Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2013-B-104 Nalmefen

Stand: Dezember 2013

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Nalmefen
zur Reduktion des Alkoholkonsums bei erwachsenen Patienten mit Alkoholabhängigkeit, deren Alkoholkonsum sich auf einem hohen Risikoniveau befindet (DRL: drinking risk level), bei denen keine körperlichen Entzugserscheinungen vorliegen und für die keine sofortige Entgiftung erforderlich ist.

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	*siehe Übersicht "II. Zugelassene Arzneimittel im Anwendungsgebiet"*
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	▪ Psychotherapie Eine Psychotherapie kann gemäß der Psychotherapie-Richtlinie des G-BA (§ 22 Abs. 2) im Falle einer Abhängigkeit von psychotropen Substanzen nur beschränkt auf den Zustand der Suchtmittelfreiheit bzw. Abstinenz angewendet werden. Abweichend davon ist eine Anwendung der Psychotherapie bei Abhängigkeit von psychotropen Substanzen dann zulässig, wenn die Suchtmittelfreiheit beziehungsweise Abstinenz parallel zur ambulanten Psychotherapie bis zum Ende von maximal 10 Behandlungsstunden erreicht werden kann.
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	▪ Verordnungseinschränkung nach Anlage III der AM-RL in Nummer 2 Mittel zur Behandlung der Alkoholabhängigkeit, […] b) ausgenommen zur Unterstützung der Reduktion des Alkoholkonsums bei alkoholkranken Patienten, die auf eine Abstinenztherapie hingeführt werden, für die aber entsprechende Therapiemöglichkeiten nicht zeitnah zur Verfügung stehen. Die Verordnung kann bis zu drei Monate erfolgen; in begründeten Ausnahmefällen kann die Verordnung um längstens weitere drei Monate verlängert werden. Die Einleitung darf nur durch in der Therapie der Alkoholabhängigkeit erfahrene Ärztinnen und Ärzte erfolgen.
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*siehe Recherche und Synopse der Evidenz*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Nalmefen N07BB05 Selincro®	Selincro® wird zur Reduktion des Alkoholkonsums bei erwachsenen Patienten mit Alkoholabhängigkeit angewendet, deren Alkoholkonsum sich auf einem hohen Risikoniveau befindet (DRL: drinking risk level), bei denen keine körperlichen Entzugserscheinungen vorliegen und für die keine sofortige Entgiftung erforderlich ist. Selincro® sollte nur in Verbindung mit kontinuierlicher psychosozialer Unterstützung, die auf Therapieadhärenz und eine Reduktion des Alkoholkonsums zielt, verschrieben werden. Die Behandlung mit Selincro® sollte nur bei Patienten eingeleitet werden, deren Alkoholkonsum sich 2 Wochen nach einer initialen Untersuchung weiterhin auf einem hohen Risikoniveau befindet.
Naltrexon N07BB04 Adepend®	Adepend® 50mg Filmtabletten werden angewendet als Teil eines umfassenden Therapieprogramms gegen Alkoholabhängigkeit zur Reduktion des Rückfallrisikos, als unterstützende Behandlung in der Abstinenz und zur Minderung des Verlangens nach Alkohol.

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2013-B-104 Nalmefen

Auftrag von: Abt. AM

bearbeitet von: Abt. FB Med

Datum: 11.12.2013

Recherche und Synopse der Evidenz zur Bestimmung der zVT:

Inhalt

Indikation für die Recherche bei Nalmefen (Selincro®):

Selincro® wird zur Reduktion des Alkoholkonsums bei erwachsenen Patienten mit Alkoholabhängigkeit angewendet, deren Alkoholkonsum sich auf einem hohen Risikoniveau befindet (DRL: drinking risk level), bei denen keine körperlichen Entzugserscheinungen vorliegen und für die keine sofortige Entgiftung erforderlich ist. Selincro® sollte nur in Verbindung mit kontinuierlicher psychosozialer Unterstützung, die auf Therapieadhärenz und eine Reduktion des Alkoholkonsums zielt, verschrieben werden. Die Behandlung mit Selincro® sollte nur bei Patienten eingeleitet werden, deren Alkoholkonsum sich 2 Wochen nach einer initialen Beurteilung weiterhin auf einem hohen Risikoniveau befindet.

Berücksichtigte Wirkstoffe/Therapien:

Naltrexon, Kurzinterventionen, psychosoziale Interventionen im stationären und ambulanten Setting

Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und Evidenz-basierten systematischen Leitlinien zur Indikation

„„Reduktion des Alkoholkonsums“ durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am **25.11.2013** abgeschlossen. Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (einschl. NHS CRD-Datenbanken), MEDLINE (PubMed), Leitlinien.de (ÄZQ), AWMF, GIN, NGC, TRIP, DAHTA, NIHR HSC. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Bei der Recherche wurde keine Sprachrestriktion vorgenommen. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab **438** Quellen, die anschließend nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Es wurden **11** Quellen in die synoptische Evidenz-Übersicht aufgenommen.

Abkürzungen

AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
ÄZQ	Ärztliches Zentrum für Qualität in der Medizin
DAHTA	Deutsche Agentur für Health Technology Assessment
G-BA	Gemeinsamer Bundesausschuss
GGT	gamma-glutamyl transpeptidase
GIN	Guidelines International Network
GoR	Grade of recommendation
GP	General Practitioner
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
LoE	Level of Evidence
MD	Mean differences
NGC	National Guideline Clearinghouse
NHS CRD	National Health Services Center for Reviews and Dissemination
NICE	National Institute for Health and Care Excellence
NIHR HSC	National Institute for Health Research Horizon Scanning Centre
RD	Risk difference
RR	Relatives Risiko
SMD	Standardized mean difference
TRIP	Turn Research into Practice Database

Cochrane Reviews

Rösner et al. Opioid antagonists for alcohol dependence. Cochrane Database of Systematic Reviews **2010**; (12): CD001867	1. Fragestellung To determine the effectiveness and tolerability of **opioid antagonists** in the treatment of alcohol dependence.
	2. Methodik Population: Individuals with alcohol dependence according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM) or the International Statistical Classification of Diseases (ICD) irrespective of any other characteristics. Patient samples including both, patients with alcohol dependence and alcohol abuse, were only included if patients with alcohol dependence constituted the majority of the sample (> 90%). Intervention: naltrexone or nalmefene. A minimum of four weeks daily treatment was required to ensure an adequate implementation of the intervention. Komparator: placebo or active control on drinking-related outcomes. Endpunkt: primary: return to heavy drinking (as defined in the primary analysis), return to any drinking, drinking days. Secondary: heavy drinking days, consumed amount per drinking day,gamma-glutamyl transpeptidase (GGT), side effects. Studiendesign: Systematic review and meta-analysis of RCTs. Suchzeitraum (Aktualität der Recherche): Up to January 2010. Anzahl eingeschlossene Studien/Patienten (Gesamt): 50 (7793)
	3. Ergebnisdarstellung Naltrexone versus placebo (RCTs: 40, patients: k.A.) Return to heavy drinking (28 studies. Patients in intervention group: 2330, control group: 2103): statistically significant difference in favour of naltrexone RR 0.83 (95% CI 0.76 to 0.90), I^2=61%. Return to any drinking (27 studies. Patients in intervention group: 2561, control group: 2132): no significant difference RR 0.96 (95% CI 0.92 to 1.00), I^2=28%. Reduction of drinking days (26 studies. Patients in intervention group: 2045, control group: 1837): statistically significant difference in favour of naltrexone MD -3.89 (95% CI - 5.75 to -2.04), I^2=94%. Reduction of heavy drinking days (15 studies. Patients in intervention group: 868, control group: 847): statistically significant difference in favour of naltrexone MD -3.25 (95% CI -5.51 to -0.99), I^2=81%. Consumed amount of alcohol on drinking days in grams (16 studies.

	Patients in intervention group: 966, control group: 872): statistically significant difference in favour of naltrexone MD- 10.83 (95%CI -19.69 to -1.97), I^2=66%. Reduction of GGT (16 studies. Patients in intervention group: 839, control group: 806): statistically significant difference in favour of naltrexone MD - 10.37 (95% CI -18.99 to -1.75), I^2=61%. side effects: statistically significant difference in favour of Placebo in abdominal pain RD 0.08 (95%CI 0.04 to 0.11), decreased appetite RD 0.07 (95% CI 0.03 to 0.11), nausea RD 0.10 (95% CI 0.07 to 0.13), vomiting RD 0.07 (95% CI 0.04 to 0.09), daytime sleepiness RD 0.09 (95% CI 0.05 to 0.14), drowsiness RD 0.10 (95% CI 0.00 to 0.19), fatigue RD0.05 (95%CI 0.01 to 0.09), insomnia RD 0.03 (95% CI 0.00 to 0.06), lethargy RD 0.13 (95% CI 0.04 to 0.23), somnolence RD 0.10 (95% CI 0.05 to 0.14), weakness RD 0.17 (95% CI 0.05 to 0.29), blurred vision RD 0.13 (95% CI 0.04 to 0.21), decreased libido RD0.08 (95%CI 0.01 to 0.16), depression RD 0.04 (95% CI 0.00 to 0.08), dizziness RD 0.06 (95% CI 0.04 to 0.08), nightmares RD0.10 (95%CI 0.04 to 0.16). Serious side effects: no significant difference RD -0.02 (CI -0.05 to 0.00). Dropping out due to adverse events: statistically significant difference in favour of Placebo RR 1.60; (95%CI 1.15 to 2.23). Subgroup injectable naltrexone: risk of any drinking: no statistically significant difference RR = 0.92 (95% CI 0.84 to 1.00); percentage of drinking days: statistically significant difference in favour of naltrexone MD - 8.54 (95% CI -15.77 to -1.31); side effects: statistically significant difference in favour of placebo in: decreased appetite, dizziness, fatigue, vomiting; Early drop-out due to side effects: statistically significant difference in favour of placebo 1.57 (95% CI 0.92 to 2.69). Nalmefene versus placebo (3 RCTs, 396 patients) (Ergebnisse zum Ende der Gabe der Studienmedikation) Return to heavy drinking (3 studies, 396 patients): no statistically significant difference (RR = 0.85; 95% CI 0.67 to 1.08), I^2=35%. Return to any drinking: no statistically significant difference (RR = 0.92; 95% CI 0.70 to 1.20). Reduction of heavy drinking days: no statistically significant difference (MD = -4.70; 95% CI -12.38 to 2.98). Amount of alcohol consumed per drinking day (2 studies, 126 patients):

	no statistically significant difference (MD = -4.16; 95% CI -32.69 to 24.37), I^2=52%. Side effects: statistically significant difference in favour of Placebo in nausea (RD = 0.20; 95% CI 0.14 to 0.26), insomnia (RD = 0.12; 95% CI 0.05 to 0.19) dizziness (RD = 0.15; 95% CI 0.05 to 0.25). Drop out due to adverse events: statistically significant difference in favour of Placebo (RR = 1.43; 95% CI 0.22 to 9.24).
	4. Anmerkungen/Fazit der Autoren Naltrexone appears to be an effective and safe strategy in alcoholism treatment. Even though the sizes of treatment effects might appear moderate in their magnitudes, these should be valued against the background of the relapsing nature of alcoholism and the limited therapeutic options currently available for its treatment. 5. Hinweise durch FB Med Die Analysen zu Naltrexone versus acamprosate, Naltrexone versus apripiprazole, nefazodone or topiramate Naltrexone + acamprosate versus placebo, Naltrexone + acamprosate versus naltrexone, Naltrexone + ondansetrone / sertraline versus placebo sind aufgrund des jeweiligen Zulassungsstatus nicht Gegenstand der vorliegenden Evidenzsynopse.
Lobmaier et al. Sustained-Release Naltrexone For Opioid Dependence. Cochrane Database of Systematic Reviews **2008**; (2): CD006140.	1. Fragestellung To evaluate the effectiveness of **sustained-release naltrexone** for opioid dependence and its adverse effects in different study populations.
	2. Methodik Population: Adults or adolescents with opioid dependence. Studies investigating naltrexone treatment for other conditions were excluded for effectiveness evaluation. For adverse effects evaluation only, any research on healthy participants and any research on treatment for other conditions than opioid dependence was included. Intervention: Any use of sustained-release formulations (i.e. depot or implant) of naltrexone. Komparator: any other pharmacological or psychosocial or no treatment. Endpunkt: primary: Opioid use during and after treatment, treatment adherence, retention in treatment, adverse effects and severe AEs. Secondary: Use of illicit drugs other than opioids during and after treatment, criminal activity and incarceration, quality of life, mental health, duration of achieved therapeutic naltrexone blood levels Studiendesign: To evaluate effectiveness only RCTs were included. To evaluate safety, any clinical trial reporting adverse effects was

	assessed. Suchzeitraum (Aktualität der Recherche): up to November 2007. Anzahl eingeschlossene Studien: effectiveness: 1 RCT, Adverse effects: 17 reports. **Alcohol**: 6 reports (4 of those were RCTs). Hier nur Ergebnisse aus RCTs dargestellt.
	3. Ergebnisdarstellung High-dose naltrexone depot injections compared to placebo injection (2 RCTs, 30 + 414 patients) Unerwünschte Ereignisse: no statistically significant differences in both studies in one or more adverse effects, severe adverse effects, injection site pain or discontinued treatment due to adverse effects. Therapieunterbrechung: statistically significant difference in favour of control group, 414 participants, RR 2.11 (CI 1.15 to 3.88). Low-dose naltrexone depot compared to placebo injection (3 RCTs, 624 + 20 + 333 patients) Unerwünschte Ereignisse: no statistically significant differences in one or more adverse effect, discontinued due to adverse effects, injection site pain, injection site induration, injection site contusion, one or more injection site reaction, severe adverse effect. In all 3 trials, pooled group differences of reporting any type of injection site related adverse effect (i.e. injection site pain, induration, contusion and one or more reaction) was statistically significant in favour of control group with pooled RR 1.18 (CI 1.02 to 1.36) (patients: 908 intervention group, 883 control group). High-dose compared to low-dose naltrexone depot injections (1 RCT, 415 patients) Therapieunterbrechung: statistically significant in favour of control, 415 participants, RR 2.12 (CI 1.02 to 3.22). Unerwünschte Ereignisse: No statistically significant differences for reporting injection site pain and for reporting severe adverse effects.
	4. Anmerkungen/Fazit der Autoren There is insufficient evidence to evaluate the effectiveness of sustained-release naltrexone for treatment of opioid dependence. For naltrexone injections, administration site-related adverse effects appear to be frequent, but of moderate intensity and time limited. For a harm-benefit evaluation of naltrexone implants, more data on side effects and adverse events are needed. Findings on supposedly naltrexone-related adverse effects revealed significant group differences for nausea, fatigue, vomiting, decreased

	appetite, dizziness and upper abdominal pain in alcohol dependent patients (Garbutt 2005; Kranzler 2004, data not shown). These adverse effects seemed to occur in a dose-related fashion and most infrequently in the placebo group. Findings are consistent with side effects of oral naltrexone treatment described earlier (Martin 1973). 5. Hinweise durch FB Med Effekte ließen sich nach Angabe der Autoren nur aus einem RCT extrahieren. In diesem waren Patienten mit unterschiedlichen Opioidabhängigkeiten eingeschlossen. Daher werden diese Ergebnisse hier nicht aufgenommen.
McQueen et al. Brief interventions for heavy alcohol users admitted to general hospital wards. Cochrane Database Syst Rev **2011**; (8): CD005191.	1. Fragestellung To determine whether **brief interventions** reduce alcohol consumption and improve outcomes for heavy alcohol users admitted to general hospital inpatient units.
	2. Methodik Population: We considered trials that included adults and adolescents (people 16 years and older) admitted to general inpatient hospital care for any reason other than specifically for alcohol treatment, where inclusion criteria for the study identified participants as regularly consuming alcohol above the recommended safe weekly/ daily amounts for the country in which the study took place. Intervention: brief interventions defined as a single session or up to three sessions involving an individual patient and health care practitioner comprising information and advice, often using counseling type skills to encourage a reduction in alcohol consumption and related problems. Komparator: assessment only (screening) or treatment as usual. Endpunkt: primary: alcohol consumption measured by self-report data or laboratory markers. Secondary: heavy drinking days, hospital re-admission rates, mortality rates, alcohol related injuries, quality of life (using standardised tools), reduction in sickness absence from work related tasks, reduction in adverse legal events as a consequence of alcohol, need for institutional care. Studiendesign: Systematic review and meta-analysis of weighted mean differences (MD) of randomised controlled trials and controlled clinical trials which provided an appropriate control arm. All hospital inpatient units that were not identified as psychiatric or addiction services were included. Suchzeitraum (Aktualität der Recherche): January 1966 to March 2011. Anzahl eingeschlossene Studien/Patienten (Gesamt): 14 (n=4041).
	3. Ergebnisdarstellung

	Mean alcohol consumption in grams per week (8 studies, 2196 participants): statistically significant difference at six months follow up MD -69.43 (95% CI -128.14 to -10.72, I^2=68% (4 Studien)) and at nine months follow up MD -182.88 (95% CI -360.00 to -5.76, 1 Studie) in favour of the brief intervention but no significant difference at one year follow up MD -33.62 (95% CI -82.27 to 15.03, I^2=0, 4 Studien). The result become not statistically significant in sensitivity analysis excluding the study with the highest risk of bias: MD -55.49 (95% CI -115.33 to 4.35). Mean alcohol consumption per week (change scores from baseline) (3 studies, 1318 participants): no statistically significant difference. Self-reports of alcohol consumption (3 studies, 603 participants): no statistically significant difference. Laboratory markers (3 studies, 426 participants): no statistically significant difference. Number of binges (1 studies, 341 participants): no statistically significant difference. Heavy drinking episodes (days per week) (1 studies, 616 participants): statistically significant differences in favour of the brief intervention group at 3 month: MD -0.56 (95% CI -1.02 to -0.10); 4 month: MD -0.78 (95%CI -1.32 to -0.24); 12 month: MD -0.71 (95% CI -1.26 to -0.16). Death (9 studies, 3256 participants): Significant difference at 6 months, RR 0.42 (95% CI 0.19 to 0.94, I^2=62%, 4 Studien) and one year, RR 0.60 (95% CI 0.40 to 0.91, I^2=0%, 7 Studien) with less deaths in the brief intervention groups than control groups; no statistical significant differences at three, four or nine months follow up. Number of days hospitalised in previous 3 months (1 study, 616 participants): no statistical significant difference.
	4. Anmerkungen/Fazit der Autoren The main results of this review indicate that there are benefits to delivering brief interventions to heavy alcohol users admitted to general hospital wards in terms of reduction in alcohol consumption and death rates. However, these findings are based on studies involving mainly male participants. Further research is required determine the optimal content and treatment exposure of brief interventions within general hospital settings and whether they are likely to be more successful in patients with certain characteristics. 5. Hinweise durch FB Med

	Die Population der Studie ist nicht eindeutig auf die Zielpopulation von Nalmefen übertragbar, da es sich nicht ausschließlich um alkoholabhängige Patienten handelt. Der Anteil alkoholabhängiger Patienten in der Studienpopulation ist nicht angegeben.
Huibers et al. Psychosocial interventions by general practitioners. Cochrane Database of Systematic Reviews **2007**; (3): CD003494	1. Fragestellung To examine the effectiveness of **psychosocial interventions** by general practitioners by assessing the clinical outcomes and the methodological quality of selected studies.
	2. Methodik Population: There were no restrictions on the type of participants in studies to be selected. Intervention: psychosocial intervention, with no restrictions on type of participant, type of disorder, problem or complaint, or type of psychosocial intervention. A GP-administered psychosocial intervention should meet the following criteria: 1) The intervention is explicitly delivered by a GP (or family physician or family doctor), although the GP intervention may be compared with a similar intervention administered by a different health professional. The GP can be the regular GP of patients or a research GP who is assigned to patients for the purpose of the study. 2) The intervention is a systematic treatment in which a psychological process is the central dynamic. 3) The intervention consists of a standardised number of at least two face-to-face contacts between patient and GP. Single session interventions are excluded, so that psychosocial interventions are distinguished from the brief psychosocial advice that is commonly given by GPs, but that cannot be accounted as a systematic treatment. Komparator: 'usual care' or another experimental intervention. Endpunkt: effectiveness of psychosocial interventions. Studiendesign: Systematic review and meta-analysis of randomised controlled trials (RCTs) controlled clinical trials (CCTs) and controlled patient preference trials (CPPTs) of psychosocial interventions delivered by general practitioners. Suchzeitraum: Bis zum 20.10.2005. Anzahl eingeschlossene Studien: 10 (all psychosocial interventions), 2 alcohol reduction studies (one high-quality RCT, one low-quality CCT). Es werden nur die Ergebnisse des RCT dargestellt.
	3. Ergebnisdarstellung Intervention des RCT: The effects of a two session cognitive behavioural intervention (CBI) administered by one research GP were compared to a CBI by a nurse practitioner and one-session brief advice

	by one of 12 regular GPs. Alkoholkonsum (Menge), alkoholbezogene Probleme: no statistical significant differences at 12 month follow-up between the groups.
	4. Anmerkungen/Fazit der Autoren a. Limited evidence (level 3) that a cognitive behavioural intervention by a GP is no more effective than a cognitive behavioural intervention by a nurse practitioner or brief advice on alcohol consumption or alcohol-related problems. b. Limited evidence (level 3) that a behavioural change programme is no more effective than brief advice, assessment of drinking behaviour only or follow-up measurement only on alcohol consumption or alcohol-related problems. 5. Hinweise durch FB Med Die Population der Studie ist nicht eindeutig auf die Zielpopulation von Nalmefen übertragbar, da es sich nicht ausschließlich um alkoholabhängige Patienten handelt. Der Anteil alkoholabhängiger Patienten in der Studienpopulation ist nicht angegeben.

Systematische Reviews

Maisel et al. Meta-analysis of naltrexone and acamprosate for treating alcohol use disorders: when are these medications most helpful? Addiction **2012**.	1. Fragestellung Relative efficacy of naltrexone and acamprosate given its presumed mechanism of action (reducing heavy drinking versus fostering abstinence).
	2. Methodik Population: populations aged 18 years or older. Other study eligibility criteria included a focus on treating alcohol misuse/alcohol use disorder (excluding studies focusing on alcohol withdrawal, alcohol detoxification, alcohol challenges, etc.). Participants could not be in an in-patient setting for the entire time of medication treatment and follow-up period. Intervention: naltrexone and acamprosate. Komparator: placebo. Endpunkt: maintenance of abstinence, heavy drinking outcomes aggregate (heavy drinking rate (five or more standard drinks per day for men and four or more standard drinks per day for women), percent days heavy drinking, time to first heavy drink, drinking quantity), craving. Studiendesign: Systematic review and meta-analysis of RCTs. Suchzeitraum (Aktualität der Recherche): 1970 to 2009. Anzahl eingeschlossene Studien/Patienten (Naltrexon): 45 Studien, 5434 Patienten.
	3. Ergebnisdarstellung Heavy drinking outcomes aggregate: statistically significant difference in favour of naltrexon compared to placebo (Hedges' g: 0.19 CI 0.12; 0.25) within the time of intervention (I^2= 38.3%, p=0,005). Follow-up: naltrexone studies tended to have effect sizes for heavy drinking outcomes at the last follow-up point (g = 0.135, n = 6) that were slightly smaller compared with end-of-treatment (g = 0.189, n = 39).
	4. Anmerkungen/Fazit der Autoren In treatment for alcohol use disorders, acamprosate has been found to be slightly more efficacious in promoting abstinence and naltrexone slightly more efficacious in reducing heavy drinking and craving. Detoxification before treatment or a longer period of required abstinence before treatment is associated with larger medication effects for acamprosate and naltrexone respectively. 5. Hinweise durch FB Med Es ist nicht klar, ob die Patienten alkoholabhängig waren. Einschlusskriterium war Alkoholmissbrauch ohne Definition der

	Intensität des Missbrauchs.
Rosner et al. Acamprosate supports abstinence, Naltrexone prevents excessive drinking: evidence from a meta-analysis with unreported outcomes. J Psychopharmacol (Oxf) **2008**; 22(1) 11-23.	1. Fragestellung Efficacy of naltrexone and acamprosate.
	2. Methodik Population: Alcohol dependence had to be diagnosed by a standardized diagnostic system. Intervention: naltrexone and acamprosate. Komparator: placebo. Endpunkt: return to any drinking, drinking frequency, gamma-glutamyl, transpeptidase, amount of alcohol consumed. Studiendesign: Systematic review and meta-analysis of RCTs. Suchzeitraum (Aktualität der Recherche): Up to 2004. Anzahl eingeschlossene Studien/Patienten: Gesamt 41 RCTs, 7462 Patienten. Naltrexon: 20 RCTs, 2182 Patienten.
	3. Ergebnisdarstellung Return to heavy drinking (18 RCTs, 2182 Patienten): statistically significant difference in favour of naltrexon (RR= 0.80; 95%CI 0.71 to 0.91), I^2=65%. Subgroup of non-abstinent patients (15 RCTs, 1455 Patienten): statistically significant difference in favour of naltrexon (RR= 0.88; 95%CI 0.80 to 0.96), I^2=56%. Drinking days per week (5 RCTs, 1259 Patienten): statistically significant difference in favour of naltrexon (SMD = -0.14; 95%CI -0.25 to -0.03). Gamma-glutamyl transpeptidase (6 RCTs, 675 Patienten): statistically significant difference in favour of naltrexon (SMD = -0.37; 95%CI -0.51 to -0.22). Amount of alcohol consumed (11 RCTs, 1444 Patienten): no statistically significant difference (SMD = -0.89; 95%CI -1.88 to 0.10). No significant result maybe due to high heterogeneity.
	4. Anmerkungen/Fazit der Autoren Naltrexone was found to have a significant effect on the maintenance of abstinence as well as the prevention of heavy drinking. Acamprosate was shown only to support abstinence; it did not influence alcohol consumption after the first drink. When the efficacy profiles of the two drugs were compared, acamprosate was found to be more effective in preventing a lapse, whereas naltrexone was better in preventing a lapse from becoming a relapse. The superiority of either one drug over the other one cannot be determined as a general rule, it rather depends on the therapeutic target. Benefits in the treatment of alcohol dependence might be optimized by matching the efficacy profiles of specific antidipsotropics with the motivational status of alcohol-dependent

	patients.
Government of South Australia. Pharmacotherapies for relapse prevention in alcohol dependence. (2nd edition). Stand: 2011. South Australia: Drug & Alcohol Services **2001**. (Monography No. 26	1. Fragestellung Efficacy of pharmacotherapies prevention in alcohol dependence.
	2. Methodik Population: Alcohol dependent. Intervention: pharmacotherapies. Komparator: placebo, other pharmacotherapies. Endpunkt: retention in treatment, alcohol consumption, adverse events. Studiendesign: Systematic review and meta-analysis of RCTs Suchzeitraum (Aktualität der Recherche): k.A. Anzahl eingeschlossene Studien/Patienten (Gesamt): overall: 56, naltrexone: 45. Patienten: k.A.
	3. Ergebnisdarstellung Alcohol consumption per drinking day (oral naltrexon) (16 trials, intervention group: 1123, control group: 933): statistically significant difference in favour of oral naltrexone compared to placebo (moderate evidence). MD -0.83, 95%CI -1.38, -0.28, p=0.003, I^2=59%. Alcohol consumption per drinking day (depot or implant naltrexon) (1 trial, intervention group: 25, control group: 5): statistically significant difference in favour of depot naltrexone compared to placebo (very low evidence). MD -2.2, 95%CI -3.19, -1.21, p<0.001. Alcohol consumption per week (oral naltrexon) (10 trials, intervention group: 595, control group: 574): no statistically significant difference between naltrexone and placebo. MD -1.80, 95%CI -3.86, 0.26, p=0.09, (low evidence). I^2=63%. Days of heavy drinking (oral naltrexon) (13 trials, intervention group: 714, control group: 714): statistically significant difference in favour of oral naltrexone compared to placebo (moderate evidence). MD -2.50, 95%CI -4.14, -0.85, p=0.003, I^2=90%. GGT: GGT or change in GGT are not significantly different in groups treated with opiod antagonsits compared to placebo. Nausea and vomiting (26 trials, intervention group: 2015, control group: 1797): statistically significant difference in favour of placebo compared to oral naltrexone (moderate evidence). RR 1.82, 95%CI 1.60, 2.07, p<0.0001, I^2=15%. AE are reflected in a greater likelihood of dose reduction compared to placebo (low evidence). Gastrointestinal symptoms: slightly more likely in opioid antagonists but

<table>
<tr><td></td><td>not statistically significant (moderate evidence).

Neuropsychiatric symptoms (23 trials, intervention group: 1592, control group: 1372): statistically significant difference in favour of placebo compared to naltrexone (moderate evidence). RR 1.20, 95%CI 1.00, 1.43, p=0.05, I^2=47%.</td></tr>
<tr><td></td><td>4. Anmerkungen/Fazit der Autoren
Evidenz wurde folgendermaßen klassifiziert:

<table><tr><td>strong</td><td>further research is unlikely to substantially change the estimate of effect</td></tr><tr><td>moderate</td><td>further research is likely to have an important impact on the confidence in the estimate of effect and may change the estimate</td></tr><tr><td>low</td><td>further research is very likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate</td></tr><tr><td>very low</td><td>any estimate of effect is very uncertain</td></tr></table>
5. Hinweise durch FB Med
Recherchestrategie ist unzureichend dargestellt.</td></tr>
<tr><td>Kaner et al. The effectiveness of brief alcohol interventions in primary care settings: a systematic review. Drug Alcohol Rev 2009; 28 (3): 301-23.</td><td>1. Fragestellung
Effectiveness of brief interventions in primary care</td></tr>
<tr><td></td><td>2. Methodik

Population: involving patients in primary care who were identified as heavy, problematic or excessive drinkers and who were not seeking alcohol treatment. Dependent users of alcohol were not the main focus of this review.
Intervention: brief interventions. Brief intervention could consist of up to five sessions of time-limited engagement with a patient in primary care which involved the provision of information, advice and/or counselling that was designed to achieve a reduction in alcohol consumption or alcohol-related problems.
Komparator: typically assessment only, treatment as usual and/or the delivery of written information.
Endpunkt: primary: quantity of alcohol consumed per week. Secondary: frequency and intensity of drinking, here ‘drinking days’, ‘drinking sessions’ and ‘occasions, gammaglutamyl transferase (GGT) and mean corpuscular volume (MCV).
Studiendesign: Systematic review and meta-analysis of RCTs.
Suchzeitraum (Aktualität der Recherche): up to 2006.
Anzahl eingeschlossene Studien/Patienten (Gesamt): 29 unique trials (reported in 39 papers). 24 trials were administered in general practice-based primary care, 5 trials were carried out in accident and emergency departments. 5800 patients.</td></tr>
<tr><td></td><td>3. Ergebnisdarstellung

Quantity of alcohol consumed per week (16 trials. Patients: 5856):</td></tr>
</table>

	significant difference in favour of brief interventions after follow up of 1 year (MD -38 g, 95%CI: -54 to -23 g week). I^2 = 58%. Intensity of drinking (heavy drinking days) (9 trials): all trials showed difference in favour of brief interventions, 6 of those were statistically significant (keine Meta-Analyse). Binge drinking (7 trials): 4 trials showed (risk difference = -11%, 95%CI: -19% to -3%) and 3 did not show significant difference in favour of brief interventions (keine Meta-Analyse). Number of drinking days per week (3 trials): no significant difference. (keine Meta-Analyse). Amount of alcohol consumed per drinking day (5 trials): no significant difference. (keine Meta-Analyse). Laboratory indicators (5 Studien): no significant difference. (keine Meta-Analyse).
	4. Anmerkungen/Fazit der Autoren Brief alcohol interventions are effective at reducing excessive drinking in primary care settings. 5. Hinweise durch FB Med Die Population der Studie ist nicht eindeutig auf die Zielpopulation von Nalmefen übertragbar, da es sich nicht ausschließlich um alkoholabhängige Patienten handelt. Der Anteil alkoholabhängiger Patienten in der Studienpopulation ist nicht angegeben.
Riper H et al. Curbing problem drinking with personalized-feedback interventions: a meta-analysis. Am J Prev Med **2009**; 36 (3): 247-55.	1. Fragestellung Effectiveness of brief, single-session **personalized-feedback** interventions without therapeutic guidance with maximum duration of 15 minutes per participant.
	2. Methodik Population: Problem drinkers. Intervention: brief, single-session personalized-feedback. Komparator: assessment only and no treatment, with wait-listing, and with a semi-placebo in the form of an alcohol-information brochure Endpunkt: frequency, quantity of alcohol consumption as defined in the trials. Studiendesign: Systematic review and meta-analysis of RCTs. Suchzeitraum (Aktualität der Recherche): Up to 2008. Anzahl eingeschlossene Studien/Patienten (Gesamt): 14 (n=3682)
	3. Ergebnisdarstellung

	Aggregate frequency and quantity of alcohol consumption (14 RCTs, 3682 Patienten): significant difference in favour of personalized-feedback d 0.22 (95% CI 0.16 to 0.29, I^2=0).
	4. Anmerkungen/Fazit der Autoren The use of single-session personalized-feedback interventions without therapeutic guidance appears to be a viable and probably cost-effective option for reducing problem drinking in student and general populations. 5. Hinweise durch FB Med Die Population der Studie ist nicht eindeutig auf die Zielpopulation von Nalmefen übertragbar, da es sich nicht ausschließlich um alkoholabhängige Patienten handelt. Der Anteil alkoholabhängiger Patienten in der Studienpopulation ist nicht angegeben. Eine Definition von problem drinkers liegt nicht vor.

Leitlinien

Lingford-Hughes et al. BAP updated guidelines: evidence-based guidelines for the pharmacological management of substance abuse, harmful use, addiction and comorbidity: recommendations from BAP. Journal of Psychopharmacology **2012**; 0 (0): 1-54	Leitlinie der British Association for Psychopharmacology Fragestellung zu Alkohol: Preventing lapse and relapse, promoting and maintaining abstinence
	Methodik Grundlage der Leitlinie: Systematischer Review nach RCTs und Meta-Analysen. Zusätzlich Konsensusprozess. Alle Aussagen sind mit Literaturstellen (Meta-Analysen oder RCTs) belegt. Methodik hinsichtlich der Berücksichtigung von RCTs nicht klar. Suchzeitraum: k.A. <u>LoE:</u> Categories of evidence for causal relationships and treatment Ia: evidence from meta-analysis of randomised controlled trials Ib: evidence from at least one randomised controlled trial IIa: evidence from at least one controlled study without randomisation IIb: evidence from at least one other type of quasi-experimental study III: evidence from non-experimental descriptive studies, such as comparative studies, correlation studies and case-control studies IV: evidence from expert committee reports or opinions and/or clinical experience of respected authorities Proposed categories of evidence for observational relationships I: evidence from large representative population samples II: evidence from small, well-designed, but not necessarily representative samples III: evidence from non-representative surveys, case reports IV: evidence from expert committee reports or opinions and/or clinical experience of respected authorities <u>GoR:</u> A: directly based on category I evidence B: directly based on category II evidence or extrapolated recommendation from category I evidence C: directly based on category III evidence or extrapolated recommendation from category I or II evidence D: directly based on category IV evidence or extrapolated recommendation from category I, II or III evidence

	S: Standard of care
	Empfehlungen Acamprosate can be used to improve abstinence rates (A). It should be continued if the person starts drinking, since there is evidence that acamprosate reduces alcohol consumption (A), at least for a period to assess whether there is overall patient benefit attributable to acamprosate. Naltrexone can be used to reduce risk of lapse becoming a relapse, but there is less evidence to support its use in maintaining abstinence (A). Naltrexone may therefore be a better choice if someone is 'sampling' alcohol regularly but wishes to be abstinent. For acamprosate and naltrexone there is no consistent evidence to suggest which types of patient will respond, and relapse prevention medication should be offered to/considered for everyone who is alcohol dependent wanting to be abstinent (A). Disulfiram is effective if intake is witnessed. Disulfiram can be offered as a treatment option for patients who intend to maintain abstinence, and for whom there are no contraindications (B). Baclofen should be considered if a patient wants to be abstinent , has high levels of anxiety and has not benefited from or is unable to take acamprosate, naltrexone or disulfiram (C). SSRIs should be avoided, or used with caution in type 2 alcoholism (B). <u>Reduktion versus Abstinenz</u> For those with cirrhosis and decompensated liver failure any drinking, even small amounts, is likely to be harmful (Tilg and Day, 2007). Complete abstinence gives them the best chance of recovery so they should be encouraged towards abstinence, though reduced drinking may be acceptable as an intermediate treatment goal in developing medicinal products for treatment of alcohol dependence (European Medicines Agency's guidelines, 2010). In addition, for those who have lost control of their drinking, reductions maybe hard to achieve and maintain, so a period of abstinence is also generally advocated. For those that are unwilling or unable to become abstinent, reduced drinking may be an appropriate intermediate goal on the way to abstinence, although ideally clinical benefit should also be evident. Due to naltrexone's proposed mechanism of action in reducing the pleasurable effects of alcohol, naltrexone has also been investigated in those who are still drinking. In addition, an alternative strategy to daily dosing is to use opioid antagonists in a targeted way, that is 'as needed', to reduce heavy drinking. In alcohol dependence, naltrexone taken only when craving is effective in maintaining reduced drinking (Heinälä et al., 2001) (Ib). In male, but not female, heavy drinkers 'targeted' naltrexone taken

	when drinking was imminent, rather than daily naltrexone or placebo, reduced 'drinks per day' by almost 20% (Kranzler et al., 2009) (Ib). With minimal psychosocial intervention, nalmefene (10 mg or 40 mg) taken prior to 'imminent drinking' has been shown to significantly reduce heavy drinking days, very heavy drinking days and total alcohol consumption (Karhuvaara et al., 2007) (Ib). <u>Naltrexon</u> There have been several meta-analyses and systematic reviews which broadly have the same conclusion that oral naltrexone significantly reduces return to heavy drinking, probably by reducing 'lapse to relapse', but does not necessarily improve cumulative or continuous abstinence rates. The meta-analysis by NICE (2011a) (Ia) revealed that compared with placebo, naltrexone significantly reduced relapse to heavy drinking (RR = 0.83, 95% CI = 0.75–0.91). A Cochrane review found naltrexone reduced the risk of heavy drinking to 83% of the risk in the placebo group RR = 0.83 (95% CI 0.76–0.90) and decreased drinking days by about 4%, MD -3.89 (95% CI -5.75 to -2.04 (Rösner et al., 2010b)) (Ia). The most common side-effects are nausea and sedation (Rösner et al., 2010b) (Ia). Naltrexone can be used safely while someone is still drinking, but in trials for relapse prevention it is started soon after stopping drinking. 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 studies of naltrexone suggest its beneficial effects did not persist for 14 or 16 weeks after stopping (Anton et al., 2001; O'Malley et al., 1996) (Ib). However, more recent evidence from the COMBINE study reported continued benefit persisting for up to a year (Donovan et al., 2008) (Ib). <u>Acamprosat</u> Reviews broadly come to the same conclusion that compared with placebo, acamprosate is moderately effective in increasing the amount of abstinence after detoxification; for example Rösner et al. (2010a) (Ia) report RR 0.86 (95% CI 0.81–0.91), and NICE CG115 (2011a) (Ia) report RR = 0.83 (95% CI = 0.77–0.88). The 'number needed to treat' (NNT) was calculated as 9–11 (e.g. Rösner et al., 2010a; Slattery et al., 2003) (Ia). Notably, later systematic reviews and meta-analyses report smaller effect sizes due to three reasonably sized recent negative studies conducted in the USA and Australia (COMBINE, Anton et al., 2006 (see below); Mason et al., 2006; Morley et al., 2006) (Ib). However, some of these studies included low-severity patients with few withdrawal symptoms, that is, patients who may be less likely to respond to acamprosate. While the most potent consistent effect of acamprosate is to improve abstinence, some but not all meta-analyses or reviews have found evidence

	that acamprosate can reduce ‘heavy drinking’ in patients who have relapsed (Chick et al., 2003; NICE 2011a) (Ia) as was also found for naltrexone by Rösner et al. (2010b) (Ia). 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).
National Institute for Health and Clinical Excellence (NICE). Alcohol-use disorders: Diagnosis, assessment and management of harmful drinking and alcohol dependence (CG115). Stand: Februar 2011. London: NICE, **2011**.	Leitlinie des National Institute for Health and Clinical Excellence zur Diagnose und Therapie des Alkoholmissbrauchs und der Alkoholabhängigkeit
	Methodik Grundlage der Leitlinie: Systematischer Review und Meta-Analyse von RCTs. Bei fehlender Evidenz aus Literatur Expertenmeinungen über Konsensusprozesse. LoE und GoR werden nicht angegeben, statt dessen Metanalysen. Keine Angaben zur Heterogenität. Suchzeitraum: 1993-2010
	Ergebnisse/Empfehlungen <u>Interventions for harmful drinking and mild alcohol dependence</u> Offer a psychological intervention (such as cognitive behavioural therapies, behavioural therapies or social network and environment-based therapies) focused specifically on alcohol-related cognitions, behaviour, problems and social networks. For harmful drinkers and people with mild alcohol dependence who have not responded to psychological interventions alone, or who have specifically requested a pharmacological intervention, consider offering acamprosate or oral naltrexone in combination with an individual psychological intervention (cognitive behavioural therapies, behavioural therapies or social network and environment-based therapies) or behavioural couples therapy. <u>Interventions for moderate and severe alcohol dependence after successful withdrawal</u> After a successful withdrawal for people with moderate and severe alcohol dependence, consider offering acamprosate or oral naltrexone71 in combination with an individual psychological intervention (cognitive behavioural therapies, behavioural therapies or

	social network and environment-based therapies) focused specifically on alcohol misuse. After a successful withdrawal for people with moderate and severe alcohol dependence, consider offering acamprosate or oral naltrexone in combination with behavioural couples therapy to service users who have a regular partner and whose partner is willing to participate in treatment. Empfehlungen für moderate bis schwere Alkoholabhängigkeit werden nur nach Durchführung einer Entzugstherapie gegeben. Empfehlungen zur Reduktion liegen für diese Patientengruppe nicht vor. **Ergebnisse aus den Meta-Analysen zu Naltrexon** Days of heavy drinking (trials: 7, participants: 797): statistically significant difference in favour of oral naltrexone compared to placebo (SMD = -0.43; 95% CI, -0.82 to -0.03). Adverse events: statistically significant difference in favour of placebo compared to oral naltrexone. Total drinks consumed (trials: 2, participants: 257): no statistically significant difference compared to placebo. Drinks per drinking day (trials: 10, participants: 1639): statistically significant difference in favour of oral naltrexone compared to placebo (SMD = -0.28; 95% CI, -0.44 to -0.11). **Ergebnisse der Meta-Analysen zu psychologischen/psychosozialen Interventionen** Motivational techniques (trials: 8, participants: 4209). Quantity of alcohol consumed: Other therapies (namely CBT and TSF) were more effective than motivational techniques in reducing the quantity of alcohol consumed when assessed post-treatment. Average drinks per day: statistically significant difference in favour of motivational techniques (SMD = -0.67; 95% CI, -1.20 to -0.15). No statistically significant difference in other reduction related outcomes. Clinical review protocol (12-step facilitation) (trials: 6, participants: 2556) Amount of alcohol consumed: significant difference in favour of TSF compared to other active interventions at 6-month follow-up (SMD = -0.09; 95% CI, -0.17 to -0.00). No significant difference between groups was observed for any other follow-up points.

	No statistically significant difference in other reduction related outcomes. <u>Cognitive behavioural therapy (12-step facilitation) (trials: 20, participants: 3970)</u> <u>Number of days with heavy alcohol use (more than 4 drinks):</u> significant difference in favour of cognitive behavioural therapy compared to treatment as usual (SMD = -0.70; 95% CI, -1.30 to -0.11). No statistically significant difference in other reduction related outcomes and no difference compared to other active interventions.

Detaillierte Darstellung der Recherchestrategie:

Cochrane Library am 25.01.2013

Suchschritt	Suchfrage
#1	MeSH descriptor: [Alcoholism] explode all trees
#2	MeSH descriptor: [Alcohol Drinking] explode all trees
#3	alcohol:ti,ab,kw (Word variations have been searched)
#4	consumption or abuse or dependence or drinking:ti,ab,kw (Word variations have been searched)
#5	(#3) AND #4
#6	#1 or #2 or #5
#7	reduction or reduce or lower or lowering or reducing or decrease:ti,ab,kw (Word variations have been searched)
#8	#6 and #7 from 2008 to 2013

MEDLINE (PubMed) am 25.11.2013

Suchschritt	Suchfrage
#1	Search ("alcoholism"[MeSH Terms]) OR "alcohol drinking"[MeSH Terms]
#2	Search (((((alcoholism[Title/Abstract]) OR alcohol abuse[Title/Abstract]) OR alcohol dependence[Title/Abstract]) OR "alcohol drinking"[Title/Abstract]) OR "alcohol use disorder"[Title/Abstract]) OR "alcohol use disorders"[Title/Abstract] OR "alcohol consumption"[Title/Abstract] OR "alcohol use"[Title/Abstract]
#3	Search (#1) OR #2
#4	Search reduction[Title/Abstract] OR reduce[Title/Abstract] OR reducing[Title/Abstract] OR lower[Title/Abstract] OR lowering[Title/Abstract] OR decrease[Title/Abstract] OR cut down[Title/Abstract]
#5	Search (#3) AND #4
#6	(#5) AND (Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp]
#7	Search (((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract]))))
#8	Search (#5) AND #7

Suchschritt	Suchfrage
#9	Search (#6) OR #8
#10	Search (#9) AND ("2008/01/01"[PDAT] : "2013/11/25"[PDAT])

MEDLINE (PubMed) nach Leitlinien am 25.11.2013

Suchschritt	Suchfrage
#1	Search ("alcoholism"[MeSH Terms]) OR "alcohol drinking"[MeSH Terms]
#2	Search (((((alcoholism[Title/Abstract]) OR alcohol abuse[Title/Abstract]) OR alcohol dependence[Title/Abstract]) OR "alcohol drinking"[Title/Abstract]) OR "alcohol use disorder"[Title/Abstract]) OR "alcohol use disorders"[Title/Abstract] OR "alcohol consumption"[Title/Abstract] OR "alcohol use"[Title/Abstract]
#3	Search (#1) OR #2
#4	Search reduction[Title/Abstract] OR reduce[Title/Abstract] OR reducing[Title/Abstract] OR lower[Title/Abstract] OR lowering[Title/Abstract] OR decrease[Title/Abstract] OR cut down[Title/Abstract]
#5	Search (#3) AND #4
#6	Search (((((Guideline[Publication Type]) OR Practice Guideline[Publication Type]) OR Consensus Development Conference[Publication Type]) OR Consensus Development Conference, NIH[Publication Type]) OR guideline*[Title])
#7	Search (#5) AND #6
#8	Search (#7) AND ("2013/01/01"[PDAT] : "2013/11/25"[PDAT])

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