Q3: Are pharmacotherapies safe and effective for the treatment of psychostimulant dependence (maintenance or relapse prevention) in non-specialized settings?

Background

Methadone, buprenorphine and naltrexone are known to be effective in the treatment of opioid dependence. Their efficacy was recently examined in the Guidelines for the Psychosocially Assisted Pharmacological Treatment of Opioid dependence (WHO, 2009) and they are not examined further here. Recent Cochrane reviews show no effect of antipsychotics, antiepileptic or antidepressants in the treatment of stimulant dependence, although there has been interest in the use of dexamphetamines, disulfiram and naltrexone. A recent review of disulfiram found no effect of disulfiram (de Lima, 2002). As there are no recent reviews of the other two medications, each of which are reviewed here. There are no medications considered feasible for the treatment of cannabis dependence reviewed here. The issue of benzodiazepine prescribing for benzodiazepine dependence has not been examined as the issue of gradual vs rapid withdrawal is covered in the section on withdrawal from benzodiazepines.

Population/Intervention(s)/ Comparison/Outcome(s) (PICO)

- **Population:** stimulant dependence (amphetamines, methamphetamines and cocaine)
- **Interventions:**
    - naltrexone
    - dexamphetamine
- **Comparison:** **p**lacebo or treatment as usual
- **Outcomes:**
    - stimulant use

- psychosocial outcomes
- adverse effects

List of the systematic reviews identified by the search process

INCLUDED IN GRADE TABLES OR FOOTNOTES

Naltrexone for stimulant dependence: New review by : Huynh N, & Clark N (2009, unpublished).

Dexamphetamine for stimulant dependence: New review by De Windt Mears J & Clark N (2009, unpublished).

Narrative description of the studies that went into the analysis

Dexamphetamine for stimulant dependence (cocaine and amphetamines and methamphetamines)

A pilot randomized controlled study (n=41) of dexamphetamine substitution in comparison to the standard of care for amphetamine dependence found that both interventions reduced street amphetamine use (Shearer et al, 2001). The standard of care treatment, or counseling, was offered to all participants. The only group difference observed was that the dexamphetamine group were significantly more likely to attend the counseling and receiving twice as many sessions as the control group who where set to receive counseling only. No serious adverse events were reported in the treatment group.

Another pilot randomized double blind placebo-controlled study (n=30) of dexamphetamine for cocaine dependence found that the proportion of cocaine-positive urine samples detected in the dexamphetamine group declined compared to no changes in the placebo control group, although the group differences was not significant (Shearer et al, 2003). Three adverse events were noted requiring hospitalization: psychotic symptoms and the two other were not related to study participation.

Grabowski et al, 2001 completed a double-blind randomized study (n=128) of dexamphetamine for cocaine dependence, which found that there were fewer cocaine-positive urine screens than the placebo group after 3 months. Six subjects stated medication side effects as reasons for dropping out.

Meta-analysis was not possible due to differences in treatment outcomes reported and lack of reporting of standard deviations of continuous measures.

Naltrexone for stimulant dependence

Hersh et al, 1998 conducted a randomized, double-blind, placebo-controlled study of Naltrexone (50mg/day) in 64 participants with comorbid cocaine and alcohol dependence during 8 weeks. They reported 17 participants achieved complete abstinence from cocaine for the entire 8-week treatment period, with no between-group difference (X2=2.7, 1df). Furthermore, 29 participants were abstinent for at least 2 continuous weeks following randomization, with no between-group difference (X2=0.8, 1df).

A double-blind, placebo-controlled study of Naltrexone (50mg) in 85 cocaine-dependent participants during 12 weeks, by Schmitz et al, 2001, found no significant effect of Naltrexone on time to first cocaine-positive urine. However, there is a significant three-way interaction (function of time, therapy and medication) indicates less cocaine use over time among subjects receiving Naltrexone. Overall, 14% of participants (n=12) abstrained from cocaine continuously over the 12 weeks.

Jayaram-Lindstrom et al, 2008 conducted a randomized, placebo-controlled study of Naltrexone (50mg/day) in 80 participants with amphetamine dependence during 12 weeks. The results showed that the Naltrexone group differed in continuous abstinence rates (Brestlow test, t=6.36, p<.05) in favor of Naltrexone treatment.

GRADE tables

Table 1

Author(s): Clark N
Date: 2009-09-16
Question: Should Naltrexone vs Placebo be used for stimulant dependence?
Settings:
Bibliography: Hersh D, van Kirk JR, Kranzler HR (1998). Naltrexone treatment of comorbid alcohol and cocaine use disorders. *Psychopharmacology (Berlin)*, 139: 44–52.

Jayaram-Lindström N et al (2008). Naltrexone for the treatment of amphetamine dependence: a randomized, placebo-controlled trial. *American Journal of Psychiatry,* 165:1442-8.

Schmitz JM et al (2001). Naltrexone and relapse prevention treatment for cocaine-dependent patients. *Addictive Behaviors,* 26:167–80.

Schmitz JM et al (2004). Treatment of cocaine-alcohol dependence with naltrexone and relapse prevention therapy. *American Journal of Addiction,* 13:333-41.

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other	Naltrexone	Placebo	Relative	Absolute		

[Treatment of psychostimulant dependence]

studies						considerations			(95% CI)			
Percentage of negative urine samples (ITT analysis) (follow-up mean 12 weeks; Better indicated by higher values)												
4[1,2]	randomized trials	very serious[3]	very serious[4]	no serious indirectness[5]	no serious imprecision[6]	none	176	175	-	MD 17.44 higher (12.89 to 21.98 higher)	VERY LOW	IMPORTANT
% days stimulants not used (self-reports) (follow-up 8-12 weeks; Better indicated by higher values)												
3[1,7]	randomized trials	very serious[8]	no serious inconsistency[4]	no serious indirectness[9]	serious[10]	none	123	127	-	MD 5.95 higher (0.64 lower to 12.55 higher)	VERY LOW	IMPORTANT
Abstinence (follow-up mean 12 weeks; either abstinence for the duration of the study or 3 weeks continuous abstinence during the study)												
3[7]	randomized trials	very serious[3]	no serious inconsistency[11]	no serious indirectness	no serious imprecision	none	30/123 (24.4%)	17/127 (13.4%)	RR 1.83 (1.06 to 3.15)	111 more per 1000 (from 8 more to 288 more)	LOW	IMPORTANT
Severe Adverse Effects (follow-up 8 weeks; Risk ratio)												
1[12]	randomized trials	serious[13]	no serious inconsistency[14]	no serious indirectness[15]	serious[16]	none	2/31 (6.5%)	11/33 (33.3%)	RR 0.19 (0.05 to 0.8)	270 fewer per 1000 (from 67 fewer to 317 fewer)	LOW	CRITICAL
Mild AE (# patients) (follow-up 8-12 weeks; Risk ratio)												
1[1,7,17]	randomized trials	very serious[8]	no serious inconsistency	no serious indirectness	serious[18]	none	14/40 (35%)	0/40 (0%)	RR 29 (1.79 to 470.15)	0 more per 1000 (from 0 more to 0 more)	VERY LOW	IMPORTANT
Mild AE (Mean # weekly events) (follow-up mean 12 weeks; Better indicated by lower values)												
2[1,19]	randomized trials	very serious[20]	no serious inconsistency[4]	no serious indirectness[21]	serious[22]	none	84	81	-	MD 0.3 higher (0.34 lower to 0.94 higher)	VERY LOW	IMPORTANT
Psychosocial function												
0	no evidence available					none	0/0 (0%)	0/0 (0%)	Not estimable	0 fewer per 1000 (from 0 fewer to 0 fewer)		CRITICAL

[1] Calculated using RevMan.

[2] Jayaram-Lindstrom et al, 2008; Schmitz et al, 2004; Pettinati 2008; Schmitz et al, 2001.

[3] Jayaram-Lindstrom et al, 2008 study had adequate randomization, drop outs with 14/40 (35%) in placebo group and 11/40 (28%) in naltrexone group, outcome assessment masked adequately. Schmitz et al, 2004 study did not describe the randomization method, overall 66% drop out rate.

[4] I squared = 89%.

[5] Schmitz et al, 2004 - cocaine/alcohol dependence. Jayaram-Lindstrom et al, 2008 - amphetamine dependence.

[6] n=351.

[7] Hersh et al, 1998; Jayaram-Lindstrom et al; 2008; Pettinati 2008.

[8] Jayaram-Lindstrom et al, 2008 study had adequate randomization, drop outs with 14/40 (35%) in placebo group and 11/40 (28%) in naltrexone group, outcome assessment masked adequately. Hersh et al, 1998 study did not describe randomization method, 29/64 (39%) drop outs.

[9] Jayaram-Lindstrom et al, 2008 - amphetamine dependence. Hersh et al, 1998- cocaine/alcohol dependence.

[10] Naltrexone n=123 and placebo n=127.

[11] I squared 28%.

[12] Hersh et al, 1998.

[13] Hersh et al, 1998 study 29/64 (39%) drop outs.

[14] Only 1 study.
[15] cocaine/alcohol dependence.
[16] n = 64 and upper confidence limit crosses a risk of 0.5.
[17] Jayaram-Lindstrom et al, 2008.
[18] n=120 and estimate with a confidence interval that crosses 1.
[19] Schmitz et al, 2001 and 2004.
[20] Schmitz et al, 2004 study did not describe the randomization method, overall 66% drop out rate. Schmitz et al, 2001 study did not describe the randomization method, 43/85(51%) drop outs.
[21] Schmitz et al, 2004 - cocaine/alcohol dependence. Schmitz et al, 2001 - cocaine dependence.
[22] n=165 and SMD with a confidence interval that crosses 0.

References

Grabowski J et al (2001). Dextroamphetamine for cocaine-dependence treatment: a double-blind randomized clinical trial. *Journal of Clinical Psychopharmacology,* 21:522-6.

Hersh D, van Kirk JR, Kranzler HR (1998). Naltrexone treatment of comorbid alcohol and cocaine use disorders. *Psychopharmacology (Berlin)*, 139: 44–52.

Jayaram-Lindström N et al (2008). Naltrexone for the treatment of amphetamine dependence: a randomized, placebo-controlled trial. *American Journal of Psychiatry,* 165:1442-8.

Pettinati HM et al (2008). A double blind, placebo-controlled trial that combines disulfiram and naltrexone for treating co-occurring cocaine and alcohol dependence. *Addictive Behaviours,* 33:651-67.

Schmitz JM et al (2001). Naltrexone and relapse prevention treatment for cocaine-dependent patients. *Addictive Behaviors,* 26:167–80.

Schmitz JM et al (2004). Treatment of cocaine-alcohol dependence with naltrexone and relapse prevention therapy. *American Journal of Addiction,* 13:333-41.

Shearer J et al (2001). Pilot randomized controlled study of dexamphetamine substitution for amphetamine dependence. *Addiction,* 96:1289–96.

Shearer J et al (2003). Pilot randomized double blind placebo-controlled study of dexamphetamine for cocaine dependence. *Addiction*, 98:1137–41.

WHO (2009). Guidelines for the psychosocially assisted pharmacological treatment of opioid dependence. Geneva, World Health Organization.

From evidence to recommendations

Factor	Explanation
Narrative summary of the evidence base	One out of the three studies (n=178) of dexamphetamine prescribing all found a reduction in stimulant drug use in the treatment arms, although meta-analysis was not possible due to incomplete data reporting. Dexamphetamine prescribing did not appear to be associated with significant side effects compared to placebo. The 5 studies (n=372) examining naltrexone for stimulant dependence showed weak evidence of an effect of naltrexone compared to placebo in reducing stimulant use and severe adverse events (psychosis). The effect was not consistent, being absent in two of the studies, but nonetheless statistically significant in meta-analysis. The results were the same for cocaine dependent and amphetamine dependent patients, and were combined in the meta-analysis. In three of the studies participants were also alcohol dependent.
Summary of the quality of evidence	Low to very low. A small number of small studies with some methodological flaws.
Balance of benefits versus harms	In the absence of other medication for amphetamine and cocaine dependence, naltrexone could have significant benefits. The risk of harm from naltrexone in non opioid dependent patients is low. An evidence for dexamphetamine benefit was not found, although the reports of adverse effects in the studies are not higher than placebo, dexamphetamine as a medication is abusable and known to induce adverse effects.
Define the values and preferences including any variability and human rights issues	Dexamphetamine prescription may be viewed as continuing the dependence on stimulants, regardless of the health impact.

Define the costs and resource use and any other relevant feasibility issues	Neither medication are particularly expensive, but availability is limited in some countries. Naltrexone is not a difficult medication to use in primary care settings. Dexamphetamines can be abused and so prescription of dexamphetamine raises a number of
Recommendation(s) Dexamphetamine should not be offered for the treatment of stimulant use disorders in non-specialized settings. **Strength of recommendation:** STRONG	

Update of the literature search – June 2012

In June 2012 the literature search for this scoping question was updated. The following systematic reviews were found to be relevant without changing the recommendation:

Brackins T, Brahm NC, Kissack JC. Treatments for Methamphetamine Abuse : A Literature Review for the Clinician. Journal of Pharmacy Practice 2011 24: 541 originally published online 17 November 201.1DOI: 10.1177/0897190011426557

Castells X, Casas M, Vidal X, Bosch R, Roncero C, Ramos-Quiroga JA, Capella D. Efficacy of central nervous system stimulant treatment for cocaine dependence: a systematic review and meta-analysis of randomized controlled clinical trials. Addiction 2007, 102, 1871–1887. doi:10.1111/j.1360-0443.2007.01943.x

Krupitsky EM, Blokhina EA. Long-acting depot formulations of naltrexone for heroin dependence: a review. Current Opinion in Psychiatry 2010, 23:210–214

Lobmaier PP, Kunoe N, Gossop M, Waal H. Naltrexone Depot Formulations for Opioid and Alcohol Dependence: A Systematic Review. CNS Neuroscience & Therapeutics (2011) , 17, 629–636. doi: 10.1111/j.1755-5949.2010.00194.x

Mannelli P, Peindl KS, Wu LT. Pharmacological enhancement of naltrexone treatment for opioid dependence: a review. Subst Abuse Rehabil. 2011 June ; 2011(2): 113–123. doi:10.2147/SAR.S15853

Minozzi S, Amato L, Vecchi S, Davoli M, Kirchmayer U, Verster A. Oral naltrexone maintenance treatment for opioid dependence. Cochrane Database of Systematic Reviews 2011, Issue 4. Art.No.: CD001333. DOI: 10.1002/14651858.CD001333.pub4. (**New search for studies and content updated (no change to conclusions), published in Issue 4, 2011**.)

Westover AN, Halm EA. Do prescription stimulants increase the risk of adverse cardiovascular events?: A systematic review. BMC Cardiovascular Disorders 2012, 12:41 doi:10.1186/1471-2261-12-41