Results with Naltrexone and Nalmefene:
Clinical Trials and Reviews
Jan. 14, 2010

PLEASE PAY CLOSE ATTENTION TO THE CODING

Notes underlined represent evidence that naltrexone and nalmefene are safe and produce significant benefits when extinction is possible (n=82; 63 with alcoholism). The notes are in chronological order with the most recent trials at the end of the list.

Notes in italics indicate evidence that naltrexone and nalmefene are not effective when extinction is not possible (e.g., during abstinence) (n=39; 37 with alcohol).

Notes in bold are from reviews or meta-analyses, all of which conclude naltrexone is effective (n=18).

Notes with results contrary to extinction or unclear are in the regular Arial font (n=6). (1 found benefits in delaying first sampling, 1 with coping failed to get significant benefits, 1 found no benefits in treating gambling, and 3 were unclear about the protocol.) (Long-lasting implant/injection studies are evaluated only as to whether the treatment was effective because the antagonist was always present.)

When the same trial has been published in several abstracts and articles, they are all listed under the same number, separated by the ¶ symbol.

Studies using antagonists but on other issues (e.g., use against smoking) are in Gill condensed font.


Six of O'Malley alcoholism. Concluding naltrexone is safe and effective especially in alcoholics with a family history of alcoholism. 


Naltrexone was safe and effective in “Coping” groups inadvertently encouraged to break abstinence, but there were no significant benefits in “Supportive” groups with instructions to abstain. No significant benefits before first drink on naltrexone. Significant interactions indicating naltrexone is better with Coping than Supportive therapy.

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10. Mason, B. (1996) Dosing issues in the pharmacotherapy of alcoholism. Alcoholism: Clin Exp Res 20: 10A-16A. Small study showing doses of 20 mg and 80 mg of nalmefene are well tolerated, concluding that 80 mg was the optimal dose 100% completing trial and 62 % having a stable response (no more than 2 heavy drinking days (>4 drinks for men, >3 drinks for women).


217-224. Significant benefits from naltrexone continue for months after the end of treatment in Coping with Drinking group, but no significant benefits with abstinence.


15. O'Malley, S.S., Jaffe, A.J., Rode, S., and Rounsaville, B.J. (1996) Experience of a “slip” among alcoholics treated with naltrexone or placebo. American Journal of Psychiatry, 153(2): 281-283. Naltrexone patients drink the same as placebo patients on first day of a slip (before extinction), but the naltrexone patients subsequently are less likely to relapse into heavy drinking and have lower craving.


18. Volpicelli, J. R., Rhines, K. C., Rhines, J. S., Volpicelli, L. A., Alterman, A. I., and O’Brien, C. P. (1997) Naltrexone and alcohol dependence: Role of subject compliance. Archives of General Psychiatry 54: 737-742. Naltrexone was safe and effective, but poor compliance limited results. No significant benefits before first drink in total population, but when only compliant patients examined, there was a significant benefit before the reported first drink.


M., and Borg, S. (1999) Interaction effect between naltrexone and coping skills. Treatment and follow-up data. Abstract to “Evidence Based Medicine of Naltrexone in Alcoholism”, satellite symposium to the 7th Congress of the European Society for Biomedical Research on Alcoholism. Barcelona, Spain, June 16-19, 1999. **Swedish dual DBPC clinical trial showing naltrexone was safe and effective with “Coping” instructions but not effective with abstinence.**


27. Sinclair, J. D., Kymäläinen, O., and Jakobson, B. (1998) Extinction of the association between stimuli and drinking in the clinical treatment of alcoholism with naltrexone. *Alcoholism: Clinical and Experimental Research* 22: suppl.: 144A. **Naltrexone treatment significantly reduced the ability of all sorts of stimuli (positive affect, negative affect, and neutral) to trigger drinking, in accord with a prediction of the extinction hypothesis.**


controlled trial. Abstract to 10th Congress of the International Society for Biomedical Research on Alcoholism (ISBRA 2000), Yokohama, Japan, July 2 – July 8, 2000 ¶ Heinälä, P., Alho, H., Kivialmaa, K., Lönnqvist, J., Kuoppasalmi, K., and Sinclair, J.D. (2001). Targeted use of naltrexone without prior detoxification in the treatment of alcohol dependence: A factorial double-blind placebo-controlled trial. Journal of Clinical Psychopharmacology, 21(3): 287-292. Finnish dual DBPC clinical trial. The Sinclair Method was tested (with no prior detoxification, instructions aimed at controlled drinking, naltrexone given only when drinking, and naltrexone continued for 8 months) and shown to be particularly safe and to produce significant benefits over placebo. Naltrexone was also tested with abstinence and found to be slightly worse than placebo and to produce significantly more side effects than when used with controlled drinking.


37. Batel, P., Lancrenon, S., and Baconnet, B. (1999) Compliance, tolerance and outcome of 3 months naltrexone treatment among 215 alcohol dependents. Alcohol Alcoholism 34; 452 (abstract 125). Open label showing good compliance in 76% of patients and relapse to heavy drinking most likely in poor compliers.


47. Pettinati, H.M., Volpicelli, J.R., Pierce, Jr., J.D., and O’Brien, C.P. (2000) Improving naltrexone response: An intervention for medical practitioners to enhance medication compliance in alcohol dependent patients *Journal of Addictive Diseases*, 19: 71-83. DBPC 12 trial with naltrexone plus BRENDA or cognitive behavioural therapy. **Naltrexone significantly better that placebo: lack of relapse to heavy drinking = 90% in NTX group vs 61.4% (or 11.4% reported on-line) with placebo. p<0.001. BRENDA produced significantly better compliance and staying in treatment but BRENDA plus NTX not yet analyzed.**


49. Ceccanti, M., Nocente, R., Calducci, G., Deiana,L., Attilia, M.L., Sasso, G.F., Sebastiani, G., Ulanio, F., and Goriale, G. (2001) Naltrexone ed alcol:esperienze cliniche in Italia. *Medicina delle Tossicodipendenze–Italian Journal of the Addictions*. 30: 47–50. Single blind, randomized trial on over 60 outpatients, showed that NTX was not more effective than placebo in treating alcoholics. This probably was done with instructions to abstain, but the article does not say what instructions were give, so this is classified as unclear.


55. Sinclair, J. D. (2001) Evidence about the use of naltrexone and for different ways of using it in the treatment of alcoholism. *Alcohol and Alcoholism* 36: 2-10. **Review concluding that naltrexone is safe and effective but only when paired with drinking; data presented of the extinction of craving from naltrexone treatment in Finland.**


59. Schmitz, J. M., Stotts, A. L., Rhoades, H. M., and Grabowski, J. (2001) Naltrexone and relapse prevention treatment for cocaine-dependent patients. Addictive Behavior 26(2):167-180. **Dual DBPC at University of Texas showed naltrexone was safe and effective in treating cocaine addiction when used with a coping protocol, but naltrexone tended to be worse than placebo when used with abstinence.**

60. Kim, S. W., and Grant, J. E. (2001) An open naltrexone treatment study in pathological gambling disorder. Int Clin Psychopharmacol 16:285-289. **Open label, showing naltrexone was safe and effective in treating gambling.**


63. Anton, R. (2002) Multisite study of nalmefene combined with modified motivational enhancement therapy in the treatment of outpatient alcoholics Presented at the 25th Annual Scientific Meeting of the Research Society on Alcoholism, June 28-July 3, 2002, San Francisco, CA, USA. **Nalmefene was safe, but with “Motivational Enhancement Therapy (MET) it was not significantly effective, probably because this therapy is generally enhancement of motivation for abstinence (see #70 below).**


67. Berglund, M. (2002) Medications for alcohol dependence. Treatment of Alcohol Abuse: An Evidence-based Review, from The Swedish Council on Technology in Health Care (SBU) *Proceedings of the 25th Annual Scientific Meeting of the Research Society on Alcoholism*, June 28-July 3, 2002, San Francisco, CA, USA, p. 43. Berglund, M., Thelander, S., Salaspuro, M., Franck, J., Andréasson, S., and Öjehagen, A. (2003) Treatment of alcohol abuse: An evidence-based review. *Alcoholism: Clinical and Experimental Research* 27(10): 1645-1656. A search of all published and unpublished evidence showed naltrexone and acamprosate are only the medications for alcoholism with well-documented benefits. Naltrexone has been effective except when used with support of abstinence. In the 2003 report, a statistical analysis showed significantly better results with Coping/Cognitive Behavioral Therapy (CBT) than with Supportive therapy (p<0.05) (even though the O'Malley et al., 1992, results were incorrectly reported as significant with Supportive) and the meta-analysis showed a significant benefit over placebo with CBT.


73. BioTie Therapies Corp., press release, April 24 (2003) Phase III clinical studies in alcoholism and alcohol abuse. http://www.biotie.com/en/research/dependence-disorders/nalmefene.html Large DBPC clinical trial found nalmefene without psychosocial therapy reduced heavy drinking days by half, highly significant difference from placebo. 570 patients in Finland and UK. Highly significantly greater reduction in heavy drinking days than with placebo. Also significantly more nalmefene than placebo patients rated much improved or very much improved in both Finland and UK separately and together.

74. BioTie Therapies Corp, press release, May 30 (2003) Results from a Phase II clinical study suggest nalmefene effective in the treatment of pathological gambling. DBPC clinical trial with 200 subjects found nalmefene significantly better than placebo in reducing craving and thoughts about gambling: the level with nalmefene was about half that in the placebo group. *Jon E. Grant, Marc N. Potenza, Eric Hollander, Renee Cunningham-Williams, Tommi Nurminen, Gerard Smits, and Antero Kallio (2006) Multicenter Investigation of the Opioid Antagonist Nalmefene in the Treatment of Pathological Gambling. American Journal of Psychiatry* 163: 303-312. DBPC trial with 207 subjects found 20 mg nalmefene tolerated well and effective in reducing compulsive feelings about gambling and in improving patient condition; 50 and 100 mg caused too many side effects.

effective with Coping with drinking but not with Motivation Enhancement Therapy (MET). Anton in 2002 (#61) had gotten similar negative results with MET and nalmefene, confirming that MET is like Support of Abstinence and not a suitable protocol for opioid antagonists.

76. O’Malley, S.S. (2003) Can alternative behavioral strategies and settings enhance the outcome of naltrexone and for whom? 26th Annual Scientific Meeting of the Research Society on Alcoholism, June 21-25, 2003, Fort Lauderdale, Florida. Alcoholism: Clinical and Experimental Research 27 (supplement): 191A (abstract S172). In one experiment, drinking alcohol while on naltrexone suppressed selection of further alcoholic beverages especially when the second presentation was not immediate but several hours later, showing that the effect was not from rational thinking after experiencing a lack of euphoria but rather caused by a slow mechanism (extinction or similar to extinction) started by the lack of reinforcement. In addition, naltrexone was effective in blocking heavy drinking in smokers taking the medicine for smoking and not intending nor instructed to reduce drinking. Author’s conclusion: naltrexone should be used initially without abstinence to reduce drinking and only after that should abstinence become the goal.


79. Oslin DW, W Berrettini, HR Kranzler, H Pettinati, J Gelernter, JR Volpicelli, CP O’Brien (2003) A functional polymorphism of the µ-opioid response in alcohol-dependent patients. Neuropsychopharmacology 28: 1546-1552. Combination of three previous trials, one published positive (Monterosso et al. 2001), one published negative (Kranzler et al., 2000) and one unpublished found significant benefit of NTX on relapse rate and time to first relapse, with significantly better results in patient with the A/G or G/G allele than the A/A allele at the gene for mu receptors, but no medication by genotype interaction. No significant effect of NTX on abstinence.

80. Alkermes, Inc., press release. (December 8, 2003) Alkermes Announces Statistically Significant Reduction in Heavy Drinking in Alcohol Dependent Patients in Phase III Clinical Trial of Vivitrex® DBPC study of 624 alcoholics. Significant 48% reduction in drinking in slow release naltrexone-treated males, but not significant in females. ¶ James C. Garbutt, MD; Henry R. Kranzler, MD; Stephanie S. O’Malley, PhD; David R. Gastfriend, MD; Helen M. Pettinati, PhD; Bernard L. Silverman, MD; John W. Loewy, PhD; Elliot W. Ehrich, MD; for the Vivitrex Study Group (2005) Efficacy and Tolerability of Long-Acting Injectable Naltrexone for Alcohol Dependence: A Randomized Controlled Trial. JAMA 293:1617-1625. Compared with placebo, 380 mg of long-acting naltrexone resulted in a 25% decrease in the event rate of heavy drinking days (P = .03)(n=205). Lower dose (190 mg) just failed to reach significance. Better results in men and with pre-treatment abstinence.

acamprosate and naltrexone are effective as adjuvant therapies for alcohol dependence in
adults. Acamprosate appears to be especially useful in a therapeutic approach targeted at
achieving abstinence, whereas naltrexone seems more indicated in programmes geared to
controlled consumption.”

label pilot study. Journal of Child and Adolescent Psychopharmacology, 15: 723-728. Small open-label study of
outpatient 13-17 year old adolescent alcoholics without detox, found naltrexone is safe and produced a
significant reduction in alcohol drinking in the 6 weeks.

of response to naltrexone in alcoholic patients: Who benefits most from treatment with naltrexone? Alcohol and
Alcoholism. 40: 227-233. 3 month open trial in 336 men, looking at results in last 28 days, “Predictors of a
positive response to NTX treatment were family history of alcoholism (P = 0.010), early age at onset of
drinking problems (P = 0.014) and comorbid use of other drugs of abuse (P < 0.001),” generally things
that usually correlate with poor results in treatment.

Spanagel and K Mann (eds): Drugs for Relapse Prevention of Alcoholism, in the series Milestones in Drug
Therapy. Basal, Switzerland; Birkhäuser, pages 125-134. Review concluding “Nalmefene appears to be an
appropriate medicine for preventing alcohol abuse but not for maintaining abstinence.”

randomized controlled trials. Int J Neuropsychopharmacol 8:267–280. Review concluding that naltrexone is
effective for preventing drinking alcoholics relapsing to heavy drinking but not for stopping the
first sampling in alcoholics who are abstaining.

secondary analysis of effects on average daily drinking. Alcoholism: Clinical and Experimental Research.
May;30(5):860-865. DBPC trial, n=150, of naltrexone with coping with drinking found naltrexone was
effective especially with targeted use. Only targeted, not daily NTX helped women.

88. Anton RF, O’Malley, SS Ciraulo DC, Cisler RA. Couper D, Donovan DM, Gastfriend DR, Hosking JD, Johnson
and behavioral interventions for alcohol dependence: The COMBINE Study: A Randomized Controlled Trial
JAMA. 2006;295:2003-2017. Largest DBPC trial in addiction (n=1383 recently detoxified alcoholic) showed
NTX with minimal medical intervention was best at increasing days of abstinence and reducing heavy
drinking days. Intensive (20 hours) therapy without medication helped increase abstinence but did not
reduce heavy drinking and did not make NTX better (the partially abstinence oriented therapy actually
tended to reduce the benefit). Acamprosate had no significant benefits and taken at the same time as
NTX did not help NTX.

Stapleford International Addiction Conference on: Latest developments in effective medical treatments for
addiction, Berlin, March 18-19. Small open-label trial found NTX safe and effective in 73% of amphetamine
addicts, reducing their injection days from 58.6 in the 3 mo before to 17.1 in the 3 mo on NTX
(p<0.0004)

psychophysiological evaluation. 3rd Stapleford International Addiction Conference on: Latest developments in
effective medical treatments for addiction, Berlin, March 18-19. Naltrexone implants in detoxified opiate
addicts produced significantly fewer relapses than levomethadone implants, better psychological results,
and subsequently less emotional-motivational involvement when seeing stimuli related to opiate use.

Latest developments in effective medical treatments for addiction, Berlin, March 18-19, Naltrexone implants
worked well in patients who had been abusing opiates or partial opiate agonists (pentazocine, buprenorphine).


94. Somaxon (press release). Somaxon Pharmaceuticals Reports Positive Results From a Pilot Phase 2 Study of Oral Nalmefene in Smoking Cessation SAN DIEGO, CA – July 26, 2006. DBPC study of 76 smokers found no significant benefits from nalmefene but report notes that one of the two nalmefene groups (40 mg) was numerically superior to placebo group (80 mg was not). (Note: Result is what would be expected by chance.)


96. Comer SD, Sullivan MA, Yu E, Rothenberg JL, Kleber HD, Kampman K, Dachis C, and O’Brian CP (2006) Injectable, sustained-release naltrexone for the treatment of opioid dependence: a randomized, placebo-controlled trial. Archives of General Psychiatry 63: 210-218. DBPC with 2 doses of sustained-release naltrexone is 60 patients for 8 weeks. In a dose-dependent manner, naltrexone significantly improved retention in the study, and when missing urine samples were considered positive, was safe and effective in reducing use of opioids, methadone, cocaine, benzodiazepines, and amphetamine.

97. O’Malley SS, Sinha R, Grilo CM, Capone C, Farren CK, McKee SA, Rounsaville BJ & Wu R (2007) Naltrexone and cognitive behavioural coping skills therapy for the treatment of alcohol drinking and eating disorders features in alcohol-dependent women: A randomized controlled trial. Alcoholism, Clinical and Experimental Research 31: 625-634. DBPC on 103 women alcoholics, 29 comorbid with eating disorders. "Naltrexone may be of benefit to women who are unable to maintain total abstinence from alcohol." Among those drinking, naltrexone significantly delayed the time to the second relapse and the time to the third relapse but had no effect on the abstinence rate. There was a tendency (p=0.06 for more loss of weight (body mass index) with naltrexone than with placebo. Both groups had improvement in eating disorders, but there were no significant differences between groups.


99. Gelernter J, Gueorguieva R, Kranzler HR, Zhan H, Cramer J, Rosenheck R, & Krystal JH (2007) Opioid receptor gene (OPRM1, OPRK1, and OPRD1) variants and response to naltrexone treatment for alcohol dependence: Results from the VA Cooperative Study. Alcoholism, Clinical and Experimental Research 31: 555-563. DBPC study of 215 subjects who gave DNA samples from the previously reported trial (#54). "Although NTX had no significant effect on relapse to heavy drinking in the overall sample in CSP 425, it significantly reduced relapse in the subgroup that provided DNA for analysis." There were no published interactions with receptor type but a significant effect with the OPRD1 T921, helping the GG and AG genotypes but not with the AA homozygotic genotype.


104. Pallesen S, Molde H, Arrestad HM, Laberg JC, Skutle A, Iversen E, Stavlen IJ, Kvale G, Holsten F (2007) Outcome of pharmacological treatments of pathological gambling: A review and meta-analysis. J Clin Psychopharmacol 27: 357-364. Pharmacological intervention (including studies with opiate antagonists, antidepressants, and mood stabilizers) produced a significant effect size (0.78; 95% confidence interval 0.62-0.92) relative to no treatment/placebo. "Pharmacological intervention may be an adequate treatment alternative in pathological gambling."


106. Grant JE, Kim SW, Hartman BK (2008) A double-blind, placebo-controlled study of the opiate antagonist naltrexone in the treatment of pathological gambling urges. Journal of Clinical Psychiatry, online preprint April 1, 2008 e1-e7 at PSYCHIATRIST.COM. An 18 week DBPC with 3 doses of naltrexone (50, 100 and 150 mg/day) on 77 pathological gamblers. Results from the doses did not differ but naltrexone produced significantly lower PG-YBOCS than 19 placebo patients (p=0.0097), urges to gamble (0.0057) and behavior (0.0134), plus better Clinical Global–Improvement scale values (CGI-I, p=0.0080). Among 49 completers, naltrexone did better than placebo on all measures.

Alcoholism: Clinical Experimental Research doi:10.1111/j.1530-0277.2008.00682. DBPC trial on 101 Alaskans including 68 natives showed naltrexone produced significant benefits over placebo including total abstinence, but sertraline plus naltrexone was no better than just naltrexone.


109. Anton RF, Oroszi G, O'Malley S, Couper D, Swift R, Pettinati H, Goldman D (2008) An evaluation of mu-opioid receptor (OPRM1) as a predictor of naltrexone response in the treatment of alcohol dependence: results from the Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence (COMBINE) study. Arch Gen Psychiatry. 65(2):135-144. The Asp40 allele is a selective marker for naltrexone efficacy, improving the success rate of naltrexone without intensive counselling to an 87.1%. Naltrexone was not effective in people with the Asn40/Asn40 genotype. The Asp40 allele did not make a difference in subjects treated with naltrexone plus intensive counselling, perhaps explaining why some other trials that included counselling did not find markers.


117. Sinclair, D. (2009) Selecting patients and replacing detoxification: How opioid antagonists work in treatment. Proceedings of the Annual meeting of the International Society on Addiction Medicine (ISAM) Calgary, Alberta, Canada, Sept. 23-29, 2009 Review showing that opioid antagonists have had no significant effect before the first alcohol is drunk while on the medication, in agreement with extinction theory but contrary to common practice by many clinicians.

118. Eskapa, R. (2009) Introducing naltrexone in developing countries and among endogenous people. Proceedings of the Annual meeting of the International Society on Addiction Medicine (ISAM) Calgary, Alberta, Canada, Sept. 23-29, 2009 Naltrexone has been safe and effective, with a 75% success rate, when introduced in northern India with an extinction protocol including no prior detox and instruction to take naltrexone always before drinking but only when drinking is expected.
