Kliiniline küsimus nr 13 ja nr 14

K 13: Kas alkoholihimu vähendavaid ravimeid saavad patsiendid peavad alkoholitarvitamise vähendamiseks ravimit kasutama igapäevaselt vs kasutama riskiolukorras?

K 14: Kas kõigile alkoholisõltuvatele patsientidele määrata tulemuslikuks raviks aversiivseid/alkoholihimu vähendavaid ravimeid 3kuud vs 6 kuud vs 12 kuud vs 24 kuud?

Kriitilised tulemusnäitajad:
K 13: 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

K 14: 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

Aversiivsete/alkoholihimu vähendavate ravimite ravi pikkuse uuringud:

1 meta-analüüs (Mann et al 2004) koosnes 17 RCT-st. 6-kuulise ravi jooksul oli akamprosaadi ravirühmas abstinentsi hulk tunduvalt suurem võrreldes platseeboga: akamprosaat 36.1%, platseebo 23.4%; RR 1.47 (95% CI: 1.29 – 1.69; p<0.001). Raviefekti suurus 3.ndal kuul oli 1.33, 6.ndal kuul 1.50 ja 12.kuul 1.95. 12.kuul oli raviefekti erinevus akamprosaadi ja platseebo vahel 13.3 % (95% CI 7.8 – 18.7%; NNT 7.5).

1 süstemaatiline ülevaade (Srisurapanot et al 2005) koosnes 29 RCT-st (2 neist hindas nalmefeeni, 27 naltreksooni). Lühiajaline naltreksoonravi võrreldes platseeboga vähendas tunduvalt relapside hulka: RR 0.64 (95% CI 0.51-0.82). Keskmise pikkusega ravi naltreksooniga ei suurendanud raviefekti relapside ennetamises, kuid pikendas aega esimese dringini ja vähendas alkoholi iha. Keskmise pikkusega ravi naltreksooniga oli efektiivsem kui ravi akamprosaadiga relapside ennetamises ja drinkide arvu vähendamises. Liialt vähese info põhjal ei osata kindlalt öelda, kui pikalt peab raviga jätkama, kui ilmneb hea raviefekt naltreksoonile. (Artiklis pole öeldud, kui pikk on lühiajaline ravi ja kui pikk keskmise pikkusega ravi). Post-treatment evaluations, provided from a subset of six RCTs, indicate that the therapeutic effects of naltrexone fade after treatment is discontinued; anyhow, 3 to 12 months after the end of the treatment period, effects on heavy drinking still reach statistical significance. Three to twelve months after treatment was discontinued, patients who were in the naltrexone group had a 14% lower risk to return to heavy drinking RR 0.86 (95% CI 0.75 to 0.99), see Analysis 1.56 and a 6% lower risk to return to any drinking RR = 0.94 (95% CI 0.79 to 1.11)

1 spetsialistide hinnangu aruanne (Slattery et al 2003) soovitab disulfiraami manustada kord päevas. Samas võib disulfiraami manustada ka 2-3 korda nädalas, kuna ravimi toime kestab veel 7 päeva pärast viimast doosi. Akamprosaadi soovituslik annustamise skeem on 666 mg kolm korda päevas (1998 mg/päevas) ja ravi pikkus peaks olema 1 aasta. Kui kehakaal on väiksem kui 60 kg tuleb annust vähendada (1332 mg/päevas). Naltreksooni soovituslik annus on 50 mg/päevas. Ravi kestvus naltreksooniga peab minimaalselt olema 3 kuud, kuid pikem ravikuur võib osutuda vajalikuks.

1 RCT (Chick et al 2000) võrdles omavahel akamprosaati (666 mg x 3) ja platseebot, uuring kestis 6 kuud. 6 kuu möödudes saavutati abstinents 12% akamprosaadi ravigrupis ja 11% platseebo rühmas. Visuaalanaloogskaala põhjal vähenes alkoholihimu akamprosaadi korral enam kui platseebo korral, samuti oli efekt suurem 4 nädala möödudes kui 2 nädala möödudes (p<0.001).

Alkoholihimu vähendavate ravimite kasutus igapäevaselt vs riskiolukorras uuringud:

1 spetsialistide hinnangu aruanne (Slattery et al 2003) soovitab disulfiraami manustada kord päevas. Samas võib disulfiraami manustada ka 2-3 korda nädalas, kuna ravimi toime kestab veel 7 päeva pärast viimast doosi. Akamprosaadi soovituslik annustamise skeem on 666 mg kolm korda päevas (1998 mg/päevas) ja ravi pikkus peaks olema 1 aasta. Kui kehakaal on väiksem kui 60 kg tuleb annust vähendada (1332 mg/päevas). Naltreksooni soovituslik annus on 50 mg/päevas. Ravi kestvus naltreksooniga peab minimaalselt olema 3 kuud, kuid pikem ravikuur võib osutuda vajalikuks.

3 RCT (Hernandez-Avila et al 2006, Kranzler et al 2003, Kranzler et al 2009) hindasid naltreksooni tarvitamist riskiolukorras. Võrdluseks olid platseebo tarvitamine riskiolukorras või kord päevas ning naltreksoon 50 mg regulaarselt kord päevas. Hernandez-Avila et al 2006 läbiviidud RCT näitab, et riskiolukorras naltreksooni kasutamine vähendab tarbitava alkoholikoguse hulka, kuid vajalikud on lisauuringud, enne kui soovitada naltreksooni kasutamist vajadusel. Kranzler et al 2003 ja 2009 poolt läbiviidud uuringud näitasid mõlemad, et naltreksooni kasutamine riskiolukorras vähendab joomasööste. Efekti suurus oli aga väike ning vajalikud on veel täiendavad uuringud.

Kokkuvõte ravijuhendites leiduvatest soovitustest

Kümnest ravijuhendist kaheksas (SIGN 2003, NICE 2011, Austraalia 2009, Soome 2010, BAP 2012, WFSBP 2008, APA 2006, SAMHSA 2009) leidus infot K13 küsimuse kohta.

Kõik ravijuhendid soovitavad alkoholihimu vähendavaid ja aversiivseid ravimeid (akamprosaat, naltreksoon, disulfiraam) kasutada regulaarselt igapäevaselt. 3 ravijuhist (Soome 2010, WFSBP 2008, SAMHSA 2009) lubavad kasutada naltreksooni ka vastavalt vajadusele riskiolukorras. 2 ravijuhist (Soome 2010, WFSBP 2008) lubada kasutada nalmefeeni vastavalt vajadusele riskiolukorras.

5 ravijuhist (NICE 2011, Austraalia 2009, WFSBP 2008, APA 2006, SAMHSA 2009) soovitavad kasutada akamprosaati 1998 mg/päevas (666 mg x 3). 3 ravijuhist (SIGN 2003, Soome 2010, BAP 2012) ei anna soovituslikke ravimiannuseid. <60 kg soovitatakse akamprosaadi annuseid vähendada: 1332 mg/päevas (NICE 2011, Austraalia 2009, WFSBP 2008).

6 ravijuhist (NICE 2011, Austraalia 2009, Soome 2010, BAP 2012, APA 2006, SAMHSA 2009) soovitavad naltreksooni algannuseks 25 mg/päevas ning säilitusannuseks 50 mg/päevas.

1 ravijuhis lubab naltreksooni kasutada kuni 150 mg/päevas (SAMHSA 2009).

Disulfiraami soovitatasek kasutada 125-500 mg/päevas (NICE 2011, Austraalia 2009, Soome 2010, WFSBP 2008, APA 2006, SAMHSA 2009).

Soome 2010 ja Austraalia 2009 ravijuhised lubavad disulfiraami kasutada ka 400 mg kaks korda nädalas, kuna viimase annuse manustamisest püsib selle toime kuni 7 päeva.

Austraalia 2009 ravijuhis lubab kasutada kõige suuremaid disulfiraami annuseid, kuni 600 mg/päevas. Ülejäänud ravijuhised soovitavad mitte ületada annust 500 mg/päevas.

Ravi pikkus

Kümnes ravijuhendist viies (SIGN 2003, NICE 2011, Austraalia 2009, BAP 2012, SAMHSA 2009) leidus infot K14 küsimuse kohta.

4 ravijuhist (SIGN 2003, NICE 2011, BAP 2012, SAMHSA 2009) soovitavad ravi pikkuseks vähemalt 6 kuud.

Austraalia ravijuhis soovitab ravi pikkuseks 3-6 kuud.

2 ravijuhist (BAP 2012 ja SAMHSA 2009) soovitavad, et ravi akamprosaadiga võiks kesta umbes aasta.

3 ravijuhises (Soome 2010, WFSBP 2008, APA 2006) ei leidunud infot ravi pikkuse kohta.

Ravijuhendite soovituste tekstid (inglise keeles):

SIGN 2003

Acamprosate or supervised oral disulfiram should usually be initiated by a specialist service. The specialist service will: ensure that the patient meets the criteria for suitability; ensure the assessment of the motivation and ability of the patient to use the medication correctly; monitor efficacy; and ensure that adjunctive psychosocial treatment is organised. Usage should be in accordance with the Summary of Product Characteristics and reviewed regularly during the first 12 weeks after initiation of treatment, at which stage transfer of prescribing to the general practitioner may be appropriate, even though specialist care may continue (shared care).

Acamprosate is not effective in all patients so its efficacy should be assessed at regular appointments and the drug withdrawn if there has not been a major reduction in drinking. Where it appears to be effective, good practice suggests prescribing for 6-12 months.

NICE 2011

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:

- usually be prescribed for up to 6 months, or longer for those benefiting from the drug who want to continue with it

- 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.

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:

- usually be prescribed for up to 6 months, or longer for those benefiting from the drug who want to continue with it

- 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.

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.

Make sure that service users taking disulfiram:

- stay under supervision, at least every 2 weeks for the first 2 months, then monthly for the following 4 months

- if possible, have a family member or carer, who is properly informed about the use of disulfiram, oversee the administration of the drug

- are medically monitored at least every 6 months after the initial 6 months of treatment and monitoring.

Austraalia 2009

Naltrexone is formulated in tablets of 50 mg; the recommended dose is 50 mg (one tablet per day, orally) with meals. It may be preferable to start with half a tablet (25 mg per day) for several days, and increase to 50 mg after any adverse effects have subsided.

The most appropriate duration of treatment continuation in alcohol-dependent patients is not yet known.The usual treatment period is at least 3 to 6 months, but the decision on treatment duration should be made on a case-by-case basis between the patient and doctor, based on side effects, history of relapse, social and family circumstances, and other factors known to affect the patient.

Acamprosate is formulated in oral tablets of 333 mg; the recommended dose for adults is 1998 mg with meals (6 tablets per day – 2 tablets in three doses). Adults under 60 kg should take 1332 mg/day (4 tablets per day in 3 doses: 2, 1, 1). The usual treatment period is 3 to 6 months. However, the decision on the duration of treatment should be made on a case-by-case basis between the patient and doctor, taking into account side effects, history of relapse, social and family circumstances and other individual factors.

Disulfiram is formulated in tablets of 200 mg; the recommended dose is 200 to 400 mg (1 to 2 tablets per day orally). Some patients can continue to drink on 200 to 400 mg without significant adverse effects, and the dose should be increased. The maintenance dose should generally not

exceed 600 mg a day. In many patients, two or three doses per week may be sufficient, and this approach may be more practical and easier to schedule with supervision. Disulfiram is likely to be a useful treatment for the first 3 to 6 months of treatment. The decision on treatment duration should be made on a case-by-case basis between the patient and doctor, based on side effects, history of relapse, social and family circumstances and other individual factors.

Soome 2010
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.
Naltrexone (50 mg daily) increases the number of non-drinking days and reduces relapses compared with placebo.
Naltrexone or nalmefene taken in situations associated with imminent relapse (targeted medication) evidently reduces alcohol consumption and increases the number of non-drinking days.

BAP 2012
Naltrexone can be used safely while someone is still drinking, but in trials for relapse prevention it is started soon after stopping drinking. Most trials conducted were for 3 or 6 months. One study has reported that those who had naltrexone for 24 weeks rather than 12 weeks had better drinking outcomes (Ib). It is not clear if there is an optimal length of time; however, 6 months of treatment is reasonable, with stopping the medication if drinking persists for 4–6 weeks. Early trials used dose of 50 mg/day, although more recent US studies have used 100 mg/day. In the UK, 50 mg/day is more typically used, and it is unclear whether or how much extra benefit is accrued from higher doses.

Given this evidence and acamprosate's potential neuroprotective effect, we recommend it should be started during detoxification, despite Kampman et al. (2009) (Ib) reporting in a preliminary trial that some drinking outcomes may worsen. Currently the SPC recommends acamprosate be given for 1 year. Mann et al. (2004) (Ia) reported from their meta-analysis that acamprosate's effect size for abstinent rates increased with time from 1.33 at 3 months, to 1.5 at 6 months and 1.95 at 12 months. NICE (2011a) recommends medication should be prescribed for 6 months but stopped if drinking persists after 4–6 weeks. Pragmatically it is sensible not to continue prescribing any medication without review if drinking behaviour is not changing.The benefits of acamprosate in maintaining abstinence have been shown to persist for 3–12 months after stopping treatment, with a 9% lower risk to return to any drinking in patients who received acamprosate than those who received placebo (RR = 0.91; 95% CI 0.87–0.96) and a 9% higher continuous abstinence duration (MD 8.92; 95% CI 5.08–12.77; Rösner et al., 2010a) (Ia). The NNT for an additional prevention of drinking until the post-treatment evaluation was estimated at NNTB 12.5 (95% CI 9.09–25.00).

WFSBP 2008
Disulfiram is usually given at a dosage of 200 500 mg/day.
Acamprosate has poor oral bioavailabilty; therefore, the dosage used clinically is comparatively high: 1998 mg (two 333-mg tablets three times daily in patients with a body weight greater than 60 kg; two 333-mg tablets twice daily in lighter patients).
However, the optimal dosage and duration of treatment are two important clinical questions that remain to be adequately addressed, along with the patient population and treatment goal (i.e., harm reduction versus abstinence) that are most likely to yield beneficial effects.

APA 2006
In nonopioid-abusing patients, the 50-mg dose of naltrexone used in most studies has been associated with mild and transient side effects, including CNS-related symptoms (headache, fatigue, dysphoria) and gastrointestinal problems (nausea, vomiting, abdominal pain).
Treatment with the aversive agent disulfiram (usually 250 mg/day, range 125–500 mg/day) is aimed at motivating abstinent alcoholic individuals to resist alcohol consumption.
At a dosage of two 333-mg pills t.i.d. (total dose of 1,998 mg), which is an approved dose in the United States, acamprosate is well tolerated, with generally self-limited and symptomatically treated diarrhea being the main adverse effect.

SAMHSA 2009
Although 50 mg of naltrexone is currently the FDA recommended daily dose for treating AUDs,

evidence from an open-label, small-scale trial suggested that higher doses (up to 150 mg/day) may be effective in reducing alcohol consumption in patients with complicated conditions. The FDA label states that naltrexone should be taken for up to 3 months to treat AUDs. Healthcare providers should tailor the length of treatment to individual patients. Naltrexone has been administered to patients who are alcohol dependent for 6 months to 1 year with no additional safety concerns. *Acamprosate must be taken three times per day. The effectiveness and safety of acamprosate have been evaluated for up to 1 year. The length of time a particular patient takes acamprosate will be determined, ideally, with input from the prescribing professional, the specialty treatment provider, and the patient. Acamprosate therapy also may be discontinued if a patient is not adhering to the medication regimen. Acamprosate should not be discontinued just because a patient returns to alcohol use.* *Disulfiram. If a patient can drink alcohol without problems when compliant with the routine starting dose (which is rare), increase the dosage (dosage may be increased up to 500 mg/day with careful monitoring). Never exceed 500 mg/day.* *Initial dose: 250 mg/day 1-2 weeks. Average maintenance dosage: 250 mg/day. Maximum dosage: 500 mg/day. Dosage range 125-500 mg/day. Daily, uninterrupted dosing may be continued until the patient has established stable, long-term alcohol abstinence. Depending on the patient, disulfiram therapy may continue for months or years.*

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
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**
NICE 2011, BAP 2012, WFSBP 2008, APA 2006, SAMHSA 2009, Austraalia 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	Mann K, Lehert P and Morgan MY (2004) The efficacy of acamprosate in the maintenance of abstinence in

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.	alcohol-dependent individuals: results of a meta-analysis. Alcohol Clin Exp Res28: 51–63 **Meta-analysis**
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, 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	Srisurapanont, M and N Jarusuraisin 2005, Opioid antagonists for alcohol dependence. Cochrane Database of Systematic Reviews (2). **Systematic review**

to NTX treatment should continue their treatment. Due to too little evidence, NMF should have no role for the treatment of alcohol dependence.	
SIGN 2003, NICE 2011, BAP 2012, Soome 2010	
Disulfiram is recommended to be administered daily, but can also be given twice or thrice weekly (at 3-4 day intervals) as the action lasts for about 7 days after the last dose. The recommended dosage for acamprosate is 2x333mg tablets three times per day over a 1 year treatment period. The dosage is reduced to 4 tablets per day (2 morning, 1 midday, 1 night) in those weighing less than 60 kg. It is licensed only for patients between 18 and 65 years of age. The recommended dosage for naltrexone is one 50 mg tablet per day. An initial treatment period of three months is suggested but longer-term treatment can be considered.	Slattery J, Chick J, Cochrane M, Craig I, Godfrey C, Kohli H, et al. Prevention of relapse in alcohol dependence. Glasgow: Health Technology Board for Scotland; 2003. Health technology assessment report 3. [cited 14 Aug 2003]. **Assessment report**
BAP 2012, NICE 2011	
A 6-month randomized controlled study of acamprosate versus placebo in preventing relapse following withdrawal from alcohol was undertaken in 20 centres throughout the UK. Patients diagnosed as alcohol-dependent and detoxified within the preceding 5 weeks were randomly assigned to treatment with either acamprosate (A) 666 mg three times/day or identical placebo (P). A total of 664 patients were screened; 581 were entered into the treatment phase. One-third were episodic drinkers, 84% were male, 44% were unmarried and 48% were unemployed. Medication was first taken on average 24 days after the start of detoxification; 32% of patients had already relapsed by this time. The 6-month study period was completed by 35% of patients; adverse events led to withdrawal of a further 14% (A) and 9% (P) respectively. Compliance was poor in that, by the end of the second week, only 57% of patients were judged to be taking at least 90% of their tablets. The mean total of abstinent days achieved was 77 (A) and 81 (P). Complete abstinence for 6 months was achieved by 12% (A) and 11% (P); drinking remained within controlled limits in a further 3% (A) and 6% (P). An effect of acamprosate on consumption was not seen when subgroups, including those defined by the Lesch typology, were analysed separately. However, the mean percentage reduction in craving for alcohol measured on a visual analogue scale was greater in the acamprosate, than placebo, patients at week 2 and week 4 ($P<0.001$) and the mean decrease in the Hamilton Anxiety score at the 4th week was greater in the acamprosate than placebo patients ($P = 0.017$). In comparison with other published trials of acamprosate, patients started study medication after a longer time following detoxification, had more often recommenced drinking before medication was started and had a higher drop-out rate, and this might have contributed to the lack of a treatment effect in this study.	Chick J, Howlett H, Morgan M, et al. (2000) United Kingdom multicentre acamprosate study (UKMAS): a 6-month prospective study of acamprosate versus placebo in preventing relapse after withdrawal from alcohol. Alcohol Alcohol35: 176–187. **Multicentre RCT**
SAMHSA 2009	
METHODS: In a double-blind, placebo-controlled study, problem drinkers (n=150, 58% men) were randomly assigned to 8 weeks of treatment with naltrexone (50 mg/day) or placebo, either daily or on a targeted schedule. All subjects also received brief coping skills therapy. To complement the traditional regression analysis conducted previously, a zero-inflated Poisson regression model was used to examine the effects of medication, schedule of administration, and gender on the number of standard drinks consumed daily.	Hernandez-Avila, C. A., Song, C., Kuo, L., Tennen, H., Armeli, S., & Kranzler, H. R. (2006). Targeted versus daily naltrexone: Secondary analysis of effects on average daily drinking. Alcoholism: Clinical and Experimental Research, 30(5), 860–865.

RESULTS: Targeted naltrexone, and to a lesser extent targeted placebo, yielded a greater reduction in daily drinking than did daily placebo, an effect that did not differ by gender and that was greater than that seen for daily naltrexone treatment. Relative to daily placebo, daily naltrexone reduced the number of drinks/day only among men, at the level of a nonsignificant trend. **CONCLUSIONS:** Although in both genders, targeted treatments appeared to reduce the volume of drinking, treatment with targeted naltrexone was somewhat better. In contrast, heavy drinking women showed no benefit from daily naltrexone treatment. Further evaluation of the efficacy of targeted treatments and of daily naltrexone and the relationship of these treatments with gender is warranted.	**Secondary analysis**
SAMHSA 2009, NICE 2011, WFSBP 2008	
Most published studies of the efficacy of naltrexone for alcohol treatment have focused on daily medication for relapse prevention among abstinent alcoholics. The present study compared the effects of naltrexone with those of placebo in a sample of early problem drinkers who received study medication either daily or targeted to situations identified by the patients as being high risk for heavy drinking. Patients (n = 153; 58% male) were randomly assigned to receive naltrexone (50 mg) or placebo on a daily or targeted basis, yielding comparable numbers of patients in each of four treatment groups. Patients were trained to use structured nightly diaries in which they recorded their alcohol consumption and medication intake. Analysis was conducted with hierarchical linear modeling. Irrespective of whether they received naltrexone or placebo, patients in the targeted condition showed a reduced likelihood of any drinking. There was a reduced likelihood of heavy drinking, both for patients who received naltrexone and for patients who were in the targeted groups (either naltrexone or placebo), although these effects diminished as the number of tablets available to the targeted groups was reduced over the 8-week treatment period. Although the effect was a modest one, daily naltrexone reduced the risk of heavy drinking in this patient group. Furthermore, use of a targeted approach to medication treatment appears to be a useful strategy for reducing both drinking and heavy drinking. Efforts to replicate these findings are warranted, since they suggest that schedules of medication administration other than daily should be evaluated for treatment of problem drinking.	Kranzler, H. R., Armeli, S., Tennen, H., Blomqvist, O., Oncken, C., Petry, N., et al. (2003). Targeted naltrexone for early problem drinkers. Journal of Clinical Psychopharmacology, 23(3), 294–304. **RCT**
NICE 2011, BAP 2012	
This study aimed to replicate and extend prior research showing that the targeted use of naltrexone is a useful strategy to reduce heavy drinking. We compared the effects of naltrexone with those of placebo in a sample of 163 individuals (58.3% male) whose goal was to reduce their drinking to safe limits. Patients received study medication (ie, naltrexone 50 mg or placebo) and were instructed to use it daily or targeted to situations identified	Kranzler, H., Tennen, H., Armeli, S., et al.(2009) Targeted naltrexone for problem drinkers. Journal of Clinical Psychopharmacology, 29, 350–357.

by them as being high risk for heavy drinking. An interactive voice response system was used to obtain daily reports of drinking and medication use during the 12-week trial. Analyses were conducted using hierarchical linear modeling, with sex as a potential moderator variable. On the primary outcome measure, mean drinks per day, at week 12, men in the targeted naltrexone group drank significantly less than patients in the other groups did. On a secondary outcome measure, drinks per drinking day, during week 12, the targeted naltrexone group drank significantly less than the other groups did, with no moderating effect of sex. These results support the use of a targeted approach to reduce drinking among heavy drinkers, particularly men, but argue for the use of additional strategies or more efficacious medications than naltrexone to increase the effects of such an intervention.	**RCT**