser had identical withdrawal symptom durations (median 4 days). Patients randomized to needle stimulation had a shorter duration of withdrawal symptoms (median 3 days; P = 0.019 versus sham intervention), and tended to have a shorter duration of sedative use, but these differences diminished after adjustment for baseline differences. Conclusions: The data from this pilot trial do not suggest a relevant benefit of auricular laser acupuncture for alcohol withdrawal. A larger trial including adequate sham interventions is needed, however, to reliably determine the effectiveness of any type of auricular acupuncture in this condition.	François Trümpler, Suzan Oez, Peter Stähli, Hans Dieter Brenner and Peter Jüni Alcohol and Alcoholism (2003) 38 (4): 369-375. doi: 10.1093/alcalc/agg091 Acupuncture for alcohol withdrawal: a randomized controlled trial
Thirty-four alcoholics were treated with acupuncture to the ear and the body in a randomized single-blind placebo-controlled design over 14 days. Orthodox points and placebo needles to orthodox points were used daily for a total of 10 treatments starting on the first day of admission as add-on therapy to standard medication with carbamazepine. The primary outcome was the Clinical Institute Withdrawal Assessment (CIWA-Ar-scale) assessed on days 1-6, 9 and 14. No initial differences were found regarding sociodemographic data, drinking history and alcohol-related data, indicating successful randomization. Longitudinal analysis of the Clinical Institute Withdrawal Assessment (CIWA-Ar-scale) data showed that patients assigned to acupuncture had a general tendency towards better outcome results and significantly fewer withdrawal symptoms on day 14 (Wilcoxon-W=177.500, Z=-2.009, p = 0.045). No significant	Matthias Karst, Torsten Passie, Steffen Friedrich, Birgitt Wiese and Udo Schneider Addiction Biology Volume 7, Issue 4, pages 415–419, October 2002 Acupuncture in the treatment of alcohol withdrawal symptoms: a randomized, placebo-controlled inpatient study

differences were found in the Beck Depression Inventory (BDI), State-Trait Anxiety Inventory (STAI X1 and X2) and Eigenschaftswoerterliste (EWL S60). We conclude that acupuncture as an adjunctive treatment to carbamazepine medication shows promise for the treatment of alcohol withdrawal symptoms. Further investigation of this treatment modality appears to be warranted.	
Background: There is increasing clinical acceptance of acupuncture as a treatment of substance-related disorders. Little is known about acupuncture as a treatment for the withdrawal syndrome in inpatient settings. We compared auricular needle acupuncture with aromatherapy in reducing the duration and severity of symptoms of alcohol withdrawal. Methods: Inpatients undergoing alcohol withdrawal were randomly allocated to needle acupuncture (n=55) and aromatherapy (n=54). Both therapies were applied daily during the first 5 consecutive treatment days. The rating scale for the assessment of the alcohol-withdrawal syndrome (AWS scale) served as the main dependent variable and was applied daily during the first 5 days of the withdrawal. Further measures included a subjective visual analog scale of craving and the Self Assessment Manikin (SAM). Results: Thirty-six of the 55 patients who received acupuncture, and 38 of the 54 patients who received aromatherapy, finished the study regularly. The groups differed in their initial self-reported arousal, which then served as a covariate in the further analyses. Neither the extent of craving nor of withdrawal symptoms differed between groups over the observation period. Self-rated arousal decreased in response to both treatments from days 1 to 2 ($p<0.001$) and within single days ($p<0.001$), and we found a significant interaction between pretreatment versus posttreatment and days ($p<0.001$). Interactions including between-subjects effects and intervention did not achieve the significance level. Conclusion: The results do not support the assumption of a superiority of acupuncture over the control therapy in its specific effects on alcohol withdrawal symptoms.	Stephanie Kunz, Michael Schulz, Miriam Lewitzky, Martin Driessen andHarald Rau Alcoholism: Clinical and Experimental Research Volume 31, Issue 3, pages 436–442, March 2007 Ear Acupuncture for Alcohol Withdrawal in Comparison With Aromatherapy: A Randomized-Controlled Trial
Drugs which reduce autonomic overactivity but have no sedative effects can be useful in alcohol withdrawal, either as the sole pharmacological intervention or in conjunction with sedative drugs. They may reduce sedative requirements, but their lack of anticonvulsant and anti-delirium effect can be a disadvantage. Beta-blockers are more effective than alpha-2 agonists. Non-sedative anticonvulsants are of questionable value. Acupuncture and neuro-electric therapy, though often popular with patients and therapists, appear to be no more than impressive placebos in this context. Non-specific treatment effects can be very prominent in withdrawal. Support, information, reassurance and good nursing can reduce the need for specific pharmacological or psychological interventions.	Colin Brewer Alcohol and Alcoholism (1995) 30 (6): 799-803. Second-line and 'alternative' treatments for alcohol withdrawal: alpha-agonists, beta-blockers, anticonvulsants, acupuncture and neuro-electric therapy
SUMMARY. Both disulfiram and placebo implant patients abstained longer and had more intense disulfiram-ethanol reactions than did two control groups.	Wilson A, Davidson WJ, Blanchard R. Disulfiram implantation: a trial using placebo implants and two types of controls. J Stud Alcohol 1980;41:429-36
Abstract NA	Borg S, Halldin J, Kuhlhorn E et al. Disulfiram implantation – en placebokontrollerad multicenter studie stödjer inte dess terapeutiska effekt. Läkartidningen

	1984;81:4381-7
Seventy-six alcohol-dependent patients participated in a study of the clinical effect of implanted disulfiram (DS). The patients were randomized to a DS group (n = 40), receiving a subcutaneous abdominal implantation of 10 × 100 mg DS tablets and a placebo group (PL group) receiving an implantation of 9 × 100 mg calcium phosphate tablets together with one calcium phosphate tablet containing 1 mg DS. Both groups believed they were receiving DS. At admission there was no significant difference between the DS and PL groups with regard to demographic characteristics, psycho-social adjustment, drinking variables, medical disorders, or laboratory results. After a study period of approximately 300 days, 63 patients (33 DS; 30 PL) were assessed using a battery of tests. There was no significant difference between the groups with regard to reduction in average alcohol consumption, number of days to the first alcohol intake after implantation, or level of psychosocial function. Nevertheless, both groups reduced their ethanol consumption significantly, probably due to the psychological deterrent effect. The DS implant did result in a significantly higher incidence of wound complications. This study does not support the idea that a 1-g DS implant has any significant clinical effect different from the implant containing only 1 mg DS (placebo).	Johnsen J, Mörland J. Disulfiram implant: a double-blind placebo-controlled follow-up on treatment outcome. Alcohol Clin Exp Res 1991;15:532-6
In an effort to examine the placebo, psychological deterrent, and pharmacological deterrent effects associated with implanted disulfiram, subjects were given either disulfiram implants or sham operations. Ethanol challenges elicited no disulfiram-ethanol reactions (DERs), indicating that at the time of the challenge neither a pharmacological deterrent nor a placebo effect was operating. Of the patients who resumed drinking, only those with disulfiram implants experienced DERs. Sham operation subjects continued to drink after their first post-challenge drink; four of five disulfiram implant recidivists remained abstinent following their experience of a DER. It is concluded that the pharmacological deterrent effect of the disulfiram implant may have been underestimated in previous reports.	Wilson A, Davidson WJ, White J. Disulfiram implantation: placebo, psychological deterrent, and pharmacological deterrent effects. Br J Psychiatry 1976;129:277-80
SUMMARY. Ten alcoholics implanted with disulfiram had longer periods of abstinence after treatment than did 10 alcoholics implanted with placebo; 7 of the disulfiram-implanted patients experienced a disulfiram-ethanol reaction in uncontrolled drinking situations, while none of the placebo-implanted patients did.	Wilson A, Davidson WJ, Blanchard R, White J. Disulfiram implantation. A placebo-controlled trial with two-year followup. J Stud Alcohol 1978;39:809-19
Abstract NA	Pharmacotherapy for alcohol dependence. In: Treating alcohol and drug abuse. An evidence based review. Berglund M, Thelander S, Jonsson E (Eds.) Wiley-VHC amp Co. KgaA, Weinheim, Germany, 2003:247-312
In a placebo-controlled, double-blind German multicenter study (seven sites) the efficacy of naltrexone as an adjunctive treatment in alcoholism to maintain abstinence was assessed for 12 weeks. A total of 171 detoxified patients (97.7% met the DSM-III-R criteria for alcohol dependence) were included. Patients had been abstinent for a mean of 19.5 ± 9.4 days at study entry. Eighty-four and 87 patients were randomized to receive naltrexone (50 mg/day) and placebo, respectively. Each site was instructed to provide its usual psychosocial alcohol treatment program. The primary effectiveness measure was the time to first heavy drinking as derived from self-reports of drinking (timeline-follow-back method). Secondary effectiveness measures included time to first drink, amount of	Gastpar M, Bonnet U, Boning J et al. Lack of efficacy of naltrexone in the prevention of alcohol relapse: results from a German multicenter study. J Clin Psychopharmacol 2002;22:592-8

alcohol consumption, intensity of craving, severity of alcoholism problems, and liver enzymes. Thirty-three (38%) placebo patients and 28 (33%) naltrexone patients discontinued the study. At endpoint, 62% of the patients in each group did not have an episode of heavy drinking. Also, there were no significant differences between the study groups concerning secondary effectiveness measures as well as compliance and adverse clinical events—with the exception of the γ-GT, which was significantly greater reduced in the naltrexone group throughout the study. Based upon an intention-to-treat population, this study confirms the safety but not the efficacy of naltrexone in prevention of alcohol relapse. Nevertheless, the question arises whether self-reports of drinking are more reliable than γ-GT as a measure of recent alcohol consumption.	
Naltrexone is widely used in therapeutic programs with abstinence as a goal. However, it has been used in only a few studies aimed at reducing alcohol consumption. The purpose of this study was to evaluate the efficacy of naltrexone as an adjunct in controlled drinking programs. This was an open randomized study of 12 weeks duration that compared two therapeutic strategies: use of naltrexone in a controlled drinking program (NTX+CD) and the controlled drinking program alone (CD), without NTX. Each group comprised 30 male patients with mild alcohol dependence. During treatment, there were no differences between groups in drinking behavior, though the NTX+CD group showed significantly less craving. In the 12-month follow-up period, the NTX+CD group showed significantly fewer drinking days and heavy drinking days and less craving than the CD group. The results of this study suggest a role for naltrexone in controlled drinking programs.	Rubio G, Manzanares J, Lopez-Munoz F et al. Naltrexone improves outcome of a controlled drinking program. J Subst Abuse Treat 2002;23:361-6
Background: Clinical studies with opioid antagonists for treatment of problem drinking have mainly been conducted in specialized alcohol treatment centers, included structured psychosocial treatment, and have focused on maintaining abstinence after a period of abstinence from alcohol. 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 γ-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 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.	Karhuvaara S, Simojoki K, Virta A 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;31:1179-87
Abstract NA	Guardia J, Caso C, Arias F

	et al. A double-blind, placebo-controlled study of naltrexone in the treatment of alcohol-dependence disorder: results from a multicenter clinical trial. Alcohol Clin Exp Res 2002;26:1381-7
Random controlled trials on the efficacy of naltrexone and acamprosate in the treatment of alcohol dependence were reviewed, using a Relative Benefit (RB) analysis approach. A total of 42 studies were included, showing acamprosate use demonstrated a modest improvement, with a RB of 1.76 at three month follow-up. Short-term administration of naltrexone significantly reduced the relapse rate, but was not associated with modification in the abstinence rate. There was insufficient data available to ascertain the efficacy of naltrexone and acamprosate over prolonged periods of time, or the effectiveness of the medications relative to each other. Read More: http://informahealthcare.com/doi/abs/10.1080/00952990802082198	Snyder JL, Bowers TG. The efficacy of acamprosate and naltrexone in the treatment of alcohol dependence: a relative benefits analysis of randomized controlled trials. Am J Drug Alcohol Abuse 2008;34:449-61
Naltrexone is an opiate antagonist that is licensed for use orally as adjunctive therapy in the treatment of detoxified formerly opioid-dependent individuals (after around 10 days of being opiate free). It is taken in a dose of 50 mg per day and blocks the pleasurable and euphoric effects of heroin and other opiates. It works to help former opioid-dependent individuals to stay off drugs through the knowledge that these drugs will produce no positive effects. It does not increase motivation to stay abstinent and thus if people choose not to take the dose daily it will not work. It is not widely used in England and Wales and the current cost to the NHS in England is around £500,000 per annum and there is no evidence of an increasing trend in use. Moreover, not all of these prescriptions will be for use in the prevention of relapse in formerly opioid-dependent individuals, as it is also used in alcohol misuse and other conditions.	Adi Y, Juarez-Garcia A, Wang D et al. Oral naltrexone as a treatment for relapse prevention in formerly opioid-dependent drug users: a systematic review and economic evaluation. Health Technol Assess 2007;11:iii-iv, 1-85
Background: Renewed interest in medications to prevent relapse in alcoholics (i.e., antidipsotropics) resulted in approval by the Food and Drug Administration of naltrexone to treat alcohol dependence. Acamprosate, although not approved in the United States, is used in alcoholism treatment in many other parts of the world. In the absence of studies that compare the effects of these medications, we used a meta-analytic approach to the literature to compare their efficacy in alcoholism treatment. Methods: All published placebo-controlled trials of naltrexone or acamprosate for alcohol dependence were examined, and, when suitable, data were extracted for calculation of a mean effect size. A sample of studies of selective serotonin reuptake inhibitors for treatment of major depression conducted over the last two decades served as a comparator for the antidipsotropics. 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	Kranzler HR, van Kirk J. Efficacy of naltrexone and acamprosate for alcoholism treatment: a meta-analysis. Alcohol Clin Exp Res 2001;25:1335-41

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.	
Many trials of naltrexone have been carried out in alcohol-dependent patients. This paper is aimed to systematically review its benefits, adverse effects, and discontinuation of treatment. We assessed and extracted the data of double-blind, randomized controlled trials (RCTs) comparing naltrexone with placebo or other treatment in people with alcoholism. Two primary outcomes were subjects who relapsed (including heavy drinking) and those who returned to drinking. Secondary outcomes were time to first drink, drinking days, number of standard drinks for a defined period, and craving. All outcomes were reported for the short, medium, and long term. Five common adverse effects and dropout rates in short-term treatment were also examined. A total of 2861 subjects in 24 RCTs presented in 32 papers were included. For short-term treatment, naltrexone significantly decreased relapses [relative risk (RR) 0.64, 95% confidence interval (CI) 0.51–0.82], but not return to drinking (RR 0.91, 95% CI 0.81–1.02). Short-term treatment of naltrexone significantly increased nausea, dizziness, and fatigue in comparison to placebo [RRs (95% CIs) 2.14 (1.61–2.83), 2.09 (1.28–3.39), and 1.35 (1.04–1.75)]. Naltrexone administration did not significantly diminish short-term discontinuation of treatment (RR 0.85, 95% CI 0.70–1.01). Naltrexone should be accepted as a short-term treatment for alcoholism. As yet, we do not know the appropriate duration of treatment continuation in an alcohol-dependent patient who responds to short-term naltrexone administration. To ensure that the real-world treatment is as effective as the research findings, a form of psychosocial therapy should be concomitantly given to all alcohol-dependent patients receiving naltrexone administration.	Srisurapanont M, Jarusuraisin N. Opioid antagonists for alcohol-dependence. Cochrane Database Syst Rev 2005;1:CD001867
Several studies have shown the opioid antagonist naltrexone to be effective when combined with psychosocial therapies for the treatment of patients who are dependent on alcohol with fixed medication and time (12 weeks). In this study, 121 nonabstinent outpatients with alcohol dependence (DSM-IV) were treated with sessions of cognitive coping skills (N = 67) or supportive therapy (N = 54) and either naltrexone 50 mg/day (N = 63) or placebo (N = 58) daily for the first 12 weeks and thereafter for 20 weeks only when craving alcohol (i.e., targeted medication) in a prospective one-center, dual, double-blind, randomized clinical trial. The dropout rate for all subjects was 16.5% during the first 12-week period and approximately twice that level by the end of the study. There were no significant group differences in study completion and therapy participation rates. After the continuous medication (12 weeks), the coping/naltrexone group had the best outcome, and coping/placebo had the worst. This difference remained during the targeted medication period (the following 20 weeks). Naltrexone was not better than placebo in the supportive groups, but it had a significant effect in the coping groups: 27% of the coping/naltrexone patients had no relapses to heavy drinking throughout the 32 weeks, compared with only 3% of the coping/placebo patients. The authors' data confirm the original finding of the efficacy of naltrexone in conjunction with coping skills therapy. In addition, their data show that detoxification is not required and that targeted medication taken only when craving occurs is effective in maintaining the reduction in heavy drinking.	Heinälä P, Alho H, Kiianmaa K, Lönnqvist J, Kuoppasalmi K, Sinclair JD. J Clin Psychopharmacol 2001;21:287-92

Viited (Süstemaatilised ülevaated)

Kokkuvõtte (abstract või kokkuvõtlikum info)	**Viide kirjandusallikale**
Abstract BACKGROUND: Acupuncture has been used in the treatment of substance-related disorders for the past 30 years. However, a systematic review to assess the effect of various types of acupuncture for alcohol dependence has not yet been performed. The present systematic review assessed the results of randomized controlled trials (RCTs). METHODS: Nineteen electronic databases, including English, Korean, Japanese, and Chinese databases, were systematically searched for RCTs ofacupuncture for alcohol dependence up to June 2008 with no language restrictions. The methodological qualities of eligible studies were assessed using the criteria described in the Cochrane Handbook. RESULTS: Eleven studies, which comprised a total of 1,110 individual cases, were systematically reviewed. Only 2 of 11 trials reported satisfactorily all quality criteria. Four trials comparing acupuncture treatment and sham treatments reported data for alcohol craving. Three studies reported that there were no significant differences. Among 4 trials comparing acupuncture and no acupuncture with conventional therapies, 3 reported significant reductions. No differences between acupuncture and sham treatments were found for completion rates (Risk Ratio = 1.07, 95% confidence interval, CI = 0.91 to 1.25) or acupuncture and no acupuncture (Risk Ratio = 1.15, 95% CI = 0.79 to 1.67). Only 3 RCTs reported acupuncture-related adverse events, which were mostly minimal. CONCLUSIONS: The results of the included studies were equivocal, and the poor methodological quality and the limited number of the trials do not allow any conclusion about the efficacy of acupuncture for treatment of alcohol dependence. More research and well-designed, rigorous, and large clinical trials are necessary to address these issues.	Acupuncture for alcohol dependence: a systematic review. Cho SH1, Whang WW. Alcohol Clin Exp Res. 2009 Aug;33(8):1305-13. doi: 10.1111/j.1530-0277.2009.00959.x. Epub 2009 Apr 30. Systematic review of RCTs
Abstract — Background and Aims: Previous trials on acupuncture in alcohol addiction were in outpatients and focused on relapse prevention. Rates of dropout were high and interpretation of results difficult. We compared auricular laser and needle acupuncture with sham laser stimulation in reducing the duration of alcohol withdrawal. Methods: Inpatients undergoing alcohol withdrawal were	François Trümpler, Suzan Oez, Peter Stähli, Hans Dieter Brenner and Peter Jüni Alcohol & Alcoholism Vol. 38, No. 4, pp. 369–375, 2003 Acupuncture for alcohol withdrawal:

randomly allocated to laser acupuncture (n = 17), needle acupuncture (n = 15) or sham laser stimulation (n = 16). Attempts were made to blind patients, therapists and outcome assessors, but this was not feasible for needle acupuncture. The duration of withdrawal symptoms (as assessed using a nurse-rated scale) was the primary outcome; the duration of sedative prescription was the secondary outcome. Results: Patients randomized to laser and sham laser had identical withdrawal symptom durations (median 4 days). Patients randomized to needle stimulation had a shorter duration of withdrawal symptoms (median 3 days; P = 0.019 versus sham intervention), and tended to have a shorter duration of sedative use, but these differences diminished after adjustment for baseline differences. Conclusions: The data from this pilot trial do not suggest a relevant benefit of auricular laser acupuncture for alcohol withdrawal. A larger trial including adequate sham interventions is needed, however, to reliably determine the effectiveness of any type of auricular acupuncture in this condition.	a randomized controlled trial
Rationale: Little is known about the effect of disulfiram on subjective and autonomic nervous system cue reactivity in the laboratory. The dissuasive psychological effect manifested as a threat would seem to prevail over the pharmacological effect. Objectives: The primary objective was to determine whether there was a difference in cue reactivity responses during a threat condition compared to a neutral condition during alcohol cue exposure. Methods: In a crossover randomized study, participants received threat and neutral messages during two cue exposure sessions. The threat condition consisted of leading the patients to believe they had ingested 500 mg of disulfiram and the neutral condition of informing them that they had ingested a placebo, while in both condition they received the same placebo. Results: Physiological cue reactivity was demonstrated by a decrease in diastolic blood pressure during the threat compared to the neutral condition (p = 0.04). Heart rate and subjective cue reactivity measures remained unchanged. There was a negative affect (assessed by the Positive and Negative Affect Scale) by condition by exposure interaction. Conclusions: The threat of a disulfiram–ethanol reaction appears to affect cue reactivity physiologically rather than subjectively. While the data does not show changes in subjective ratings, it is possible that there are alternative beneficial effects arising from other cognitive processes that are not captivated by self-reported craving scales, reflected by decreases in negative affect and blood pressure. From this perspective, disulfiram might be recast to be more acceptable to patients.	Skinner MD, Coudert M, Berlin I, Passeri E, Michel L, Aubin HJ. Effect of the threat of a disulfiram-ethanol reaction on cue reactivity in alcoholics. Drug Alcohol Depend. 2010 Dec;112(3):239-46.
BACKGROUND:The placebo effect often undermines efforts to determine treatment effectiveness in clinical trials. A significant placebo response occurs in alcohol trials, but it is not well understood. The purpose of this study was to characterize the placebo response across multiple naltrexone and acamprosate studies. METHODS:Fifty-one trials, 3 with a naltrexone and an acamprosate arm, 31 with at least 1 naltrexone arm, and 17 with at least 1 acamprosate arm, were identified from Cochrane reviews and PubMed search. To be included in this study, patients had to be at least 18 years old, abstinent from alcohol before randomization, and meet a diagnosis of alcohol dependence. Pearson correlation coefficients (rp) and simple linear regression were used to describe the strength of linear relationships between placebo response and treatment effect size. Spearman's rank correlation coefficients (rs) were used to examine the strength of associations between study	Litten RZ, Castle IJ, Falk D, Ryan M, Fertig J, Chen CM, Yi HY. The placebo effect in clinical trials for alcohol dependence: an exploratory analysis of 51 naltrexone and acamprosate studies. Alcohol Clin Exp Res. 2013 Dec;37(12):2128-37.

characteristics and placebo response. RESULTS:For the end point measures of percent days abstinent and total abstinence, a negative relationship was evident between placebo response and treatment effect size in the naltrexone trials (rp = -0.55, p < 0.01 and rp = -0.20, p = 0.35, respectively) as well as in the acamprosate trials (rp = -0.45, p = 0.09 and rp = -0.56, p = 0.01, respectively). The placebo response for percent days abstinent was negatively correlated with mean age of participants (rs = -0.42, p = 0.05) across naltrexone trials and positively correlated with publication year (rs = 0.57, p = 0.03) across acamprosate trials. However, these 2 study characteristics were not significantly correlated with treatment effect size. CONCLUSIONS:The placebo response varied considerably across trials and was negatively correlated with the treatment effect size. Additional studies are required to fully understand the complex nature of the placebo response and to evaluate approaches to minimize its effects.	
OBJECTIVE:The purpose of this study was to examine the nature of the effect of placebo medication plus accompanying medical management in the treatment of alcohol dependence. METHOD:The National Institute on Alcohol Abuse and Alcoholism COMBINE (Combining Medications and Behavioral Interventions) study, a randomized controlled double-blind trial of 1,383 alcohol-dependent patients, compared combinations of medications (acamprosate [Campral] and naltrexone [ReVia]) and behavioral therapy (medical management and specialist-delivered behavioral therapy) for alcohol dependence. This report focuses on a subset of that study population (n = 466) receiving (1) specialized behavioral therapy alone (without pills), (2) specialized behavioral therapy + placebo medication + medical management, or (3) placebo + medical management. RESULTS:During 16 weeks of treatment, participants receiving behavioral therapy alone had a lower percentage of days abstinent (66.6%) than did the participants receiving placebo and medical management (73.1%) or those receiving specialized behavioral therapy + placebo + medical management (79.4%). The group receiving behavioral therapy alone relapsed to heavy drinking more often (79.0%) than those receiving behavioral therapy + placebo + medical management (71.2%). This report focuses on potential explanations for this finding. The two groups of participants receiving placebo + medical management were more likely to attend Alcoholics Anonymous meetings during treatment (32.7% and 32.0% vs 20.4%) and were less likely to withdraw from treatment (14.1% and 22.9% vs 29.3%). CONCLUSIONS:There appeared to be a significant "placebo effect" in the COMBINE Study, consisting of pill taking and seeing a health care professional. Contributing factors to the placebo response may have included pill taking itself, the benefits of meeting with a medical professional, repeated advice to attend Alcoholics Anonymous, and optimism about a medication effect.	Weiss RD, O'malley SS, Hosking JD, Locastro JS, Swift R, COMBINE Study Research Group. Do patients with alcohol dependence respond to placebo? Results from the COMBINE Study. J Stud Alcohol Drugs. 2008 Nov;69(6):878-84.
Background: Oral naltrexone is an FDA-approved medication for treating alcohol use disorders. Although its efficacy has been supported in multiple clinical trials, an earlier review found that its effect sizes (ESs) on relapse to heavy drinking and, to a lesser extent, percent days drinking were smaller in more recent trials and in multicenter than in single-site studies. We examined whether these findings held when studies from 2004 to 2009 were taken into account, and whether single-site versus multicenter trials, the use of placebo run-in periods, and placebo group improvement accounted for variation in naltrexone effects and decreasing effects over time. Methods: A multivariate meta-analysis of naltrexone pharmacotherapy trials for alcohol use disorders was conducted. All analyses simultaneously modeled	A. C. Del Re, Natalya Maisel, Janet Blodgett, and John Finney Alcohol Clin Exp Res, Vol 37, No 6, 2013: pp 1064–1068 The Declining Efficacy of Naltrexone Pharmacotherapy for Alcohol Use Disorders Over Time: AMultivariate Meta-Analysis

ESs on outcomes of percent days abstinent and relapse to heavy drinking. Potential moderators of medication effects that were examined included publication year, multicenter design (vs. single site), placebo run-in period, and placebo group improvement. Results: Statistically significant between-group differences on percent days abstinent (the inverse of percent days drinking) and relapse to heavy drinking favored naltrexone over placebo. Year of publication was a significant moderator for both outcomes, with more recent trials having smaller ESs. Neither multi- versus single-site study, the interaction between multi- versus single-site study and year of publication, nor placebo run-in period was a significant moderator of naltrexone effects. Although placebo group improvement was modestly associated with smaller between-group naltrexone versus placebo ESs, only 21 studies provided usable information on placebo group improvement. Within those studies, there was no relationship between naltrexone ESs and time, so placebo group improvement was not examined as a moderator of that relationship. Conclusions: Naltrexone ESs have attenuated over time. Moderators that explain why effects have been decreasing remain to be determined.	
Background: Alcohol use disorders (AUD) involving hazardous, harmful, and addictive misuse of alcohol are widespread in most parts of the world. The aim of this study was to review the effect of disulfiram in the treatment of patients with AUD. The effect of disulfiram was evaluated according to the primary outcome of an intake of alcohol below 30 and 20 g / d for men and women, respectively, as well as secondary outcomes such as days until relapse, alcohol intake, and numbers of drinking days. Methods: A systematic review of the literature was conducted using MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL). Results: Eleven randomized controlled trials were included with a total of 1,527 patients. They compared disulfiram treatment with placebo, none or other abstinence-supportive treatments. Overall, 6 studies reported of a significant better effect on abstinence for patients treated with disulfiram. Six of 9 studies measuring secondary outcomes reported that patients treated with disulfiram had significantly more days until relapse and fewer drinking days, respectively. The quality of the included studies was moderate. Heterogeneity was significant in most of the metaanalyses, but valid results were found regarding the effect of disulfiram versus placebo over 12 months and unsupervised disulfiram versus other or no treatment. The vast majority of significant studies were of shorter duration, while only 3 studies of 12 months were significant regarding more days until relapse and / or reduction in drinking days. Conclusions: Supervised treatment with disulfiram has some effect on short-term abstinence and days until relapse as well as number of drinking days when compared with placebo, none, or other treatments for patients with alcohol dependency or abuse. Long-term effect on abstinence has not been evaluated yet. However, there is a need for more homogeneous and high quality studies in the future regarding the efficacy of disulfiram.	Charlotte H. Jørgensen, Bolette Pedersen, and Hanne Tønnesen Alcohol Clin Exp Res, Vol 35, No 10, 2011: pp 1749–1758 The Efficacy of Disulfiram for the Treatment of Alcohol Use Disorder
Background: There is increasing clinical acceptance of acupuncture as a treatment of substancerelated disorders. Little is known about acupuncture as a treatment for the withdrawal syndrome in inpatient settings. We compared auricular needle acupuncture with aromatherapy in reducing the duration and severity of symptoms of alcohol withdrawal. Methods: Inpatients undergoing alcohol withdrawal were randomly allocated to needle acupuncture (n555) and aromatherapy (n554). Both therapies were applied daily during	Stephanie Kunz, Michael Schulz, Miriam Lewitzky, Martin Driessen, and Harald Rau Alcohol Clin Exp Res, Vol 31, No 3, 2007: pp 436–442 Ear Acupuncture for Alcohol Withdrawal in Comparison With Aromatherapy: A Randomized-Controlled Trial

the first 5 consecutive treatment days. The rating scale for the assessment of the alcohol-withdrawal syndrome (AWS scale) served as the main dependent variable and was applied daily during the first 5 days of the withdrawal. Further measures included a subjective visual analog scale of craving and the Self Assessment Manikin (SAM). Results: Thirty-six of the 55 patients who received acupuncture, and 38 of the 54 patients who received aromatherapy, finished the study regularly. The groups differed in their initial self-reported arousal, which then served as a covariate in the further analyses. Neither the extent of craving nor of withdrawal symptoms differed between groups over the observation period. Self-rated arousal decreased in response to both treatments from days 1 to 2 (po=.001) and within single days (p=0.001), and we found a significant interaction between pretreatment versus posttreatment and days (p=0.001). Interactions including between-subjects effects and intervention did not achieve the significance level. Conclusion: The results do not support the assumption of a superiority of acupuncture over the control therapy in its specific effects on alcohol withdrawal symptoms.	
For many years, placebos have been conceptualised by their inert content and their use as controls in clinical trials and treatments in clinical practice. Recent research demonstrates that placebo effects are genuine psychobiological phenomenon attributable to the overall therapeutic context, and that placebo effects can be robust in both laboratory and clinical settings. Evidence has also emerged that placebo effects can exist in clinical practice, even if no placebo is given. Further promotion and integration of laboratory and clinical research will allow advances in the ethical harnessing of placebo mechanisms that are inherent in routine clinical care and the potential use of treatments to primarily promote placebo effects.	Damien G Finnissa, Ted J Kaptchukb, Franklin Millerc, and Fabrizio Benedettid Lancet. 2010 February 20; 375(9715): 686–695. Placebo Effects: Biological, Clinical and Ethical Advances