APPENDIX A

Annotated Bibliography: Results with Naltrexone and Nalmefene— Clinical Trials and Reviews, February 28, 2008

NOTES THAT ARE underlined represent evidence that naltrexone and nalmefene are safe and produce significant benefits when extinction is possible (n=72; 58 with alcoholism). The notes are listed 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* (for example, during abstinence) (n=37; 35 with alcohol).

Notes in **bold** are from reviews or meta-analyses, all of which conclude naltrexone is effective (n= 17).

There are five studies that are contrary to extinction or that were unclear as to methodology. (One found naltrexone delaying the first sampling of alcohol, one with coping failed to get significant benefits, one found no benefits in treating gambling, and two were unclear about the protocol used.) (Long-lasting implant/injection

studies are evaluated only in terms of 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, but separated by the ¶ symbol.

Studies using antagonists for other issues (for example, used to discourage smoking) are included in the lists but not in the counts above.

1. Renault, P. F. (1978) Treatment of heroin-dependent persons with antagonists: Current status. *Bulletin on Narcotics* 30: 21–29. ¶ Renault, P. F. (1980) Treatment of heroin-dependent persons with antagonists: Current status. In: Willett, R. E., and Barnett, G., (eds.) *Naltrexone: Research Monograph 28,* Washington, DC: National Institute of Drug Abuse, 11–22. First clinical trial of naltrexone and only controlled trial for opiate addiction. Large double-blind placebo-controlled (DBPC) trial (n=197) plus 1005 open-label patients. Naltrexone was effective but only in patients who disobeyed instructions not to use opiates while on medication. *Not effective with abstinence.* It was concluded that naltrexone works by extinction. Basis for FDA acceptance of naltrexone for opiate addiction.

2. Volpicelli, J. R., O'Brien, C. P., Alterman, A. I., and Hayashida, M. (1990) Naltrexone and the treatment of alcohol dependence: Initial observations. In: Reid, L. D., (ed.) *opioids, bulimia, and alcohol abuse & alcoholism.* New York: Springer, 1990; 195–214. ¶ Volpicelli, J. R., Alterman, A. I., Hayashida, M., and O'Brien, C. P. (1992). Naltrexone in the treatment of alcohol dependence. *Archives of General Psychiatry* 49: 876–880. First DBPC clinical trial for alcoholism. Naltrexone was safe and effective, with the primary effects being found in patients drinking while on medication, as required by extinction. *No significant benefits before first drink on naltrexone.*

3. O'Malley, S. S., Jaffe, A., Chang, G., Witte, G., Schottenfeld, R. S., and Rounsaville, B. J. Naltrexone in the treatment of alcohol dependence. (1990) In: Reid, L.D., (ed.) *opioids, bulimia, and alcohol abuse & alcoholism.* New York: Springer; 149–157. ¶ O'Malley, S. S., Jaffe, A. J., Chang, G., Schottenfeld, R. S., Meyer, R. E., and Rounsaville, B. (1992). Naltrexone and

coping skills therapy for alcohol dependence. *Archives of General Psychiatry*
49: 881–887. The other DBPC trial in addition to Volpicelli used for FDA approval of naltrexone for 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.

4. Mason, B. J., Ritvo, E. C., Salvato, F., Zimmer, E. Goldberg, G., and Welch, B. (1993). Nalmefene modification of alcohol dependence: A pilot study. *Proceedings of American Psychiatric Association Annual Meeting,* San Francisco, CA, May 1993, p. 170, abstract NR442. ¶ Mason, B. J., Ritvo, E. C., Salvato, F. R., Goldberg, G. (1994) Preliminary dose finding for nalmefene treatment of alcoholism. *Alcohol Clin Exp Res* 18: p. 464 (abstract 270). ¶ Mason, B. J., Ritvo, E. C., Morgan, R. O., Salvato, F. R., Goldberg, G., Welch, B., and Mantero-Atienza, E. (1994) A double-blind, placebo-controlled pilot study to evaluate the efficacy and safety of oral Nalmefene HCL for alcohol dependence. *Alcoholism: Clinical and Experimental Research* 18: 1162–1167. Small DBPC trial showing nalmefene (similar to naltrexone) is safe and effective in treating alcoholism. *No significant benefits before first drink on Nalmefene; the article says this finding confirms Sinclair's hypothesis that the medication is working through extinction.*

5. Bohn, M. J., kranzler, H. R., Beazoglou, D., and Staehler, B. A. (1994) Naltrexone and brief counseling to reduce heavy drinking. *The American Journal on Addictions* 3: 9 1–99. Naltrexone was safe and effective in open-label study for reducing drinking and craving when used without detoxification and with instructions not to abstain but to try to cut down drinking. Protocol similar to that used by Sinclair in preclinical studies and in the Sinclair Method.

6. Agosti, V. (1994) The efficacy of controlled trials of alcohol misuse treatments in maintaining abstinence. *International Journal of Addictions* 29: 759–769. ¶ Agosti, V. (1995) The efficacy of treatment in reducing alcohol consumption: A meta-analysis. *International Journal of Addictions* 30: 1067– 1077, 1995. **Meta-analyses of all alcoholism treatment methods for which control data were provided. Concluded that the best method was naltrexone combined with a Coping with drinking protocol.**

7. Sinclair, J.D. (1995) The story in Finland behind the new Naltrexone treatment for alcoholism (and how I got the patent for it). *Life and Education In Finland* 3/95: 2–16. **Popular review concluding naltrexone is safe and effective.**

8. Agosti V. (1995) The efficacy of treatment in reducing alcohol consumption: A meta-analysis. *International Journal of Addictions* 30: 1067– 1077. **Naltrexone with Coping with drinking is effective and safe.**

9. World Health Organization (1996) Programme on Substance Abuse, Pharmacological Treatment of substance use disorders: International issues in medications development. WHO/PSA/96. 10 **General review concluding: "One medication, naltrexone, has been identified as a safe and effective treatment for alcohol dependence." (p. 24).**

10. Mason, B. (1996) Dosing issues in the pharmacotherapy of alcoholism. *Alcoholism: Clinical and Experimental Ressearch* 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 with 100% completing trial and 62 % having a stable response (no more than 2 heavy drinking days: >4 drinks for men, >3 drinks for women).

11. Monti, P. M., Rohsenow, D. J., Swift, R. M., Abrams, D. B., Colby, S. M., Mueller, T. I., Brown, R. A., and Gordon, A. (1996) Effects of naltrexone on urge to drink during alcohol cue exposure: preliminary results. *Alcoholism: Clinical and Experimental Research* 20 Supplement: 92A. After seeing their own usual alcoholic beverage, naltrexone patients had significantly smaller urge to drink than did placebo patients.

12. Anton, R. F., Romach, M. k., kranzler, H. R., Pettinati, H., O'Malley, S., and Mann, k. (1996). Pharmacotherapy of alcoholism—10 years of progress. *Alcoholism: Clinical and Experimental Research* 20: 172A–175A. **Review concluding naltrexone is safe and effective especially in alcoholics with a family history of alcoholism.**

13. O'Malley, S. S., Jaffe, A. J., Chang, G., Rode, S., Schottenfeld, R. S., Meyer, R. E., and Rounsaville, B. (1996). Six-month follow-up of naltrexone and psychotherapy for alcohol dependence. *Archives of General Psychiatry* 53: 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.*

14. Litten, R. Z., Croop, R. S., Chick, J., McCaul, M. E., Mason, B., and Sass, H. (1996) International update: New findings on promising medications. *Alcoholism: Clinical and Experimental Research* 20: 216A–218A. Preliminary reports from the British naltrexone trial, the Baltimore naltrexone trial, and the Miami Nalmefene trial, all with significant benefits, as well as the large scale DuPont open-label study showing safety for naltrexone.

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): 28 1–283. *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.

16. Croop, R. S., Faukner, E. B., Labriola, D. F. (1997) The Naltrexone Usage Study Group. The safety profile of naltrexone in the treatment of alcoholism: Results from a multicenter usage study. *Archives General Psychiatry* 54:1130–1135. The large DuPont safety study showing naltrexone was safe and effective.

17. Maxwell, S., and Shinderman, M. S. (1997) Naltrexone in the treat-

ment of dually-diagnosed patients. *Journal of Addictive Diseases* 16: A27, 125. ¶ Maxwell, S., and Shinderman M. S. (2000) Use of Naltrexone in the treatment of alcohol use disorders in patients with concomitant severe mental illness. *Journal of Addictive Diseases,* 19: 61–69. Naltrexone was safe and effective in dual diagnosis alcoholics who were allowed to drink while on medication *but it was not effective in regular alcoholics who were told to abstain while on medication.* **Discussion concludes the results support Sinclair's hypothesis that naltrexone works by extinction.**

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.

19. Oslin, D., Liberto, J., O'Brien, C. P., krois, S., and Norbeck, J. (1997) Naltrexone as an adjunct treatment for older patients with alcohol dependence. *American Journal of Geriatric Psychiatry* 5: 324–332. Naltrexone was safe and effective in older patients who drank, *but of no benefit until the first drink on medication.*

20. Lifrak, P. D., Alterman, A. I., O'Brien, C. P., and Volpicelli, J. R. (1997). Naltrexone for alcoholic adolescents. *American Journal of Psychiatry* 154 (3): 439–440. Naltrexone was safe and effective in adolescent alcoholics.

21. kranzler, H. R., Tennen, H., Penta, C., and Bohn, M. J. (1997). Targeted naltrexone treatment of early problem drinkers. *Addictive Behaviors* 22: 431–436. ¶ kranzler, H. R., Tennen, H., Blomqvist et al. (2001) Targeted naltrexone treatment for early problem drinkers. *Alcohol: Clinical and Experimental Research* 25 (Supplement 5): 144A. First trial to give naltrexone only when patients were drinking, in accord with the Sinclair Method; naltrexone was safe and produced significant benefits, *but none before first drink while on medication.*

22. O'Connor, P. G., Farren, C. k., Rounsaville, B. J., and O'Malley, S. S. (1997) A preliminary investigation of the management of alcohol dependence with naltrexone by primary care providers. *American Journal of Medicine* 103 (6): 477–482. Open label study concluding: "Naltrexone and counseling by primary care providers appeared to be both feasible and effective."

23. McCaul, M. E., Wand, G. S., Sullivan, J., Mummford, G., and Quigley, J. (1997) Beta-naltrexol level predicts alcohol relapse. *Alcoholism: Clinical and Experimental Research* 21: 32A. Naltrexone was safe and effective in

patients with higher levels of the metabolite beta-naltrexol and with higher dose (100 mg). Benefits no longer significant at six months.

24. Balldin, J., Berglund, M., Borg, S., Månsson, M., Berndtsen, P., Franck, J., Gustafsson, L., Halldin, J., Hollstedt, C., Nilsson, L.-H., and Stolt, G.. (1997) A randomized 6 month double-blind placebo-controlled study of naltrexone and coping skills education programme. *Alcohol and Alcoholism* 32: 325. ¶ Månsson, M., Balldin, J., Berglund, M., and Borg, S. (1999) Six-month follow-up of interaction effect between naltrexone and coping skills therapy in outpatient alcoholism treatment. *Alcohol and Alcoholism* 34: 454. ¶ Månsson, M., Balldin, J., Berglund, 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.*

25. Sinclair, D. (1997) Development in Finland of the extinction treatment for alcoholism with naltrexone. *Psychiatrica Fennica* 28: 76–97. ¶ Sinclair, J. D. (1998) Pharmacological extinction of alcohol drinking with opioid antagonists. *Arqivos de Medicina* 12 (Supplement 1): 95–98. ¶ Sinclair, J. D., kymäläinen, O., Hernesniemi, M., Shinderman, M. S., and Maxwell S. (1998). Treatment of alcohol dependence with naltrexone utilizing an extinction protocol. *Abstracts: 38th Annual Meeting, National Institute of Mental Health (NIMH)–sponsored New Clinical Drug Evaluation unit (NCDEu) Program,* Boca Raton, Florida, June 10–13, 1998. ¶ Sinclair, J. D. (1998) New treatment options for substance abuse from a public health viewpoint. *Annals of Medicine* 30: 406–411. Publication of the highly significant reductions in craving and drinking found in the first Finnish clinics using the Sinclair Method.

26. Rybakowski, J. k., Ziólkowski, M., and Volpicelli, J. R. (1997) A study of lithium, carbamazepine and naltrexone in male patients with alcohol dependence—results of four months of treatment. Abstract from the annual meeting of the European Society for Biomedical Research on Alcoholism. *Naltrexone with Support of abstinence was not effective.*

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 (Supplement): 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.

28. Anton, R. (1998) Naltrexone compared to placebo when combined

with cognitive behavioral therapy in the treatment of outpatient alcoholics. Presented at the Ninth Congress of the International Society for Biomedical Research on Alcoholism (ISBRA), Copenhagen, Denmark, June 27–July 2, 1998. ¶ Anton, R. (1999) Neurobiologial approach to alcoholism therapy: The role of naltrexone. 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. ¶ Anton, R. F., Moak, D. H., Waid, L. R., Latham, P. k., Malcolm, R. J., and Dias, J. k. (1999) Naltrexone and cognitive behavioral therapy for the treatment of outpatient alcoholics: Results of a placebo-controlled trial. *American Journal of Psychiatry* 156: 1758–1764. DBPC trial showing naltrexone with coping to be safe and effective. *No benefit before first drink on medication.*

29. Hersh, D., Van kirk, J. R., and kranzler, H. R. (1998) Naltrexone treatment of comorbid alcohol and cocaine use disorders. *Psychopharmacology* (Berlin). September 139 (1–2): 44–52. Small study with no significant benefits of naltrexone over placebo in patients addicted to both alcohol and cocaine.

30. Sinclair, J. D. (1998) From optimal complexity to the naltrexone extinction of alcoholism. In: Hoffman, R., Sherrick, M. F., and Warm, J. S. (eds.) *Viewing Psychology as a Whole: The Integrative Science of William N. Dember.* Washington, D.C.: American Psychological Association, 491–508. **Review concluding naltrexone is effective and works by extinction.**

31. O'Malley, S. (ed.) (1998) *Naltrexone and Alcoholism Treatment.* Rockville, MD: U.S. Department of Health and Human Services, Public Health Service. Treatment Improvement Protocol (TIP) Series Vol. 28. **Book showing safety and efficacy of naltrexone and how it has been used. Includes "Why Isn't Naltrexone More Widely Used" on p. 75.**

32. Heinälä, P., Alho, H., kuoppasalmi, k., Sinclair, D., kiianmaa, k., and Lönnqvist, J. (1999) Use of naltrexone in the treatment of alcohol dependence—a double-blind placebo-controlled Finnish trial. *Alcohol and Alcoholism* 34: 433. ¶ Heinälä, P., Alho, H., kuoppasalmi, k., Lönnqvist, J., Sinclair, D., and kiianmaa, k. (1999) Naltrexone in alcoholism treatment: Patient efficacy and compliance. In: *New Research. Program and Abstracts. American Psychiatric Association 1999 Annual Meeting.* Washington, DC. May 15–20, 1999. ¶ Alho, H., Heinälä, P., kiianmaa, k., and Sinclair, J. D. (1999) Naltrexone for alcohol dependence: double-blind placebo-controlled Finnish trial. *Alcoholism: Clinical and Experimental*

Research 23: 46A (abstract 246) ¶ Heinälä, P., Alho, H., kuoppasalmi, k., Lönnqvist, J., kiianmaa, k., and Sinclair, J. D. (2000) Targeted naltrexone with coping therapy for controlled drinking, without prior detoxification, is effective and particularly

well tolerated: An 8-month controlled trial. Abstract to 10th Congress of the International Society for Biomedical Research on Alcoholism (ISBRA 2000), Yokohama, Japan, July 2l–July 8, 2000. ¶ Heinälä, P., Alho, H., kiianmaa, 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 (no prior detoxification, instructions aimed at controlled drinking, naltrexone given only when drinking, and naltrexone continued [here 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.*

33. Garbutt, J. C., West, S. L., Carey, T. S., Lohr, k. N., and Crews, F. T. (Agency for Health Care Policy and Research, AHCPR) (1999) Evidence Report/Technology Assessment: Number 3: Pharmacotherapy for Alcohol Dependence. Pharmacological Treatment of Alcohol Dependence: A Review of the Evidence. *Journal of the American Medical Association* 281:1318–1325. **Review of all pharmaceutical treatments for alcoholics, concluding that naltrexone is safe and effective, and with better evidence than any other medication.**

34. Mason, B. J., Salvato, F. R., Williams, L. D., Ritvo, E. C., and Cutler, R. B. (1999) A double-blind, placebo-controlled study of oral Nalmefene for alcohol dependence. *Archives of General Psychiatry* 56: 7 19–725. Second Nalmefene study, DBPC trial showing it to be safe and effective, *but not beneficial until first drink on medication.*

35. Rubio, G. (1999) How to use naltrexone in different alcoholic patient groups. 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. Open-label but placebo-controlled study showing naltrexone was safe and effective. *No benefit until first drink on medication.*

36. Swift, R.M. (1999) Drug therapy for alcohol dependence. *New England Journal of Medicine* 340: 1482–1490. **Review concluding "of all drugs studied for the treatment of alcohol dependence, the**

evidence of efficacy is strongest for naltrexone and acamprosate."

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

38. knox, P. C., and Donovan, D. M. (1999) Using naltrexone in inpatient alcoholism treatment. *Journal of Psychoactive Drugs* 31 (4): 373–388. *Naltrexone with abstinence (in an inpatient program) was of no benefit; 63 alcoholics, DBPC.*

39. Oslin, D. W., Pettinati, H. M., Volpicelli, J. R., Wolf, A. L., kampman, k. M., and O'Brien, C. P. (1999) The effects of naltrexone on alcohol and cocaine use in dually addicted patients. *Journal of Substance Abuse and Treatment,* 16 (2): 163–167. Naltrexone produced significant decreases in alcohol and cocaine use.

40. Morris, P. (1999) A controlled trial of naltrexone for alcohol dependence: An Australian perspective. Presented at the 1999 Scientific Meeting of the Research Society on Alcoholism, June 26–July 1, 1999, Santa Barbara, California .¶ Morris, P. L. P., Hopwood, M., Whelan, G., Gardiner, J., and Drummond, E. (2001) Naltrexone for alcohol dependence: A randomised controlled trial. *Addiction* 96: 1565–1573 Naltrexone was safe and effective with Coping with Drinking protocol. *No benefit until first drink on medication.*

41. Sinclair, J. D., Sinclair, k., and Alho, H. (2000). Long-term follow up of continued naltrexone treatment. *Alcoholism: Clinical and Experimental Research* 24 (Supplement): 182A. (S16:4) Significant benefits of naltrexone are still present three years after start of treatment in patients always taking medication before drinking, on craving, drinking levels, and liver damage markers.

42. World Health Organization (2000). Management of substance dependence. Review Series. A systematic review of opioid antagonists for alcohol dependence, 4. WHO/MSD/MSB 00.4 **Naltrexone is effective in treating alcoholism.**

43. Chick, J., Anton, R., Checinski, k., Croop, R., Drummond, D. C., Farmer, R., Labriola, D., Marshall, J., Moncrieff, J., Morgan, M. Y., Peters, T., and Ritson, B. (2000) A multicentre, randomized, double-blind, placebo-controlled trial of naltrexone in the treatment of alcohol dependence or abuse. *Alcohol and Alcoholism* 35 (6): 587–593. DBPC trial showing naltrexone was safe and effective in complying patients. *No benefit until after first drink on medication.*

44. kranzler, H., Modesto-Lowe, V., and Van kirk, J. (2000) Naltrexone vs. nefazadone for treatment of alcohol dependence. *Neuropsychopharmacology* 22: 493–503. DBPC trial failed to find significant benefit from naltrexone with Cognitive Behavioral Therapy, but same subjects contributed to significant naltrexone effect in Oslin et al., 2003.

45. Auriacombe, M., Robinson, M., Grabot, D., and Tignol, J. (2000) Naltrexone is ineffective to prevent relapse to alcohol in a realistic out-patient

setting. A double-blind one-year controlled study. Abstract to the 62nd Meeting of the College on Problems of Drug Dependence, Bal Harbor, Florida. *Naltrexone with Supportive therapy was ineffective.*

46. O'Malley, S. S. (2001) Getting beyond the research clinic studies: comments on Morris et al. (2001). *Addiction* 96 (12): 1859–1860. **Points out the main effects in patients who sample alcohol while on medication.**

47. 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 naltrexone 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 given, so this is classified as unclear.

48. kranzler, H. R., and Van kirk, J. (2001) Efficacy of naltrexone and acamprosate for alcoholism treatment: A meta-analysis. *Alcoholism: Clinical & Experimental Research* 25 (9): 1335–1341, 2001. **Review concluding naltrexone is safe and generally effective.**

49. Anton, R. F., Moak, D. H., Latham, P. k., Waid, L. R., Malcolm, R. J., Dias, J. k., and Roberts, J. S. (2001) Post-treatment results of combining naltrexone with cognitive-behavior therapy for the treatment of alcoholism. *Journal of Clinical Psychopharmacology* 21 (1): 72–77. Naltrexone was safe and effective. Benefits continue after termination of medication but eventually disappear, in accord with extinction.

50. Monti, P. M., Rohsenow, D. J., Swift, R. M., Gulliver, S. B., Colby, S. M., Mueller, T. I., Brown, R. A., Gordon, A., Abrams, D. B., Niaura, R. S., and Asher, M. k. (2001) Naltrexone and cue exposure with coping and communication skills training for alcoholics: Treatment process and 1-year outcomes. *Alcoholism: Clinical & Experimental Research* 25 (11): 1634–1647. Naltrexone plus coping therapy was safe and effective. *No benefit until first drink on medication.*

51. Rubio, G., Jiménez-Arriero, A., Ponce, G., and Palomo, T. (2001) Naltrexone versus acamprosate: one year follow-up of alcohol dependence treatment. *Alcohol and Alcoholism* 36: 419–425. Naltrexone was safe and effective with Coping with Drinking protocol. *No benefit until first drink on medication.*

52. Monterosso, J. R., Flannery, B. A., Pettinati, H. M., Oslin, D. W., Rukstalis, M., O'Brien, C. P., and Volpicelli, J. R. (2001) Predicting treatment response to naltrexone: the influence of craving and family history. *American*

Journal of Addiction 10: 258–268. Naltrexone was safe and effective, especially with a family history of alcoholism.

53. 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.**

54. krystal, J. H., Cramer, J. A., krol, W. F., kirk, G. F., and Rosenheck, R. A. (2001) Naltrexone in the treatment of alcohol dependence. *New England Journal of Medicine* 345: 1734–1739. *DBPC trial of naltrexone with abstinence on 627 veterans found no significant benefits over placebo.*

55. Streeton, C., and Whelan, G. (2001) Naltrexone, a relapse prevention maintenance treatment of alcohol dependence: A meta-analysis of randomized controlled trials. *Alcohol and Alcoholism* 36 (6): 544–552. **Meta-analysis of all published and unpublished trials concluded naltrexone was safe and effective in alcoholism treatment.**

56. Gual, S. A. (2001) Evolucion clinica del alcoholismo tratado con naltrexona. Efectividad y seguridad en una muestra de 198 pacientes. *Medicina Clinica (Barcelona)* 116 (14): 526–532. Open label study showing safety of naltrexone.

57. 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.*

58. kim, S. W., and Grant, J. E. (2001) An open naltrexone treatment study in pathological gambling disorder. *International Clinical Psychopharmacology* 16: 285–289. Open label, showing naltrexone was safe and effective in treating gambling.

59. kim, S. W., Grant, J. E., Adson, D. E., and Shin, Y. C. (2001) Double-blind naltrexone and placebo comparison study in the treatment of pathological gambling. *Biological Psychiatry* 49: 914–921. DBPC trial showing naltrexone was safe and effective in treating gambling.

60. Mäkelä, R., kallio, A., and karhuvaara, S. (2001) Nalmefene in the treatment of heavy drinking. Programme & Abstracts of the 2001 ISAM Meeting, Trieste, Italy, September 12–14. ¶ Mäkelä, R. (2002) Multisite study of Nalmefene for the treatment of heavy alcohol drinkers with impaired control. Presented at the 25th Annual Scientific Meeting of the Research Society on Alcoholism, June 28–July 3, 2002, San Francisco, CA. Nalmefene was safe

and effective, especially in family history positive alcoholics, without extensive counseling.

61. Anton, R. (2002) Multisite study of Nalmefene combined with modi-

fied 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. *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).*

62. Guardia, J. (2002) A double-blind placebo-controlled study of naltrexone in the treatment of alcohol-dependence. Results from a multicenter clinical trial. *Proceedings of the 25th Annual Scientific Meeting of the Research Society on Alcoholism,* June 28–July 3, 2002, San Francisco, CA. ¶ Guardia, J., Caso, C., Arias, F., Gual, A., Sanahuja, J., Ramirez, M., Mengual, I., Gonzalvo, B., Segura, L., Trujols, J., and Casas, M. (2002) A double-blind, placebo-controlled study of naltrexone in the treatment of alcohol-dependence disorder: results from a multicenter clinical trial *Alcoholism: Clinical and Experimental Research* 26 (9): 138 1–1387 Naltrexone was safe and effective in 202 patients reducing relapses to heavy drinking. *No benefit until first drink while on medication.*

63. kiefer, F. (2002) Randomized controlled trial of naltrexone, acamprosate, and the combination in the treatment of alcoholism. *Proceedings of the 25th Annual Scientific Meeting of the Research Society on Alcoholism,* June 28–July 3, 2002, San Francisco, CA. ¶ kiefer, F., Jahn, H., Tarnaske, T., Helwig, H., Briken, P., Holzbach, R., kampf, P. Stracke, R., Baehr, M., Naber, D., and Wiedemann, k. (2003) Comparing and combining naltrexone and acamprosate in relapse prevention of alcoholism: A double-blind, placebo-controlled study. *Archives of General Psychiatry* 60 (1): 92–99. ¶ Lesch, O. M. Diagnostic categories. European College of Neuropsychopharmacology Consensus Meeting, Nice, France, March 12–14, 2003. DBPC study showing naltrexone was safe and effective alone and in combination with acamprosate, with naltrexone alone or in combination with acamprosate better than acamprosate alone. *An analysis of the results by lesch showed that* naltrexone benefited those who drank while on the medication *but not those getting it with abstinence, but acamprosate produced benefits with abstinence.*

64. Rukstalis, M.(2002) Comparing responses to alcohol, naltrexone in males and females. *Proceedings of the 25th Annual Scientific Meeting of the Research Society on Alcoholism,* June 28–July 3, 2002, San Francisco, CA. Naltrexone was equally effective in men and women.

65. 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, 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.

66. Alkermes, Inc. press release. (January 3, 2002) Alkermes reports positive results of phase II clinical trial of VIVITREX for alcohol dependency at annual meeting of the American College of Neuropsychopharmacology. The company's sustained-release naltrexone was found to be safe and effective in treating alcoholism.

67. Gastpar, M., Bonnet, U., Böning, J., Mann, k., Schmidt, L. G., Soyka, M., Wetterlingm,T., kielstein, V., Labriola, D., and Croop, R. (2002) Lack of efficacy of naltrexone in the prevention of alcohol relapse, results from a German multicenter study. *Journal of Clinical Psychopharmacology* 22 (6): 592–598. *DBPC trial with strict abstinence, finding no benefit of naltrexone over placebo.*

68. Latt, N. C., Jurd, S., Houseman, J., and Wutzke, S. E. (2002) Naltrexone in alcohol dependence: a randomised controlled trial of effectiveness in a standard clinical setting. *The Medical Journal of Australia*176 *(11):* 530–534. DBPC trial without counseling found naltrexone to be safe and effective.

69. Leavitt, S. B. (2002) Evidence for the efficacy of naltrexone in the treatment of alcohol dependence (alcoholism). Addiction Treatment Forum (March), Special Report, available on the Internet at http://www.atforum.com/SiteRoot/pages/addiction resources/naltrexoneWhitePaper.pdf. **Review concluding naltrexone is safe and effective, except in combination with support of abstinence.**

70. Sinclair, J. D. and Salimov, R.M. (2002) New effective method of treatment of addiction to alcohol: extinction with the help of opiate receptor antagonists. (in Russian) *Narcologia* 5: 37–40. **Review concluding naltrexone is safe, effective, and works with extinction.**

71. 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 Fin-

land 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.

72. 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. ¶ Grant, J. E., Potenza, M. N., Hollander, E., Cunningham-Williams, R., Nurminen, T., Smits, G., and kallio, A. (2006) Multicenter Investigation of the Opioid Antagonist Nalmefene in the Treatment of Pathological Gambling. *American Journal of Psychiatry* 163: 303–3 12. 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.

73. Anton, R. F., Moak, D. M., Latham, P. k., Myrick, D. L., and Waid, L. R. (2003) A double-blind comparison of naltrexone combined with CBT or MET in the treatment of alcohol dependence. 26th Annual Scientific Meeting of the Research Society on Alcoholism, June 21–25, 2003, Fort Lauderdale, FL. *Alcoholism: Clinical and Experimental Research* 27 (supplement): 191A (abstract S170) Dual DBPC trial showed naltrexone was 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.*

74. 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 2 1–25, 2003, Fort Lauderdale, FL. *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.

75. killeen, T., Brady, k., Faldowski, R., Gold, P., Simpson, k. (2003)

The effectiveness of naltrexone in a community treatment program. Abstracts of the 65th Annual Scientific Meeting, College on Problems of Drug Dependence, June 14–19, 2003, Bal Harbour, FL. ¶ killeen, T., Brady, k., Faldowski, R., Gold, P., Simpson, k., Anton, R. (2003) The efficacy of naltrexone in a community treatment program. *Alcoholism: Clinical and Experimental Research* 27 (Supplement): 146A (abstract 846). DBPC trial found naltrexone significantly improved drinking-related outcomes in patients drinking during the two weeks before treatment began *but not in patients abstinent at that time of treatment onset.* Authors conclude "naltrexone may be more effective for patients who fail to abstain upon entry into treatment for alcohol abuse." [CPDD and naltrexone is best for "those that are actively drinking at the time of initiation of treatment" [RSA].

76. krupitsky, E., Zvartau, E., Masalov, D., Tsoi, M., Burakov A., Egorova, V., Didenko, T., Romanova, T., Ivanova, E., Bespalov, A., Verbitskaya, E. V., Neznanov, N. G., Grinenko, A. Y., and Woody, G. E.(2003) A double-blind, placebo controlled trial of naltrexone for heroin addiction treatment in St. Petersburg, Russia. Proceeding of NIDA-Pavlov Workshop "Pharmacotherapies for Addiction: Basic and Clinical Science," St. Petersburg, Russia, Sept. 28–Oct. 1. ¶ krupitsky, E., Zvartau, E., Masalov, D., Tsoi, M., Burakov A., Egorova, V., Didenko, T., Romanova, T., Ivanova, E., Bespalov, A., Verbitskaya, E. V., Neznanov, N. G., Grinenko, A. Y., **O'Brien, C. P., and G.E. Woody** (2006) Naltrexone with or without fluoxetine for preventing relapse to heroin addiction in St. Petersburg, Russia. *Journal of Substance Abuse Treatment* 31: 319–328. DBPC trial found addicts sampled opiates while on naltrexone but a significantly lower percentage than among placebo patients relapsed to full-scale drug addiction. krupitsky agrees that results support extinction.

77. Oslin, D. W., Berrettini, W., kranzler, H. R., Pettinati, H., Gelernter, J., Volpicelli, J. R., and O'Brien, C. P. (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 naltrexone 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 naltrexone on abstinence.*

78. 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. ¶ Garbutt, J. C., kran-

zler, H. R., O'Malley, S. S., Gastfriend, D. R., Pettinati, H. M., Silverman, B. L., Loewy, J. W., and Ehrich, E. W., for the Vivitrex Study Group (2005) **Efficacy and Tolerability of Long-Acting Injectable Naltrexone for Alcohol Dependence: A Randomized Controlled Trial.** *Journal of the American Medical Association* 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.

79. Laaksonen, E. (2004) Comparing disulfiram, acamprosate, and naltrexone treatment of alcoholism. International Society on Addictive Medicine (ISAM) meeting Helsinki, Finland, June 2–5, 2004. Naltrexone was safe and more effective than acamprosate.

80. Bouza, C., Magro, A., Muñoz, A., Amate, J. M. (2004) Efficacy and safety of naltrexone and acamprosate in the treatment of alcohol dependence: a systematic review. *Addiction* 99: 811–828. **Review concluding "Both 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."**

81. Jayaram-Lindström, N., Wennberg, P., Hurd, Y. L., and Franck, J. (2004) Effects of naltrexone on the subjective response to amphetamine in healthy volunteers. *Journal of Clinical Psychopharmacology* 24 (6): 665–669. ¶ Jayaram-Lindström, N., konstenius, M., Eksborg, S., Beck, O., Hammarberg, A., and Franck, J. (2007) Naltrexone Attenuates the Subjective Effects of Amphetamine in Patients with Amphetamine. *Dependence Neuropsychopharmacology* advance online publication. October 24, 2007; doi: 10.1038/ sj.npp.1301572. DBPC on 20 subjects. "Pretreatment with naltrexone also significantly blocked the craving for dexamphetamine ($p<0.001$)... The potential of naltrexone as an adjunct pharmaceutical for amphetamine dependence is promising."

82. Jayaram-Lindström, N., Wennberg, P., Hurd, Y. L., Franck, J. (2005) An open clinical trial of naltrexone for amphetamine dependence: compliance and tolerability. *Nordic Journal of Psychiatry* 59 (3): 167–171. ¶ Jayaram-Lindström, N., Hammarberg, A., Beck, O., Franck, J. (2007) Naltrexone for the treatment of amphetamine dependence: A randomized placebo controlled trial. Submitted ¶ Jayaram-Lindström, N. (2007) Evaluation of naltrexone as a treatment for amphetamine dependence. Dissertation from karolinska University Hospital, presented Dec. 18, 2007. After tests with volunteers and a compliance test with amphetamine addicts, a 12 week randomized DBPC clinical trial on addicts eventually reduced craving and produced fewer urine positives for amphetamine.

83. Deas, D., May, k., Randall, C., Johnson, N., and Anton, R. (2005) Naltrexone treatment of adolescent alcoholics: An open-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 six weeks.

84. Rubio, G., Ponce, G., Rodriquez-Jiménez, R., Jiménez-Arriero, M. A., Hoenicka, J., and Palomo, T. (2005) Clinical predictors 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 naltrexone 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.

85. Sinclair, J. D. (2005) The Second Generation of Anti-Relapse Drugs: Opioidergic Compounds: Clinical. In: R. Spanagel and k. Mann (eds) *Drugs for Relapse Prevention of Alcoholism,* in the series Milestones in Drug Therapy. Basal, Switzerland; Birkhäuser, 125–134. **Review concluding "Nalmefene appears to be an appropriate medicine for preventing alcohol abuse but not for maintaining abstinence."**

86. Hernandez-Avila, C. A., Song, C., kuo, L., Tennen, H., Armeli, S., and 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. DBPC trial, n=150, of naltrexone with coping with drinking found naltrexone was effective

especially with targeted use. Only targeted, not daily naltrexone helped women.

87. Anton R. F., O'Malley, S. S., Ciraulo, D. C., Cisler, R. A., Couper, D., Donovan, D.M., Gastfriend, D.R., Hosking, J. D., Johnson, B.A., LoCastro, J. S., Longabaugh, R., Mason, B. J., Mattson, M. E., Miller, W. R., Pettinati, H. M., Randall, C. L., Swift, R., Weiss, R. D., Williams, L. D., Zweben, A. Z., for the COMBINE Study Research Group (2006) **Combined pharmacotherapies and behavioral interventions for alcohol dependence: The COMBINE Study: A Randomized Controlled Trial** *Journal of the American Medical Association* 295: 2003–2017. Largest DBPC trial in addiction (n=1383 recently detoxified alcoholic) showed naltrexone 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 naltrexone better (*the partially abstinence oriented therapy actually tended to reduce the benefit).* Acamprosate had no significant benefits and taken at the same time as naltrexone did not help naltrexone.

88. O'Neil, G., Parsons, Z., O'Neil, P., Xu, J. X., and Hulse, G. (2006) Naltrexone implants for amphetamine dependence. 3rd Stapleford International Addiction Conference on: Latest developments in effective medical treatments for addiction, Berlin, March 18–19. Small open-label trial found naltrexone 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 naltrexone ($p<0.0004$)

89. Grüsser, S. M., Ziegler, S., Thalemann, C., Partecke, L. (2006) Naltrexone as anticraving treatment: A psychophysiologicical 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.

90. Singh, J. (2006) Naltrexone implants—an Indian experience. 3rd Stapleford International Addiction Conference on: 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).

91. kunøe, N., Lobmaier, P., Waal, H. (2006) A matched case-control study of naltrexone implants for relapse prevention in detoxified opioid addicts. 3rd Stapleford International Addiction Conference on: Latest developments in effective medical treatments for addiction, Berlin, March 18–19. Controlled pilot study suggesting "that naltrexone implants are an effective aid in preventing opioid relapse after completion of inpatient treatment."

92. Revill, J. (2006) An audited 24 month comparison of the George O'Neill 3-vial naltrexone implant with supervised methadone, in a general practice population. 3rd Stapleford International Addiction Conference on: Latest developments in effective medical treatments for addiction, Berlin, March 18–19. 100% of 25 naltrexone patients but only 26% of 25 adequate-dose methadone patients had urines clear of illicit opiates at the end of 2 years.

93. Somaxon press release. (July 26, 2006) Somaxon Pharmaceuticals Reports Positive Results From a Pilot Phase 2

Study of Oral Nalmefene in Smoking Cessation. 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.)

94. Morley, k. C., Teesson, M., Reid, S. C., Sannibale, C., Thomson, C., Phung, N., Weltman, M., Bell, J. R., Richardson, k., and Haber, P. S. (2006)

Naltrexone versus acamprosate in the treatment of alcohol dependence: a multi-centre, randomized, double-blind, placebo-controlled trial. *Addiction* 10: 1451–1462. DBPC on 169 Australian alcoholics finds naltrexone significantly delays relapse to heavy drinking *but not time to first drink.* "The results of this study support the efficacy of naltrexone in the relapse prevention of alcoholism amongst those with low levels of clinical depression and alcohol dependence severity. No effect of acamprosate was found in our sample."

95. Comer, S. D., Sullivan, M. A., Yu, E., Rothenberg, J. L., kleber, H. D., kampman, k., Dachis, C., and O'Brien, C. P. (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 in 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.

96. O'Malley, S. S., Sinha, R., Grilo, C. M., Capone, C., Farren, C. k., Mckee, S. A., Rounsaville, B. J., and 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.

97. Baros, A. M., Lathan, P. k., Moak, D. H., Voronin, k. and Anton, R. F. (2007) What role does measuring medication compliance play in evaluating the efficacy of naltrexone? *Alcoholism, Clinical and Experimental Research* 31: 596–603. DBPC on 160 patients with coping. Naltrexone significant better than placebo in the most compliant patients, with about twice as much treatment effect than in the less compliant patients.

98. Gelernter, J., Gueorguieva, R., kranzler, H. R., Zhan, H., Cramer, J., Rosenheck, R., and krystal, J. H. (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

naltrexone had no significant effect on relapse to heavy drinking in the overall sample in CSP 425 [#54], it significantly reduced relapse in the subgroup that provided DNA for analysis." There were no published interactions with receptor type but there is a significant effect with the OPRD1 T921, helping the GG and AG genotypes but not with the AA homozygotic genotype.

99. karhuvaara, S., Simojoki, k., Virta, A., Rosberg, M., Löyttyniemi, E., Nurminen, T., kallio, A., and Mäkela, R. (2007) Targeted nalmefene with simple medical management in the treatment of heavy drinkers: A randomized double-blind placebo-controlled multicenter study. *Alcoholism: Clinical and Experimental Research* 31 (No 7): 1–9. In DBPC trial on 403 subjects for 7 months without intensive counselling, nalmefene decreased drinking more than placebo (p=0.0065), reduced the risk of heavy drinking 32.4% (95% CI: 14.2–46.8%; p=0.003) more than placebo, and progressively reduced markers that increased in placebo group (GGT p=0.009 and ALT p=0.002).

100. Toneatto, T., Brands, B., Selby, P. and Sinclair, D. (2007) A Randomized, Double-Blind, Placebo-Controlled Trial of Naltrexone in the Treatment of Concurrent Alcohol Dependence and Pathological Gambling. preliminary report at http://clinicaltrials.gov/ct/show/NCT00326807;jsessionid=5057BD239D3C012928C684806432A673?order=20. Naltrexone failed to provide significant benefits in patients with both alcoholism and pathological gambling.

101. Pallesen, S., Molde, H., Arnestad, H. M., Laberg, J. C., Skutle, A., Iversen, E., Støylen, I. J., kvale, G., and Holsten, F. (2007) Outcome of pharmacological treatments of pathological gambling: A review and meta-analysis. *Journal of Clinical Psychopharmacology* 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."**

102. Tidey, J. W., Monti, P. M., Rohsenow, D. J., Gwaltney, Cj., Miranda, R. Jr., McGeary, J. E., Mackillop, J., Swift, R. M., Abrams, D. B., Shiffman, S., and Paty, J. A. (2008) Moderators of naltrexone's effects on drinking, urge, and alcohol effects in non-treatment-seeking heavy drinkers in the natural environment. *Alcoholism: Clinical and Experimental Research* 32: 58–66. doi:10.1111/j.1530–0277.2007.00545.x DBPC on 180 heavy drinkers (63% alcohol dependent) for three weeks found naltrexone reduced drinking days and heavy drinking days, plus craving in early onset drinkers and time between drinks in patients with more alcoholic relatives.

APPENDIX B

How Addiction to Alcohol Is Learned

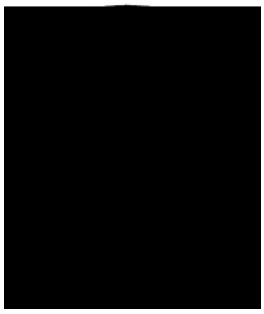
(All biological images courtesy of Dr. David Sinclair)

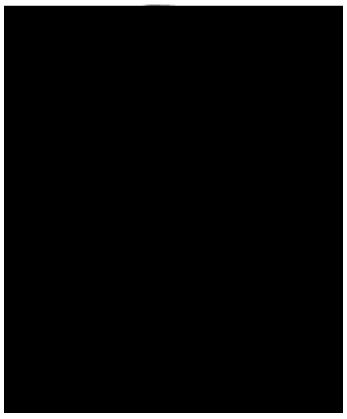
understanding how the Sinclair Method works is easy once you understand how an addiction develops in the first place.

THE ILLUSTRATIONS in this appendix show the rewiring of the nervous system that causes drinking to go from a weak behavior occurring only occasionally to being such a powerful response that it is almost automatic, easily stimulated, and nearly impossible to interrupt or control. They show the development of an addiction.

Understanding Addiction and the Sinclair Method

Comprehending the process by which addiction to alcohol develops was the key for discovering the Sinclair Method. Readers using the Method should also understand the process. The Method and the mechanism of addiction are difficult to explain verbally,





but many people find them rather easy to understand from illustrations, so it is important to show them rather than just describe them.

It is hard to explain them in words because language itself imposes upon us a particular theory of what causes behavior. From ancient times people have imagined that there was a little homunculus in the head who actually saw the world and rationally decided what one should do on the basis of expected pleasure and pain. Our language still reflects this rational-choice theory of behavior.

Once alcohol drinking has developed into alcoholism, it no longer is under rational control. Mistakenly treating alcoholism as rational behavior has probably resulted in more harm to alcoholics than any other single factor. If a homunculus rationally decides whether or not to drink on the basis of maximizing pleasure and minimizing pain, there is a simple cure for alcoholism: punish drinking; increase the pain produced by drinking. We have treated alcoholism with punishment for thousands of years. It has not worked yet. Nevertheless, we continue because it is so . . . rational.

In 1981 Sinclair wrote a book with this new view of the homuncu-

The cause of behavior: a nerve cell

lus, now somewhat crowded.* By then the mechanics of the visual system were understood to be something like color television, the auditory system like a stereo, and output something like a computer. Most people still tended to imagine decisions being made rationally by a homunculus. We showed in that book, however, that behavior could be explained as only the output of nerve cells, without any homunculus even making the decisions and with pleasure not as a goal but an aftereffect of some behavior.

Francis Crick (co-discoverer of the structure of DNA) called this idea the "Astonishing Hypothesis." Crick admitted, "I myself find it difficult at times to avoid the idea of a homunculus. One slips into it so easily . . . People often prefer to believe that there is a disembodied soul that, in some utterly mysterious way, does the actual seeing. . . . Our Astonishing Hypothesis says . . . it's all done by nerve cells."**

All behavior is caused by the firing of nerve cells. This is the starting point for an understanding of addiction.

When the doctor taps your knee and your foot rises, the behavior is caused by the firing of nerve cells. That is the way you are wired.

---

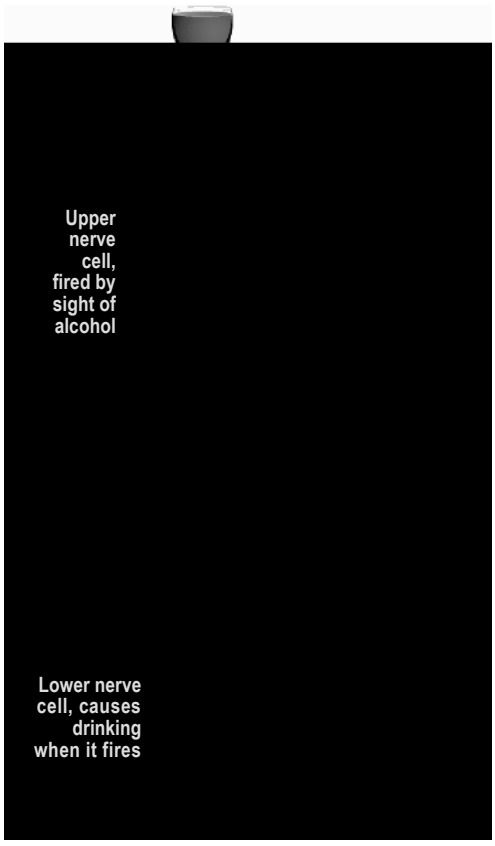
* Sinclair, J. D. (1981) *The Rest Principle: A Neurophysiological Theory of Behavior,* Hillsdale, N.J.: Lawrence Erlbaum Associates.

** Crick, F. (1994) *The Astonishing Hypothesis,* London: Simon & Schuster, p. 258 and p. 33.

When you raise a wine glass to your lips and drink, the behavior is caused by the firing of nerve cells.

Pictures help liberate our thinking. Language alone leads us back to a rational homunculus, but the behavior of the alcoholic is not rational. Pictures free us from these restrictions, making it possible for us to understand how alcohol drinking can come to dominate our behavior.

The Scene of the Action



The rewiring that produces addiction occurs at the connection where one nerve cell makes another one fire.

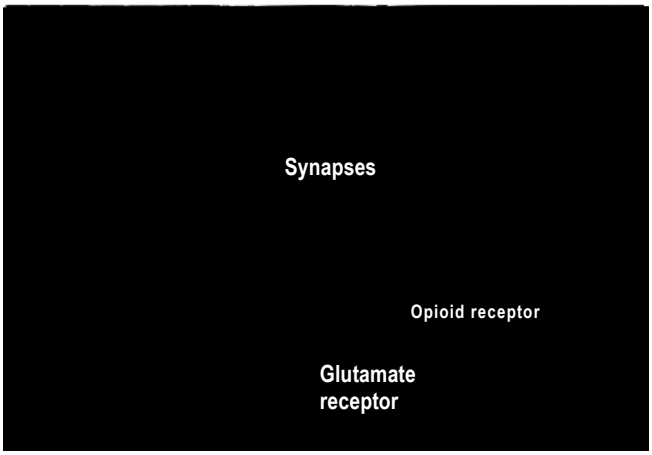
The connection shown in the lower circle here, between a nerve cell fired by the sight of alcohol and one that triggers drinking when it fires, is initially weak. *The upper nerve cell may have to fire one hundred times to make the lower one fire and thus start drinking.* Before addiction develops, just seeing alcohol seldom results in drinking.

The addiction develops because the connection becomes more effective, until *the upper nerve cell only has to fire once to make the lower cell fire.*

In order to see the changes in the connection, we have to go closer. Imagine that you are here, standing on the lower nerve cell and looking off into the distance . . .

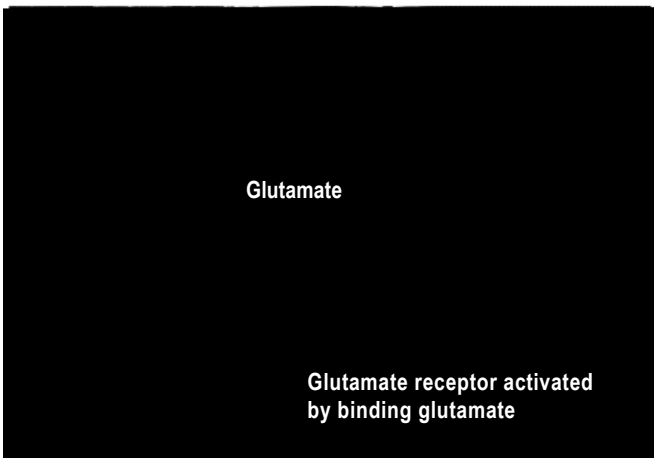
Here is what you see.

You are standing on the lower nerve cell, looking out at syn-



apses from the upper cell. On the left, one synapse is so close that you can look inside it.

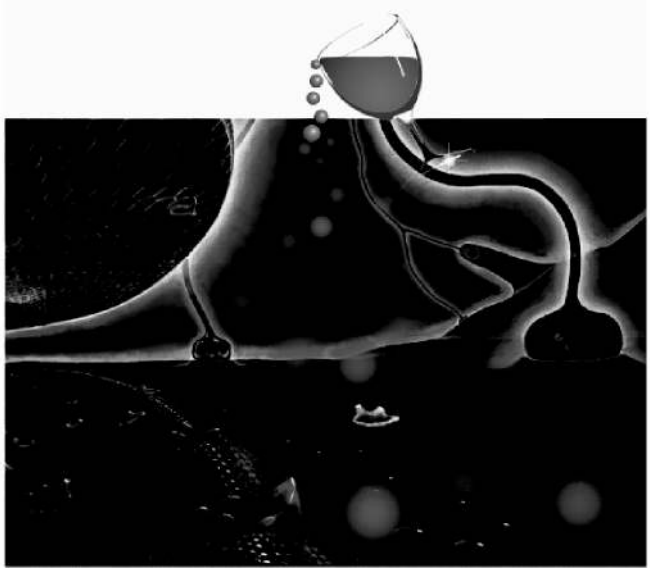
Here, the upper nerve cell has fired, releasing molecules of glu-



tamate from the spheres where they are stored. The glutamate diffuses across the space inside of the synapse. If glutamate touches and binds to a glutamate receptor on the surface of the lower nerve cell, and then the receptor is activated. *If enough receptors are ac-*

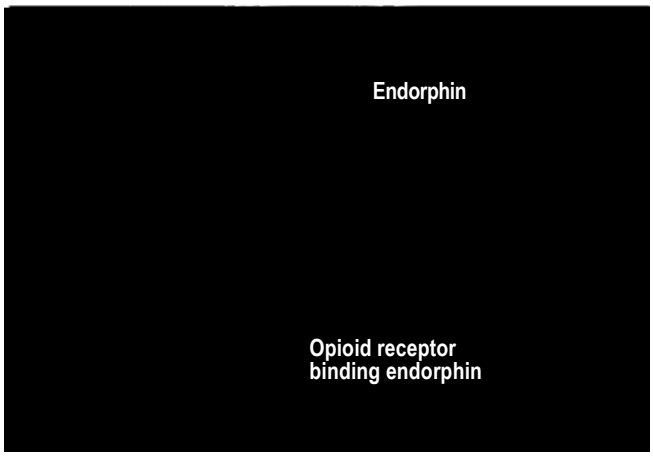
tivated (by the upper nerve cell firing one hundred times), the lower cell itself fires, and its firing causes alcohol drinking.

The alcohol is absorbed and then diffuses around the brain . . .



. . . where it causes some nerve cells (not shown) to release endorphin.

Endorphin binding to an opioid receptor triggers the mechanism

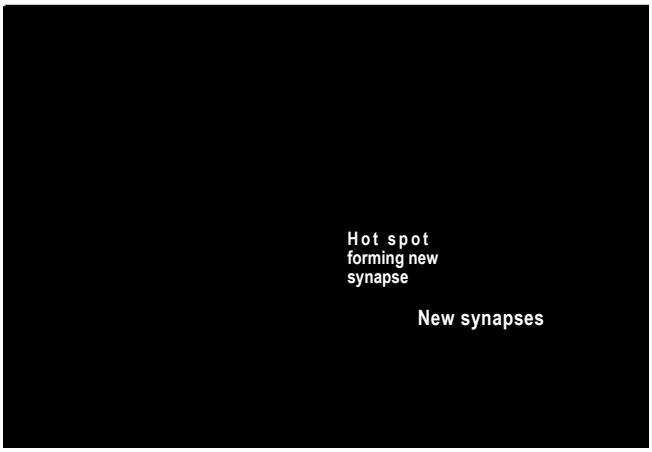


called reinforcement . . .

Reinforcement

Reinforcement produces new glutamate receptors on the lower nerve cell and changes the upper one so it releases more glutamate when it fires. *Now the upper cell only has to fire ten times (not one hundred) to make the lower one fire.*

Reinforcement also produces new synapses that help the



strengthened existing synapses to make the lower nerve cell fire. Repeated reinforcement causes the connection to become strong enough that the upper nerve cell ***only has to fire once*** to make the lower nerve cell fire and thus to start drinking. *The nervous system has become rewired so the person is now an alcoholic.*

The connection shown here—between seeing alcohol and starting to drink—is only one of many connections contributing to the development of alcoholism. For example, endorphin also reinforces the connections onto nerve cells that cause the acquisition of alcohol, and thus going to the pub or the liquor store becomes a way of life. Endorphin reinforces the connections firing nerve cells that cause thinking about alcohol. Consequently, thoughts about alcohol pop up continually and spontaneously, not because of any rational choice but because that is how the person has become wired.

Prevention of Alcoholism

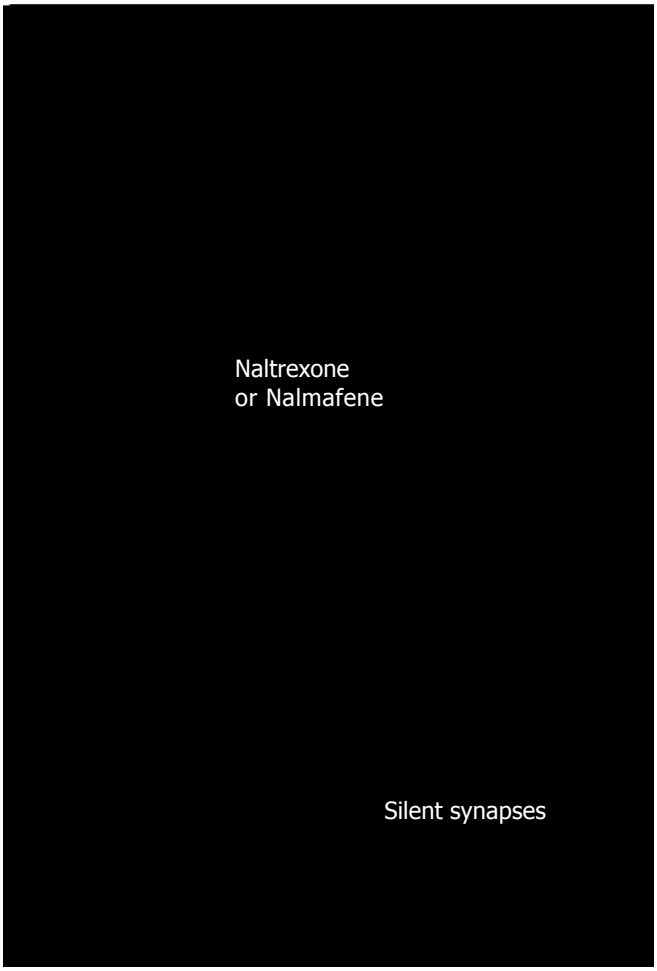
The development of alcoholism can be prevented by blocking the reinforcement from the endorphin released by alcohol.

Naltrexone or nalmefene (N), taken before drinking, blocks the opioid receptors; like putting the wrong key in a lock, it does not activate the receptor, but it blocks endorphin from binding to the receptor. The endorphin bounces off with no effect. It cannot cause reinforcement.

With the medication stopping reinforcement, the synapses from the upper nerve cell onto the lower one will not become stronger. New synapses will not form. The upper nerve cell will continue to have to fire one hundred times to make the lower one fire. Drink-

ing remains a weak, easily controlled response. With naltrexone or nalmefene, most people can drink safely without becoming an alcoholic.

Reversal of Alcoholism



If alcoholism has already developed, taking naltrexone or nalmefene and then drinking alcohol starts a mechanism called "extinction." Extinction reverses the changes previously produced by

reinforcement, thus weakening the connection between the nerve cells.

Synapses become weaker and can even be burned out completely. Eventually, the upper nerve cell again will have to fire one hundred or more times to make the lower nerve cell fire and produce drinking. Thus the cause of the alcoholism is removed, and controlled drinking is possible again.

APPENDIX

C

Sinclair Method Awarded a U.S. Patent—Establishes the Research as the First to Suggest and Use Pharmacological Extinction for Alcoholism*

United States Patent **Sinclair**	**4,882,335** **November 21, 1989**

Method for treating alcohol-drinking response

ABSTRACT

A therapeutic method is provided for use as an adjunct in the treatment of alcoholism. The method consists of extinguishing the alcohol-drinking response of alcoholics during a relatively short period of time by having them drink alcoholic beverage repeatedly while an opiate antagonist blocks the positive reinforcement effects of ethanol in the brain.

•Note: Figures not included here. Download patent from: http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=%2Fnetahtml%2FPTO%2Fsrchnum.htm&r=1&f=G&l=50&s1=4,882,335.PN.&OS=PN/4,882,335&RS=PN/4,882,335

Inventors:	**Sinclair; John D.** (Espoo, Finland)
Assignee:	**Alko Limited** (Helsinki, Finland)
Appl. No.:	**205758**
Filed:	**June 13, 1988**

Current U.S. Class:	**514/282;** 514/811
Intern'l Class:	A61k 031/44
Field of Search:	514/810,811,812,282

Other References

Chem. Abst., 106-12821P, (1987).
"Naloxone Persistently Modifies Water-Intake," Pharmacology Biochemistry & Behaviour, Mar. 25, 1986, vol. 29, pp. 331-334.
"Feasibility of Effective Psychopharmacological Treatments for Alcoholism," J. D. Sinclair, Ph.D, British Journal of Addition, 1987, 82, 1213-1223.

Claims

1. A method for treating alcoholism by extinguishing the alcohol-drinking response, comprising the steps of:

   repeatedly administering to a subject suffering from alcoholism, an opiate antagonist selected from the group consisting of Naloxone, Naltrexone, cyclazocine, diprenorphine, etazocine, levalorphan, metazocine, nalorphine and salts thereof in a daily dosage sufficient to block the stimulatory effect of alcohol;

   while the amount of antagonist in the subject's body is sufficient to block the stimulatory effect of alcohol, having the subject drink an alcoholic beverage; and

   continuing the steps of administration of the opiate antagonist and drinking of an alcoholic beverage until the alcohol-drinking response is extinguished.

2. The method of claim 1 further comprising the step of punishing the patient after the alcoholic beverage is consumed, said step of punishment being selected from the group consisting of administration of electric shock, administration of emetics, and administration of an alcohol sensitizing compound.
3. The method of claim 2 wherein the alcohol sensitizing compound is disulfiram or cyanamide.
4. The method of claim 1 further comprising continuing the administration of an opiate antagonist after the alcohol-drinking response is extinguished.
5. The method in accordance with claim 1 wherein the opiate antagonist is Naloxone.
6. The method in accordance with claim 5 wherein the dose of Naloxone is from 0.2 to 30 mg daily.
7. The method in accordance with claim 1 wherein the opiate antagonist is Naltrexone.
8. The method in accordance with claim 7 wherein the dose of Naltrexone is from 20 to 300 mg daily.

Description

FIELD OF THE INVENTION

The invention is a treatment for alcohol abuse in which the alcohol-drinking response is extinguished over a limited number of sessions by being emitted while the reinforcement from alcohol is blocked with an opiate antagonist such as Naloxone or Naltrexone.

BACKGROUND OF THE INVENTION

Alcoholism is the most costly health problem in many countries. The cost, e.g., in America is estimated to be about $117,000,000,000 per year. The treatment methods currently used are not very effective. Most alcoholics drop out of treatment within a month or two. Few alcoholics, regardless of the type of treatment, are able to avoid relapses and renewed alcohol abuse.

No one is born an alcoholic. The drinking of alcohol (ethanol or ethyl alcohol) is a learned response, reinforced largely by the rewarding effects of alcohol in the central nervous system—the euphoria from lower, stimulatory doses of ethanol. An alcoholic is a person who, through an interplay of genetic and environmental factors, has had the alcohol-drinking response reinforced so often and so well that it becomes too strong for the individual to continue functioning properly in society. The strong alcohol-drinking response—i.e., the drive for alcohol—then dominates the person's behaviour and life.

The current methods for treating alcoholism are not very successful probably because they do not effectively weaken the alcoholic's alcohol-drinking response. Some methods (e.g., counselling, Alcoholics Anonymous) are aimed at increasing the alcoholic's ability or willpower to withstand the drive for alcohol. The drive, however, is not weakened and the patient is told that he will remain an alcoholic, that is, a person with an overly strong alcohol-drinking response, for the rest of his life. These methods succeed in some alcoholics, but in most the time eventually comes when a momentary decrease in willpower causes a resumption of alcohol drinking and alcohol abuse.

Other treatments use punishment of various sorts (e.g., electric shock, disulfiram reactions, loss of a job) to try to stop alcohol drinking. Punishment is, however, a poor method for changing behaviour and has many limitations. In particular, it is ineffective when positive reinforcement is still being received for the same response that is punished. Since the treatments that punish alcohol drinking do not block the positive reinforcement of the same response coming from alcohol in the brain, they should not be expected to be very effective.

A third type of treatment has been proposed. Alcohol and opiates appear to cause positive reinforcement largely through the same neuronal system in the brain. Consequently, opiates such as morphine or methadone might be able to satisfy the drive for alcohol and thus abolish alcohol drinking. This does indeed occur in rats and other animals, and there is evidence suggesting opiates could also succeed in making alcoholics stop drinking alcohol.

The treatment probably would, however, turn alcoholics into opiate addicts, which is, of course, not a good solution.

Instead of counteracting the drive for alcohol or temporarily satisfying it, a successful treatment for alcoholics should permanently weaken the alcohol-drinking response. Fortunately, there is a well-established method for weakening a learned response: "extinction." Extinction consists of having the response emitted repeatedly in the absence of positive reinforcement.

It is relatively simple to remove external sources of positive reinforcement, such as the food a rat gets for pressing a lever or even the social reinforcement a person sometimes gets for drinking alcohol. But much of the positive reinforcement for alcohol drinking is internal, from the rewarding effects of alcohol in the brain.

The results showing that alcohol and opiates share a common mechanism of reinforcement show how the internal positive reinforcement from alcohol might be blocked. Various substances, called opiate antagonists, are able to block the receptors for opiates and thus prevent the effects of, e.g., morphine. Furthermore, there is already evidence that the two most commonly used opiate antagonists, Naloxone and Naltrexone, do block positive reinforcement from alcohol. First, they block the stimulatory effect of alcohol, which is generally thought to be related to the euphoria and positive reinforcement. (Note: Sinclair avoids the term "pleasure"—not to be confused with "positive reinforcement.") Second, it has been shown that while they are in the body they reduce voluntary alcohol drinking and intragastric self-administration of alcohol by animals.

Naloxone and Naltrexone were originally intended for use in treating overdoses of opiates (like heroin or morphine). They have since been suggested for use against a wide variety of problems including respiratory failure, anorexia nervosa, bulimia, obesity, emesis and nausea, shock, severe itching, constipation, growth of neoplasms, and sexual impotence and frigidity. There have been many studies attempting to use Naloxone to reverse alcohol intoxication and especially the coma produced by very large amounts of alcohol; although the results have been mixed and there is still controversy as to whether Naloxone can antagonize severe alcohol

intoxication, it is important to note that none of these studies reported any bad effects from giving Naloxone in conjunction with alcohol. The doses of Naloxone have ranged between about 0.2 and 30 mg daily, and Naltrexone from about 20 to 300 mg daily. Other suggested uses are for the opiate antagonists in conjunction with other drugs, particularly, opiate agonists. For instance, U.S. Pat. No. 3,966,940 is for a compound containing narcotics or analgesics plus Naloxone to be given especially to narcotic addicts. In these cases the opiate or other drug is seen to be active pharmacological agent and the opiate antagonist is included to counteract some of its effects.

Continual treatment with opiate antagonists should reduce the alcohol intake of alcoholics: so long as the antagonist is in the body, the alcoholic should have little incentive for drinking because alcohol is not rewarding. This maintenance treatment, however, has the same problem found with other long-term deterrent treatments, such as that with disulfiram: how to keep the alcoholic on the medication. Since there is still a strong drive for alcohol, the alcoholic is likely to drop out of treatment and stop taking the antagonist so that he or she can satisfy the drive by drinking again.

However, combining the well-established procedure of extinction from psychology with the pharmacological findings that opiate antagonists block reinforcement from alcohol provides a new and much more promising way of treating alcoholism. Indeed, it provides what could be called the first true cure for alcoholism. After a relatively short period of treatment during which an opiate antagonist is employed in extinction therapy, the patient is no longer an alcoholic, because the overly-strong alcohol-drinking response that made the patient be an alcoholic is extinguished. The method for using this extinction procedure is the present invention.

The idea of using extinction therapy with an opiate antagonists for alcoholics has not been suggested previously. A similar idea with Naltrexone has, however, been suggested for opiate addicts (see P. F. Renault, NIDA Research Monograph No. 28, pp. 11–22, 1981), but extinction was not included in the design of the clini-

cal tests. The patients were simply detoxified, given Naltrexone or placebo, and released. There was no program for encouraging them to take opiates while under the influence of Naltrexone, as required for extinction. Consequently, the general result was what would likely happen also with such a Naltrexone maintenance program with alcoholics: a very large percentage of the addicts dropped out, stopped taking Naltrexone, and started taking opiates again. Of the total of 1005 subjects, however, "17 of the Naltrexone and 18 of the placebo subjects actually tested the blockade by using an opiate agonist" when Naltrexone would have been active, and "in this subsample, the Naltrexone patients had significantly fewer subsequent urines positive for methadone or morphine . . . The pattern in the Naltrexone group was to test once or twice with heroin or methadone and then to stop. The use of these drugs in the placebo group was sporadic during the entire course of treatment . . . [Also, on an analog craving scale] the Naltrexone patients reported significantly less craving toward the end of their evaluation than did the placebo-treated patients."

These results suggest that Naltrexone would be much more useful against opiate addiction if the addicts were given extinction sessions in which they were encouraged to use narcotics while the positive reinforcement was blocked. Furthermore, in relation to the present invention, by showing the extinction therapy with Naltrexone does work in humans, they support the hypothesis that it would reduce alcohol abuse and the craving for alcohol in alcoholics.

The example included here shows that the extinction procedure progressively decreases and eventually almost abolishes alcohol drinking by rats and that alcohol intake remains reduced long after all Naloxone should have been removed from the body. The high predictive validity of this animal model for indicating treatments that affect human alcohol consumption is discussed in Sinclair, British Journal of Addiction 82, 1213-1223 (1987).

SUMMARY OF THE INVENTION

The present invention contemplates a therapeutic method, utilizing the ability of opiate antagonists to block the positive reinforce-

ment from alcohol, to extinguish the alcohol-drinking response of alcoholics. The extinction program consists of numerous sessions in which the alcoholic has an opiate antagonist administered and then drinks alcohol.

The extinction procedure abolishes the alcoholic's strong alcohol-drinking response. Optimally, the patient's drive for alcohol is returned to the level present before he or she ever tasted alcohol. Thus, by definition, the patient is no longer an alcoholic.

Admittedly, the patient can relearn the alcohol-drinking response and become an alcoholic again, and relearning a response that has been extinguished occurs more rapidly than the initial acquisition. But with the first-hand knowledge of the consequences of the first acquisition of alcoholism, and with even a moderate level of willpower and outside support, most alcoholics will avoid making the same mistake twice.

This extinction procedure is a useful adjunct for various other methods of treating alcoholics, including punishment of alcohol drinking, procedures to improve willpower and social rehabilitation, and maintenance procedures for preventing renewed use of alcohol. These other methods have previously been very limited because of the continuing high drive for alcohol, but they should be much more effective once the alcohol-drinking response has been extinguished.

BRIEF DESCRIPTION OF THE DRAWINGS (Drawings not reprinted here)

FIG. 1 shows the apparent extinction of alcohol drinking in Long Evans and AA rats caused by 4 daily sessions of drinking alcohol after administration of Naloxone (mean.+-.standard error).
FIG. 2 shows the apparent extinction of alcohol drinking in Wistar rats caused by 4 daily sessions when Naloxone was administered 5 minutes before the hour of drinking alcohol ("paired Naloxone" group) and the lack of effect of Naloxone injected each day 3 hours after alcohol drinking ("unpaired Naloxone" group).
FIG. 3 shows the continued reduction in alcohol drinking by the Long Evans rats that had previously undergone extinction (see

FIG. 1) relative to their controls. No Naloxone was administered during this time, but the rats treated before with Naloxone drank significantly less than the controls on each of the first 7 days. They eventually returned to the control level, apparently because they were not made to abstain completely, did drink some alcohol, and thus relearned the alcohol-drinking response.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The extinction procedure can be used in all individuals classified by any of various means as alcoholics or alcohol abusers, except those in which the administration of an opiate antagonist is contraindicated and those suffering from korsakoff's syndrome. (The extinction procedure would probably work poorly in patients with korsakoff's syndrome.)

The patients can be interviewed to determine the alcoholic beverages they usually drink and the drinking situations in which they normally imbibe. They can then be informed that unlike most treatments, this one does not involve immediately becoming abstinent; instead, their alcohol drinking is to be slowly diminished over many days and only after that will they have to abstain. This procedure should also help to reduce the severity of withdrawal symptoms that are often produced by abrupt termination of alcohol intake.

The patient can then have an opiate antagonist administered shortly before beginning to drink an alcoholic beverage. Examples of opiate antagonists are Naloxone, Naltrexone, cyclazocine, diprenorphine, etazocine, levalorphan, metazocine, nalorphine, and their salts. The preferred opiate antagonists are Naloxone and Naltrexone, both of which have been approved for use in humans and have been shown to be free of severe side-effects. Neither is addicting or habit forming. The preferred dose range for Naloxone is 0.4 to 10 mg daily if taken by injection; the dose would have to be much larger if it were taken orally. The preferred dose range for Naltrexone is 50 to 200 mg daily. The dose administered in a specific case will depend upon the age and weight of the patient, the frequency of administration, and the route of administration, but must be sufficient to assure that the antagonist will be present

in sufficient quantities in the body throughout the entire evening of alcohol drinking. The antagonist could be administered in such a way that it is continually present in the body throughout the weeks of extinction therapy. Administration in a way that allows the patient to be free of pharmacologically-active quantities of the antagonist during the following day may be preferred, since it allows the alcoholic to eat food and drink non-alcoholic beverages during the daytime without interference from the antagonist. In the latter case, the patient will be under strict orders to confine all alcohol drinking to the evening hours after the antagonist has been administered.

Examples of routes of administration for the antagonist are injection, oral consumption in any form, transdermal administration, slow-release injection, nasal administration, sublingual administration, implantable drug delivery depots, and the like. A non-obtrusive, non-painful route would be preferred.

The first extinction session (i.e., drinking after administration of the antagonist) can be conducted under close supervision in the treatment center. It is important that later extinction sessions be conducted in the same drinking situations and with the same alcoholic beverages that the patient usually has employed in the past. The stimuli from these specific beverages and situations help to elicit somewhat separate alcohol-drinking responses for the individual. For example, in a particular alcoholic, the alcohol-drinking response of having beers while watching a game on TV may be at least partly independent of his responses of imbibing cocktails at a party or drinking whiskey at a bar. Each should be extinguished in order to assure the generality of the treatment. Although the alcoholic should be encouraged to drink in the extinction sessions, there should be no social reinforcement for doing so.

The number of extinction sessions required for each patient will depend upon the severity of his or her alcoholism and the number of specific drinking situations in which the alcohol-drinking response must be extinguished. The duration of the extinction program may therefore range from about 1 to 5 weeks.

Once the alcohol-drinking response has been sufficiently weakened, the final extinction sessions could be conducted along with

an element of punishment. Examples of punishment include mild electric shock when the alcohol is consumed, production of conditioned taste aversion from very large doses of alcohol with or without emetics, aversion therapy with an alcohol-sensitizing compound such as disulfiram or cyanamide, and the like.

After the final extinction session, the patient is told to abstain from all alcohol in the future. Various procedures can then be used to help ensure that the patient does in fact refrain from drinking alcohol. Such procedures include counselling, psychotherapy, family therapy, job therapy, joining Alcoholics Anonymous and the like. Efforts should also be taken to help the patient resume a normal productive life.

The patient should also be informed that although his or her alcohol-drinking response has been extinguished in the most frequently used drinking situations, it is possible that some have been missed. Consequently, if the patient anticipates or is experiencing a situation in which the response has not been extinguished, he or she should request additional extinction sessions involving this new situation. Alternatively, the patient could be kept on a maintenance program with continued administration of the opiate antagonist.

The present invention is further illustrated by the following example.

EXAMPLE

Extinction of alcohol drinking in 3 strains of rats.

Methods

The effects of drinking alcohol after being injected with Naloxone was studied in male rats of the AA strain developed for very high levels of alcohol drinking by selective breeding, in male Long Evans rats, and in male Wistar rats. In each case the animals first had several weeks of continual access to 10% (v/v) ethanol, plus food and water, during which time their alcohol drinking increased rapidly at first and eventually, after 3 to 4 weeks, approached a stable asymptotic level. They were then switched to having access to 10% alcohol for only 1 hour each day. After alcohol consump-

tion had stabilized, the rats of each strain were divided into groups matched for alcohol consumption during the last week of 1 hour daily access. One group in each strain was then injected with 10 mg/kg Naloxone hydrochloride 5 minutes before their hour of alcohol access for the next 4 days and a control group was injected with a similar volume of saline. There was a third group ("unpaired Naloxone") of Wistar rats that was injected with 10 mg/kg of Naloxone 3 hours after the end of their hour of alcohol access. The alcohol drinking during 1 hour on the day after the last inj ection was also recorded. The Long Evans rats were then switched back to continual access to alcohol and their intake measured for the next 13 days.

RESULTS

Administering Naloxone before providing access to alcohol progressively decreased alcohol drinking in all 3 strains (FIGS. 1 and 2). By the fourth day it was almost abolished in each strain, and the alcohol intake was significantly ($p<0.05$) lower than both the "pre" level (during the preceding week) and the level after the first Naloxone injection. The saline controls tended to increase their alcohol intake across days, perhaps due to the stress of injection, and drank significantly more alcohol than the rats given Naloxone before alcohol on at least the last 3 extinction days and on the "post" day, 24 hours after the last injection.

The subsequent alcohol drinking by the Long Evans rats is shown in FIG. 3. The rats subjected to extinction with Naloxone continued to drink significantly less alcohol than their saline controls on each day of the first week and then gradually returned to the control level. The latter is probably the result of relearning the alcohol-drinking response. Consistent with the common finding that a response is reacquired after extinction more rapidly than it is initially acquired, they took less than 2 weeks to reacquire the response, whereas naive Long Evans rats (i.e., ones that have never had alcohol before) require 3 to 4 weeks to reach this level of alcohol intake.

The Wistar rats given Naloxone 3 hours after alcohol drinking ("unpaired Naloxone") did not differ significantly from the con-

trols at any time (FIG. 2); their slightly lower intake can probably be attributed to the fact that, unlike the controls, they were not stressed by injection immediately before having access to alcohol. The "unpaired Naloxone" group drank significantly more alcohol than the "paired Naloxone" group on each of the 4 extinction days. This suggests that the reduction in alcohol drinking was caused specifically by the experience acquired while Naloxone was paired with alcohol drinking.

These results are all consistent with the hypothesis that consuming alcohol while Naloxone is present causes the alcohol-drinking response to be extinguished. Water intake and body weight were not reduced and there were no indications of any effects detrimental to the health of the animals.

APPENDIX D

World Health Organization Statement on the Safety and Efficacy of Naltrexone and Open Letter from Enoch Gordis, Director, NIAAA (1995)

Report of a joint consultation
organized by the Addiction
Research Foundation, Toronto, and
the WHO Programme on Substance
Abuse, Geneva

Toronto, Ontario, Canada, October 1995

WORLD HEALTH ORGANIZATION

At least one medication, naltrexone, has been identified as a safe and effective treatment for alcohol dependence . . . The demonstration of the efficacy of naltrexone and current studies underway examining related opiate antagonists (e.g., nalmefene) might serve to encourage pharmaceutical companies that medications development in this area is possible. Disulfiram, useful for some patients, might also be effective though its efficacy has been difficult to prove in controlled trials.