Nugget 15.2

Naltrexone aids primary care alcohol treatment

Findings Evidence is building that naltrexone is a valuable supplement for the kind of dependent drinkers and the kind of treatments suited to primary care settings.

Latest findings come from the large-scale US COMBINE study. 11 clinics screened nearly 5000 applicants. 1383 were alcohol dependent, achieved at least an initial four days without drinking, agreed to join the study, and were randomly allocated to one of nine combinations of abstinence-oriented pharmacological and psychosocial treatments. Though more socially integrated and less severely dependent than some UK alcohol treatment caseloads, they were heavy drinkers, averaging 21 UK units most days.

Over the 16 weeks of treatment, most were offered nine appointments intended to represent a medical management programme deliverable by non-specialist primary care staff given adequate training and supervision. Typically sessions lasted under 20 minutes and focused on assessing, monitoring and feeding back the medical consequences of the patient's drinking, and promoting adherence to pharmacotherapy. For half these patients, medical care was supplemented by typically 10 sessions of psychological therapy incorporating motivational interviewing, cognitive behavioural and 12-step elements. For both sets of patients, pharmacotherapy consisted of placebo pills, acamprosate, naltrexone, or both medications.

The key question was how far the extra therapies improved on the study's most basic intervention – medical management with inactive placebo pills. Adding psychological therapy improved drinking outcomes to the point where medication failed to create further improvements. But roughly the same gains resulted from adding naltrexone, even without psychological therapy. These were the only supplements which created significant gains. Combining them and even also adding acamprosate did not further improve outcomes, and acamprosate alone did not augment outcomes from the basic intervention. For example, across the 16 weeks of

treatment, 58% of patients receiving basic care achieved a "good clinical outcome" – drinking at most moderately with few adverse consequences – compared to 71–78% when either naltrexone or psychological therapy were added. Abstinence and relapse outcomes followed the same pattern as did outcomes a year after treatment, though by this time the differences had faded to the point where none were statistically significant.

In context For these relatively stable and compliant patients, well structured but straightforward medical care plus naltrexone (in this case, 100mg a day) seems at least as likely to achieve good outcomes as specialist psychological therapy. A similar message emerged from another US study which used the more typical 50mg a day dose: with naltrexone, primary care-style consultations were as effective as specialist cognitive-behavioural therapy; without the drug, cognitive-behavioural therapy was the more effective option.

Other studies have also found naltrexone effective in caseloads of the kind who might be treated in primary care, including one in which non-specialist nurses (the main therapists in the featured study) delivered both medication and counselling. The featured study also confirms findings that acamprosate plus naltrexone at best only marginally betters naltrexone alone, which is generally more effective than acamprosate alone.

Seemingly contradicting the featured study, several studies have found that naltrexone improves outcomes from cognitive-behavioural therapy. However, none compared this combination against naltrexone plus a systematic, compliance-promoting medical management programme.

Practice implications Naltrexone can be a valuable supplement to the medical counselling (by GPs or nurses) of dependent drinkers of the kind who might be treated in primary care, especially when specialist alcohol therapy is refused or unavailable. It is likely to be more effective than acamprosate, though more limited in its application due to contraindications and side-effects. The researchers stress the importance of the content (motivational support, compliance management, and education) and extent of the medical consultations accompanying the drugs. Though manageable in primary care, this is both more structured and more extensive than typical primary care approaches. In terms of which patients are suitable, level of consumption seems less important than whether they have retained sufficient stability to comply with treatment and are not so multiply problematic that more intensive care is required.

Featured studies Anton R.F. *et al*. "Combined pharmacotherapies and behavioral interventions for alcohol dependence. The COMBINE Study: a randomized controlled trial." *Journal of the American Medical Association*: 2006, 295, p. 2003–2017 AC Order manuals at http://pubs.niaaa.nih.gov/publications/COMBINE.htm.

Contacts Raymond Anton, Center for Drug and Alcohol Programs, Medical University of South Carolina, 67 President Street, PO Box 250861, Charleston, SC 29425, USA.

Nuggets **13.5 12.1 11.4 9.8 7.2 5.1**

Appendix to Nugget 15.2

NB This appendix is not nor is it intended to be a comprehensive review of the literature but to be sufficient to support the statements made in the main text. It consists of the uncut and referenced text used for the main entry, extracts from prior Findings commentaries, and abstracts and notes on other relevant studies.

Uncut and referenced text

Findings

Evidence is building that naltrexone can be a valuable supplement to the treatment dependent drinkers with moderately severe problems might receive in primary care settings.

Latest findings come from the large-scale US COMBINE study.[1] 11 clinics screened nearly 5000 applicants who had answered ads or been referred by their clinicians. 1383 were diagnosed as alcohol dependent, achieved an initial four days without drinking, agreed to join the study, and were randomly allocated to one of nine combinations of abstinence-oriented pharmacological and psychosocial treatments. Though more socially stable and less severely dependent than some UK alcohol treatment caseloads, they were very heavy drinkers, averaging 21 UK units most days.

Over the 16 weeks of treatment, most patients were offered nine consultations intended to represent a structured medical management regime deliverable by non-specialist primary care staff (in this case, mainly nurses) given training and supervision. Typically sessions lasted under 20 minutes. The focus of the was on assessing and continuing to monitor the medical consequences of the patient's drinking, feeding this back with warmth but also with authority, and facilitating adherence to pharmacotherapy. For half these patients, medical care was supplemented by up to 20 specialist sessions (though typically just 10 sessions were delivered) of psychological therapy based on motivational interviewing and cognitive behavioural therapy. For both sets of patients, pharmacotherapy consisted either of placebo pills only, acamprosate, naltrexone, or both acamprosate and naltrexone.

The key questions are how far the extra therapies improved on the study's most basic level of care – medical management with inactive placebo pills. Supplementing this with psychological therapy improved drinking outcomes to the point where drug therapies of whatever kind failed to create further improvements. But roughly the same degree of improvement was achieved when naltrexone was added to basic care, even without psychological therapy. These were the only supplements which created significant gains. Combining the two did not further improve outcomes and acamprosate failed to add to the outcomes achieved by basic care. For example, across the 16 weeks of treatment, 58% of patients receiving basic care achieved a "good clinical outcome" – drinking at most moderately with few adverse consequences. achieved a good outcome compared to 71–78% when either naltrexone or psychological therapy were added. Abstinence outcomes and relapse to heavy drinking followed the same pattern as did outcomes a year after treatment ended, though by this time the differences between the treatments had faded to the point where none were statistically significant.

One of the study's groups received no medical management or pills as part of the study but only the psychological therapy. During treatment, drinking outcomes suggested that this was slightly less effective than medical management plus naltrexone, but post-treatment outcomes were broadly equivalent.

In context

The message of the study appears to be that for these kinds of relatively stable and compliant patients (they took over 80% of the eight pills a day they were prescribed), well structured but fairly straightforward medical care plus naltrexone (in this case, 100mg a day) is at least as likely to achieve good outcomes as specialist psychological therapy. A similar message emerged from another US study which unlike the featured study used the typical 50mg a day dose.[2] It too found that as long as naltrexone was prescribed, primary care-style consultations were as effective as specialist cognitive-behavioural therapy in initiating and sustaining recovery from alcohol dependence. Without the drug, cognitive-behavioural therapy was the more effective option. In both studies the systematic focus on promoting adherence to pharmacotherapy allied with a relatively socially integrated caseload probably accounted for the fact that generally patients took the pills they were prescribed, a prerequisite of effective pharmacotherapy.

Several other studies have also found naltrexone effective in alcohol dependent populations of the kind which might be treated in primary care.[3 4 5 6] Among them was a US study in which non-specialist nurses delivered both the medication and a systematic, primary care-style counselling programme.[7] The study also confirms earlier less extensive studies which found the combination of acamprosate and naltrexone at best only marginally more effective than naltrexone alone.[8 9 10] These and other studies which have compared the drugs prescribed singly have found naltrexone the more effective of the two.[11 12 13]

Seemingly contradicting the featured study, several studies have found outcomes from cognitive-behavioural therapy were improved by naltrexone.[14 15 16 17 18 19] However, none compared this combination with naltrexone plus the kind of systematic, compliance-promoting medical management programme used in the featured study.

In the major British trial of naltrexone, across a more multiply problematic alcohol-clinic caseload, the drug was only marginally more effective than placebo, but this was because most patients failed to take it as directed.[20] Among those who did comply with therapy, naltrexone halved the amount drunk after a return to drinking. Though a similar UK trial of acamprosate found it ineffective even among patients who started taking their pills,[21] limitations of the study and positive experiences elsewhere[22 23] mean that the drug should not be dismissed.

Practice implications

Naltrexone can be considered as a supplement to the medical counselling of dependent drinkers of the kind who might be treated in primary settings, especially when specialist alcohol therapy is unavailable or the patient prefers to be treated by their family doctor's practice. It is likely to be more effective than acamprosate though somewhat more limited in its application due to contraindications and side-effects. The quantity the patient drinks seems less important then whether they

have retained sufficient stability to comply with treatment and are not so multiply problematic that more intensive care is required. The main clinical task is to get patients to take the drug. Systematic approaches suitable for use in primary have now been developed to aid this process.[24]

The researchers stress[25] the importance of the content (motivational support, compliance management, and educational component) and extent of the medical consultations accompanying the drugs. Though manageable in primary care, this is both more structured and more extensive than typical primary care approaches.

Although licensed in North America and several European countries, naltrexone is not licensed in the UK for treating alcohol dependence, though because it is licensed for treating opiate dependence it is readily available. Some centres are using it, on the basis of the physician's own responsibility.

About the study

Patients excluded from the study included those also diagnosed as abusing drugs other than cannabis and tobacco, with severe medical/psychiatric conditions including abnormal liver function, seeking or continuing in additional alcohol treatment, recently in over a week's inpatient treatment or being prescribed the study's medications, or unable to provide an associate close enough to them to help locate them for follow-up.[26] Together with the initial requirement of abstinence and the recruitment methods, the effect would have been to exclude the multiply problematic drinkers, the socially isolated, those with a long and damaging history of very heavy drinking, or whose current drinking had recently required intensive or continuing intervention or was such that the patients were seeking further help. Very few had or required medically supervised detoxification before joining the study, just under half were married and about three quarters were employed. The abstinence requirement would also have excluded patients not prepared or able to interrupt their drinking prior to treatment starting. Despite these ceilings on severity the sample as a whole were drinking very heavily – on about three-quarters of days in the last month, an average of about 21 UK units each.

The need to take placebo as well as 'real' pills meant patients were asked to take eight a day when in normal practice just one or two would have sufficed. Still typically nearly all the pills were taken, a testament to the therapies but also indicative of a motivated and relatively compliant caseload. The structure, training and supervision afforded the clinicians delivering the medical management regime, and their location at prestigious academic and clinical centres, may have raised performance above that to be expected in normal practice, and at typically 17 minutes, the sessions after the initial one were longer than most GP consultations in Britain.[27] But also the regime was in some ways hobbled by the ban on supplementary interventions or the use of motivational interviewing or cognitive-behavioural techniques.

The specialist therapy's greatest limitation (and perhaps to a lesser extent the medical management regime also) was possibly the choice of abstinence as the sole treatment goal. While not forced on patients, this did exclude interventions aimed at supporting moderate drinking for which cognitive behavioural interventions have been developed,[28] yet the great majority of the patients returned to drinking at some

stage[29] in the study.

The same limitation would have tended to limit the degree to which naltrexone could exert its most prominent effect, preventing lapses becoming relapses to heavy drinking rather than preventing drinking as such.[30 31 32 33 34 35 36 37 38 39 40 41 42 43] Also naltrexone boosts psychosocial treatments most noticeably for patients with an otherwise poor prognosis, including some whom the featured study did or would have tended to exclude (eg, abusing other drugs, high craving, still drinking at treatment entry).[44 45 46 47 48 49 50 51] Both these factors might have been led to an underestimate the potential impact of the drug.

Side effects

Naltrexone's side-effects trouble up to 15%[52 53] of patients and threaten compliance. Nausea seems the most consistently and frequently reported and together with the number of symptoms[54 55 56] encourages patients to skip medication and some to terminate treatment prematurely especially in the early stages.[57] Even among polydrug users and patients with serious physical and psychiatric illness including medicated depression,[58] adverse effects at recommended doses, though unpleasant, have not been found to be dangerous.[59]

On the basis of preliminary indications that effectiveness might increase with dose, and to provide some cover for missed doses,[60] the featured study used 100mg daily doses, twice the usual amount. Another US study also prescribed this dosage.[61] 15% of naltrexone patients had to reduce the dose typically for just under a month due to adverse effects which matched the side effect profile of the drug, primarily nausea. This was also the case for about 7% of the placebo patients. In the featured study full dosage was built up to over a week rather than initiated abruptly as seems to have been the case in the earlier study. Due to adverse effects 12% of the naltrexone patients were given ongoing or recurrent dose reductions (how many had short-term one-off reductions is not reported), just 4% more than on placebo. The figure for naltrexone plus acamprosate patients was 21%. 12 of the 309 naltrexone patients withdrew from the study due to adverse effects emerging during treatment. A third experienced nausea, 13% more than on placebo. Again this was more common when both drugs were prescribed (42%). Loss of appetite (21%) and somnolence (37%) were among the other symptoms about 10% more common than on placebo. Six naltrexone patients had signs of abnormal liver function (there were none on placebo) which generally resolved once medication was stopped.

Meta-analyses

Two meta-analyses which combined findings from the most rigorous trials have provided reassurance that acamprosate and naltrexone help prevent relapse after alcohol detoxification.

The analyses included trials in which alcoholics had been randomised to a placebo or to one of the two drugs. Study 1 covered only naltrexone,[62] study 2 both drugs.[63] Typically, the pills supplemented psychosocial therapy. Results were analysed only for the duration of the treatments.

Despite differences in the trials and data analysed, for naltrexone the results were similar: compared to placebo, a statistically significant 14% (1) or 16% (2) fewer patients relapsed to heavy drinking and 10% (1) or 12% (2) more did not drink at all.

Findings on alcohol consumption were less consistent. In study 1 the percentage of days on which patients drank was slightly (3%) less on naltrexone, in study 2 much less (19%) but with significant variation across trials. The reduction in the amount consumed on a drinking day was very small (1, 1%) or insignificant (2). Nevertheless, study 1 concluded that naltrexone reduces average alcohol consumption. It also found no evidence that more naltrexone patients suffered adverse effects severe enough to prompt treatment termination, though certain effects such as gastrointestinal complaints were more common. In line with these findings, study 2 found no evidence that retention in treatment was worse on naltrexone.

In both analyses the issue addressed was not whether on their own naltrexone or acamprosate are effective but whether they add value to psychosocial relapse prevention therapy. The answer was yes, but study 1 observed that the only study to address longer term naltrexone outcomes (see below) found that the benefits did not persist once treatment was stopped. Neither analysis was able to document whether the changes in drinking they found translated into fewer patients relapsing to dependent (as opposed to heavy) drinking or to fewer alcohol-related ill-effects, though such benefits can be expected to accrue from long-term naltrexone treatment (which at least up to a year continues to be efficacious[64]) just as they can be expected to accrue from acamprosate.[65 66]

A later review and meta-analysis of studies since 1990 found that naltrexone significantly reduced the rate of relapse both during and after the prescribing period but did not improve rates of complete abstinence.[67] Also reduced was alcohol consumption overall and in terms of the number of drinking days and the amount drunk on each of those days. The authors comment that unlike acamprosate, there are indications that naltrexone does not require an initial period of abstinence or detoxification and that it is best suited to controlled drinking programmes. Nausea was the most common side-effect and the one which prompted most treatment terminations.

The following is the abstract of a meta-analysis of acamprosate in alcohol treatment.[68] “A number of clinical trials have been undertaken to determine the efficacy of acamprosate in the maintenance of abstinence in alcohol-dependent individuals. However, the reported differences in patient populations, treatment duration, and study endpoints make comparisons difficult. An assessment of the efficacy of treatment with acamprosate was, therefore, undertaken using meta-analytical techniques. METHODS: All randomized, placebo-controlled trials (RCTs) that fulfilled predetermined criteria were identified using (1) a language unrestricted search of 10 electronic databases; (2) a manual search of relevant journals, symposia, and conference proceedings; (3) cross-referencing of all identified publications; (4) personal communications with investigators; and (5) scrutiny of Merck-Sante's internal reports of all European trials. Study quality was assessed, independently, by three blinded workers. Key outcome data were identified; some outcome variables were recalculated to ensure consistency across trials. The primary outcome measure was continuous abstinence at 6 months; abstinence rates were determined by estimating Relative Benefit (RB). RESULTS: A total of 19 published 1 unpublished RCTs were identified that fulfilled the selection criteria; 3 were excluded because the documentation available was

insufficient to allow adequate assessment. The remaining 17 studies, which included 4087 individuals, 53% of whom received active drug, were of good quality and were otherwise reasonably comparable. There was no evidence of publication bias. Continuous abstinence rates at 6 months were significantly higher in the acamprosate-treated patients (acamprosate, 36.1%; placebo, 23.4%; RB, 1.47; [95% confidence intervals (CI): 1.29-1.69]; $p < 0.001$). This effect was observed independently of the method used for assigning missing data. The effect sizes in abstinent rates at 3, 6, and 12 months were 1.33, 1.50, and 1.95, respectively. At 12 months, the overall pooled difference in success rates between acamprosate and placebo was 13.3% (95% CI, 7.8-18.7%; number needed to treat, 7.5). Acamprosate also had a modest but significant beneficial effect on retention (6.01%; [95% CI, 2.90-8.82]; $p = 0.0106$). CONCLUSION: Acamprosate has a significant beneficial effect in enhancing abstinence in recently detoxified, alcohol-dependent individuals."

Is naltrexone suited to CBT?

A recent meta-analysis observed that the benefits of naltrexone were noticeable (if not always to the point of statistical significance) with varied patient groups and in alliance with different forms of psychosocial therapy.[69] But it was also the case that the two studies with the most consistently positive results (six significant outcomes in favour of naltrexone) were also the ones with the highest rates of employment (about 80%) among the naltrexone patients and the only ones which employed cognitive-behavioural therapies. In the remaining five studies just one out of 16 comparisons was statistically significant. Similarly, in another meta-analysis[70] these two studies accounted for half of all the statistically significant outcome differences[71] across the nine studies included in the naltrexone analysis.

The first was a major US study in which abstinence was significantly better on naltrexone but even greater effects were seen in terms of the amount of alcohol drunk.[72] This study also randomised subjects to coping skills or supportive therapy. In both the objective was abstinence but the coping skills option included strategies for preventing lapses becoming relapses. During treatment, continuous abstinence was most common among naltrexone patients in supportive therapy. Naltrexone in alliance with coping skills did not significantly elevate abstinence rates compared to placebo. However, regardless of the therapy it accompanied, patients on naltrexone were two-thirds less likely to relapse into excessive drinking. Among patients who did drink (the majority), relapse to heavy drinking was far less common when naltrexone was allied with coping skills therapy than when it was not, or when placebo was allied with coping skills. It seemed that coping skills therapy only worked better than supportive when it was supported by the urge-reducing properties of naltrexone and when patients had given themselves a chance to experience this by trying alcohol. Over the six months after treatment ended naltrexone maintained a significant advantage in terms of relapse to heavy, abusive or dependent drinking, most noticeably when it had been allied with coping skills therapy. For example, 43% of the coping skills/naltrexone group had relapsed to heavy drinking compared to over three-quarters of placebo patients. However, by the end of the six months the impact on heavy drinking had faded into insignificance.[73] Nearly all the placebo patients who drank during the follow-up period also relapsed to heavy drinking[74] but fewer of the patients who had been on

naltrexone, especially when this had been allied to coping skills therapy.[75] Since they were no longer taking the pills this result is suggestive[76] of a learned coping response to drinking aided by the reward-diminishing effect of naltrexone. In this study the non-directive supportive therapy was not specifically geared to compliance with pharmacotherapy and seems to have been a minimal unstructured counselling approach not comparable with the featured study's medical management programme.

The second study was also conducted in the USA and again, though naltrexone improved outcomes from cognitive-behavioural therapy, the study did not also combine the drug with a systematic medical management approach aimed at maintaining compliance.[77] Abstract follows: "OBJECTIVE: The opiate antagonist drug naltrexone has been shown in a few studies with limited sample sizes to be effective when combined with psychosocial therapies for the treatment of alcohol dependence. The goal of this study was to obtain additional information regarding its efficacy in pertinent alcoholic populations and with a well-defined therapy. METHOD: In this study, 131 recently abstinent alcohol-dependent outpatients were treated with 12 weekly sessions of manual-guided cognitive behavioral therapy and either 50 mg/day of naltrexone (N = 68) or placebo (N = 63) (with riboflavin added as a marker of compliance) in a double-blind, randomized clinical trial. Alcohol consumption, craving, adverse events, and urinary riboflavin levels were assessed weekly. Levels of blood markers of alcohol abuse were also ascertained during the trial. RESULTS: The study completion, therapy participation, and medication compliance rates in the trial were high, with no differences between treatment groups. Naltrexone-treated subjects drank less, took longer to relapse, and had more time between relapses. They also exhibited more resistance to and control over alcohol-related thoughts and urges, as measured by a subscale of the Obsessive Compulsive Drinking Scale. Over the study period, 62% of the naltrexone group did not relapse into heavy drinking, in comparison with 40% of the placebo group. CONCLUSIONS: Motivated individuals with moderate alcohol dependence can be treated with greater effectiveness when naltrexone is used in conjunction with weekly outpatient cognitive behavioral therapy. Naltrexone increases control over alcohol urges and improves cognitive resistance to thoughts about drinking. Thus, the therapeutic effects of cognitive behavioral therapy and naltrexone may be synergistic."

A Finnish study allocated 121 alcohol dependent patients seeking outpatient treatment in response to advertisements to naltrexone or placebo each allied either with abstinence-oriented supportive group therapy or cognitive-based group therapy aimed at preventing 'slips' proceeding to heavy drinking relapses.[78] [79] [80] 55% of the 302 people invited to participate had refused. The drinkers all satisfied accepted criteria for alcohol dependence but were a relatively stable group. A stable living situation and availability of associates close enough to report on their drinking were inclusion criteria and people with severe medical or psychiatric conditions or other drug abuse were excluded. Nearly three-quarters of the resulting sample were married and living with their families, just 13% were unemployed, two-thirds had not previously been in alcohol treatment, and compliance and retention were high. There was no requirement on patients to be abstinent or to have undergone detoxification before therapy started, making this the first randomised controlled

trial to test naltrexone in currently drinking alcoholics.[81] However, patients were visited one week before starting the trial and there was a one-week lead-in when all patients received the placebo; at the start of treatment few if any were drinking heavily. For the first 12 weeks of active medication patients took the drugs daily then for the next 20 weeks were instructed to use them 'as needed' when they feared being overcome by a strong desire to drink or when there was a risk of drinking. In terms of relapse to heavy drinking,[82] the naltrexone/coping skills combination significantly outperformed the other combinations. This was not because these patients took more naltrexone; when they could choose to take them or not they took fewer pills (about two a week) than the other groups and significantly fewer than patients on naltrexone and in abstinence therapy. Naltrexone made no difference to the impact of the abstinence-oriented therapy (about 1 in 10 avoided relapse) but transformed the coping skills therapy from a relatively ineffective approach (just 3% of coping patients on placebo did not relapse) to the most effective of the combinations tested (27% of coping patients on naltrexone did not relapse). Among these who did relapse they did so less frequently in the naltrexone/coping skills combination. 62% of all the patients in this group had at two or more relapses compared to 94% of the coping skills placebo and about 80% of the two groups in supportive therapy. In the last eight weeks of the study the tendency for coping skills/naltrexone patients to on average drink less became statistically significant; they drank about 29 units a week compared to about 40+ in the other groups. However, naltrexone did not delay a return to drinking or lead more patients to completely abstain. Adverse effects on naltrexone were no more numerous than when not on it either overall or in the coping skills group, but among patients in abstinence-oriented therapy naltrexone did was associated with more side-effects. Compared to trials in which prior detoxification had been required, side-effects were no more prominent. Neither in this trial nor in other studies in which naltrexone has been given to non-detoxified alcoholics have any safety problems been recorded.[83]

A Swedish study has found that during treatment patients randomly allocated for 24 weeks to cognitive behavioural therapy plus naltrexone did better on every one of 11 self-report and biological indicators of drinking amount and problems than patients not prescribed naltrexone or prescribed it but with supportive therapy of the kind normally provided in addiction treatment centres.[84] However, the only statistically significant naltrexone-treatment interaction was the survival time to the first day of heavy drinking, 57 days for the CBT/naltrexone combination and around 20 days for the other three permutations. When the treatment period was combined with a five and half month follow-up CBT/naltrexone patients were found to be persistently and significantly less likely to drink heavily.[85] In this study patients tended to return to drinking fairly quickly giving the naltrexone patients a chance to experience the diminished rewards from drinking due to the drug, presumably decreasing the incentive to drink more and more often whole CBT gave them the tools to actualise this in reduced drinking. As in most such studies patients were excluded if they had severe social or psychiatric or medical problems and most were employed and married. Rather than being continuous drinkers they drank on about 6 out of 10 days before treatment but on each of those days tended to drink very heavily, averaging about 19 UK units. To enter the study patients had to have been abstinent for at least 14 days, a condition which would presumably exclude many

daily drinkers.

An Australian study found that during 12 weeks of treatment, drinking outcomes from cognitive behavioural therapy were improved by naltrexone, though not health-related quality of life.[86] Note that patients chose to have naltrexone or not. Following is the abstract. "Objectives: To examine the health-related quality of life of alcohol-dependent patients across a 12-week cognitive behaviour treatment (CBT)program and identify whether the patient selection of the anticraving medication naltrexone further enhanced these outcomes. Method: One hundred and thirty-six consecutive alcohol-dependent subjects voluntarily participated and were offered naltrexone, of which 73 (54%)participants declined medication. A matched design was used. Of the 136 subjects,86 (43 naltrexone and CBT;43 CBT only) could be individually matched (blind to outcome measures)for gender, age, prior alcohol detoxification and dependence severity. Measures of health status and mental health wellbeing included the Rand Corporation Medical Outcomes Short Form 36 Health Survey (SF-36)and the General Health Questionnaire (GHQ-28). Results: Pre-treatment,all had SF-36 and GHQ-28 scores markedly below national norms. Post-treatment,significant improvement in seven of the eight SF-36 subscales and all of the GHQ-28 subscales occurred, approximating national normative levels. Patients in the CBT +naltrexone group were significantly more likely to have increased days abstinent (p =0.002)and to complete the program abstinent (p =0.051). The adjunctive use of naltrexone did not provide additional benefit as reflected in SF-36 and GHQ-28 scores, beyond CBT alone. Conclusions: Patients who completed the CBT-based treatment program reported significant improvements in self-reported health status (SF-36)and wellbeing (GHQ-28). The adjunctive use of naltrexone demonstrated no additional improvement in these measures."

British studies

A British study has provided the largest test to date of naltrexone in the treatment of alcohol dependence. In conditions typical of NHS alcohol treatment centres, it confirmed that taken as directed the drug reduces alcohol consumption.[87]

At six centres 175 patients recently abstinent from alcohol and either receiving or about to receive outpatient treatment were randomised also to receive 50mg daily of naltrexone for 12 weeks or an identical placebo pill. All but 11 started taking the pills and were included in the analysis. Typically they were men in their late 30s and early 40s and most were not in a stable relationship or in full time work. Before treatment, on average they were drinking over 16 units[88] of alcohol a day.

Measures taken before treatment and then every two weeks showed that naltrexone did not delay a return to drinking or to heavy drinking but it did (non-significantly) tend to reduce the amount drunk in the last month of the study, a trend partially reflected in biochemical markers of heavy drinking. Patients on naltrexone also experienced significantly less craving for alcohol and by the end of the study nearly two-thirds were judged by their doctors to have improved, about 20% more than in the placebo group.

These results assumed that the nearly 60% of patients who were lost to the study (only a minority seem to have 'dropped out' in the sense of not complying with

treatment or simply not turning up) had resumed heavy drinking. When the analysis was confined to the 70 patients who completed the study and had largely complied with the treatment, there was still no evidence that naltrexone had delayed a return to drinking, but the reduction in the amount subsequently drunk (on average half that in the placebo group) was statistically significant, corroborated by improved biochemical markers. Other results were similar to that seen in the full sample.

Possible side-effects seen more often in the naltrexone group included nausea and pain but adverse effects did not result in noticeably more naltrexone patients having to terminate treatment. However, the study excluded patients with serious physical illness, medicated psychiatric conditions, or who also abused other drugs.

The study's strengths are that it ironed out the idiosyncrasies of treatment at a single unit and enabled an estimate of the added value to be expected from naltrexone as a supplement to routine NHS practice. It confirmed earlier work recording no delay in a return to drinking but a worthwhile reduction in the amount subsequently drunk while patients were taking naltrexone. Previous studies have also recorded that fewer patients relapsed to heavy drinking during the study period.[89]

A different treatment regime might have further improved outcomes. Naltrexone was introduced only after patients had been abstinent for on average 10-11 days. However, the drug seems to work mainly by reducing the experienced rewards of drinking,[90 91] probably by blocking the relevant neural pathways, a mechanism which can only be activated if drinking occurs. Consistent with this theory, the featured study found that drinking was not delayed but (presumably because they 'got less out of it' so were mot tempted to lose control of their drinking) patients on naltrexone went on to drink less than those receiving placebo pills.

The major trial of acamprosate in Britain found no added benefits from the drug.[92] At least a week after detoxification at one of 20 specialised British treatment units, the study randomised 581 alcohol dependent outpatients either to acamprosate three times a day or to identical placebo tablets taken for six months. The medication was additional to usual treatment. High drop-out and non-compliance rates meant that just a third of the sample completed the study and by the end under 30% were taking at least 90% of their tablets. Subjects lost to follow-up were assumed to have relapsed. Acamprosate did not improve abstinence rates among the patients as a whole, nor in certain types of patients thought to respond well to the drug. Even among those who at least took the tablets for the first two weeks there was no added benefit. Whether taking acamprosate or placebo, both groups drank on most days. Neither did acamprosate prevent relapse to heavy regular or binge drinking (over 80% of each group[93]), though there was evidence of reduced craving and anxiety. About a month after medication ended researchers interviewed 385 of the 581 patients. Abstinence rates had remained similar to those seen at the end of the medication period. 21% of patients from the two main centres had died. In contrast to some earlier research which provided high quality care characteristic of academic centres,[94] apart from the tablets patients received 'treatment as usual'. For many of the patients this seems to have been insufficient to prevent a high rate of pre-medication relapse and subsequent drop-out, making it much harder for acamprosate to demonstrate its worth. 32%[95] of patients did not remain abstinent

for the week before being randomised into the study, a requirement in the featured study. Outcomes in the British study may have suffered from not giving the drug in the immediate post-withdrawal period (it was commenced on average 24 days after the start of detoxification, with an interval of over 5 weeks in some patients), when theory suggests its effectiveness should be at its height. Like most previous studies,[96] the UK study did not report on consumption levels but only on whether patients drank or exceeded certain limits. Had this been reported, it might have found that relapses were less frequent and severe on acamprosate than on placebo.

Studies of primary care approaches or populations potentially treatable in primary care settings

Indications that naltrexone could aid the treatment of dependent drinkers in primary care settings have come from a US trial which tested the drug's efficacy allied with the kind of consultations normally undertaken by GPs and practice nurses.[97]

As a first stage the study randomly allocated 197[98] alcohol dependent patients to 10 weeks of daily naltrexone plus either weekly cognitive-behavioural therapy by experienced psychologists and social workers, of the kind normally delivered in specialist clinics, or briefer (and three fewer) primary care-type consultations. During these, primary care medical assistants and nurses reviewed the patient's history and progress and dealt with medical and treatment adherence issues. In this relatively low-severity population (eg, over three-quarters were employed) for whom frequent heavy rather than continuous drinking seemed the norm, two-thirds completed treatment and most did well. By the end 85% drank heavily on no more than two days out of 28 (the study's criterion for a good response) and on each drinking day they consumed on average just six UK units compared to 16 before treatment. The one significant difference between the two forms of support was that cognitive-behavioural patients were more able to sustain abstinence; over the last four weeks 61%[99] did not drink at all compared to 46%[100] of the primary care patients. Overall, this stage of the study established that allied with naltrexone, a primary care management approach could produce short-term results as good as more specialist approaches.

The next stage of the study aimed to test whether continuing with naltrexone was required to sustain the initial benefits. Broadly, the answer was 'yes' for the primary care group but 'no' for cognitive-behavioural patients. In this stage, 'good responders' from the earlier stage[101] continued for 24 weeks with less intensive 'maintenance' forms of their original therapeutic approaches, but were randomly allocated to either continue with naltrexone or to switch to a placebo. Naltrexone did tend to help cognitive-behavioural patients avoid heavy drinking and sustain abstinence but not sufficiently to reach statistical significance. Even without the drug, patients avoided drink on over 9 out of 10 days, 70% maintained a good treatment response, and when they did 'lapse', they drank only about two UK units. In contrast, outcomes this good were sustained by the primary care group only when still being prescribed naltrexone. Without this, outcomes tended to fall off over the 24 weeks until by the end placebo patients were drinking on 17% more days than those still on naltrexone and drank twice as much when they did drink.

The study reinforces earlier work indicating that primary care approaches and

practitioners can provide a platform for effective naltrexone-based treatment to dependent patients of the kind (non-continuous drinkers not requiring intensive social and psychiatric inputs or detoxification) seen and potentially managed in primary care. The caveats relate mainly to a possibly atypical set of patients,[102] the setting (consultations all took place in a research clinic), and the fact that both therapies aimed at abstinence[103] yet naltrexone's strength is in promoting controlled drinking.

Two Spanish studies[104 105] tested naltrexone on relatively socially integrated and not severely dependent drinkers without significant comorbidity, potentially extending its role from alcoholics seeking treatment at specialist clinics to problem drinkers identified in other settings such as primary care. In the first, of 214 male primary care patients referred to the research project, 74 dependent drinkers were assessed as suitable for a controlled drinking programme (not so severely dependent as to require detoxification and free of liver, neurological and psychiatric illness).[106] The 60 who could attend began three months of weekly individual therapy. For a randomly selected half this was supplemented by 50mg of naltrexone daily. Typically patients were quite young (30 years of age) and moderately dependent, drinking fairly heavily when they did drink (average 12 UK units of alcohol) but not drinking every day. Abstinence was advised for the first month of therapy. All but three achieved this and none drank heavily. Over the next two months the aim was to apply strategies and skills learned in the first month to moderate drinking rather than to sustain abstinence. During the remaining year of the study they were seen monthly by their therapists, and quarterly by researchers to assess outcomes. In either group only a handful drank heavily (three or more units a day) during the three months of weekly therapy and though the naltrexone patients reported less desire to drink, this was reflected only in a non-significant trend to actually drink less. However, in the following year patients who had been on naltrexone not only continued to crave alcohol less but also drank significantly less. Overall about four in ten resumed heavy drinking but those who had taken naltrexone did so on fewer days (on average just over once a week compared to twice a week) and consumed less (averaging under two units a week compared to over four). In the study it seems that the patients were referred to a hospital addiction centre and treated there by specialist staff rather than at the primary care centres from which they were referred. Patients and therapists (but not researchers) knew whether the patients were taking naltrexone. The control group were not given placebo pills. This means that the study more closely approximates normal treatment conditions than 'blind' placebo-controlled studies, including the possibility that patients prescribed naltrexone responded well partly because of their and their therapists' expectations of the drug rather than due to its pharmacological effects. Compared to acamprosate, the centre which hosted the study has found naltrexone effective in delaying and preventing relapse to heavy drinking among its more (but typically still not severely dependent) male detoxification patients.[107]

Three other small-scale naltrexone studies have also targeted heavy or problem drinkers rather than those severely dependent. The first trialed naltrexone as an adjunct to a brief motivational intervention,[108] the second as an adjunct to four sessions of relapse prevention skills training.[109] In both studies the therapy/drug combination had a marked effect on reducing heavy drinking, one greater than that

seen in other studies which did not supplement therapy with naltrexone. However, neither study incorporated a non-naltrexone control group. The third study randomised 38 non-dependent heavy drinkers who responded to media adverts to brief counselling (two 30 minute sessions which included strategies for coping with high-risk situations) supplemented by 50mg naltrexone daily for 10 weeks or placebo pills.[110] The last research follow-up took place 22 weeks after treatment started. On all consumption measures including number of drinks on a drinking day the placebo group did better. The difference was apparently not due to greater drop-out from the naltrexone treatment due to side-effects. In this study subjects did not meet clinical criteria for alcohol dependence, scored on average below the AUDIT indication for alcohol dependence,[111] were not drinking very intensively (about 76g on drinking days), and had not been referred from a clinical setting. In this group naltrexone did not reduce craving for alcohol compared to placebo (in fact, the reverse). However, the follow up period may have been to short to register any benefits from naltrexone.

Normally naltrexone trials have used the drug to supplement intensive therapies delivered by specially trained addiction specialists. A US study instead used nurses without specialist training to deliver both the medication and the therapy, a weekly session lasting up to half an hour which consisted of feedback on the patient's background and functioning as they related to their drinking, empathic listening and advice on strategies for achieving their treatment goals, described as a primary care treatment model.[112] Unusually, patients randomised to naltrexone in this study were prescribed 100mg daily, twice the normal dose, a dose which 1 in 7 had to reduce due to side effects, primarily nausea. All subjects had been abstinent for at least three days before entering the trial. Before treatment they had drunk at least 9 UK units of alcohol on nearly two-thirds of days and ASI scores clustered around a level indicating high alcohol problem severity. Over 80% of patients completed treatment. During the 12 weeks when the drug was being prescribed, naltrexone patients relapsed to heavy drinking on fewer days (5% v 9%) and were less likely to consistently drink heavily over a two-week period. Naltrexone was most effective in patients with high levels of craving for alcohol before medication started. At low to moderate levels of craving it did not reduce the number of days of heavy drinking.

Other studies demonstrating an anti-relapse impact of naltrexone have sampled dependent drinkers who consume greater quantities than in the latest Spanish study[113] (in some cases considerably greater[114]) but in most the patients have been relatively socially integrated, free of psychiatric illness or dependence on other drugs, and not very severely dependent on alcohol.[115] [116] [117] [118] [119] [120] [121] Positive effects have most consistently been seen in samples with high levels of employment.[122] [123] Limits on the severity and length of alcohol dependence, and on alcohol-related and other problems, are mandated partly because naltrexone is contraindicated in liver disease, due to the need for subjects to be able to meet research requirements, because some studies require patients to be sufficiently socially integrated to be able to nominate a family member or other close associate to supervise naltrexone consumption, and because most samples have first had to be able to achieve and sustain at least a short period of abstinence. Compared to alcoholics who lack social supports and are very severely dependent, such patients may be more able to profit from therapy aimed at sustaining non-dependent

drinking, the outcome for which naltrexone too seems particularly appropriate. They also seem more likely to take naltrexone as directed. Severely dependent drinkers and those lacking social supports may require special measures to raise compliance to the point where naltrexone can exert an anti-craving impact.[124 125] However, while sufficient stability to comply with medication may be important, two small non-controlled studies[126 127] and one controlled study[128] suggest that psychiatric illness need not be a bar to the effectiveness of naltrexone.

The two major studies which have reported overall negative results involved relatively severely problematic and more socially marginalised patients. In a large randomised US trial of naltrexone versus placebo, naltrexone's lack of impact may have been partly due to the fact that the male, ex-military patients differed from those in previous naltrexone studies.[129] On average they were nearly 50 years old, had started regularly drinking to intoxication in their early twenties, suffered from chronic, severe alcoholism and had a history of alcoholism in their immediate family, most were unmarried and living alone, and nearly a third were disabled. The psychosocial treatment was less intensive than in some previous studies and was oriented to abstinence and attendance at abstinence-based support groups. Perhaps as a result the main treatment effect was to greatly reduce the number of days on which any alcohol was consumed rather than the number of drinks consumed on those days. In this study there was no indication that patients who tended more often to take their pills as directed benefited from naltrexone, suggesting that the overall lack of impact was not due to non-compliance.

In a similar British study of in some ways a similar population (mostly single, unemployed, long-term dependent drinkers seen at NHS treatment units), just 40% of the patients took their pills and attended therapy as directed, and among these patients naltrexone halved alcohol consumption relative to placebo.[130] However, in the full sample there was no significant impact. Compliant patients may have benefited from naltrexone in this study but not in the US study because the British treatment system is less reliant on 12-step approaches in which abstinence is the only acceptable goal and outcome. Some other US studies have also reported that high compliance patients benefit more from naltrexone than from placebo.[131]

Head to head: naltrexone v acamprosate

A Spanish study has directly compared acamprosate and naltrexone prescribed to outpatients over a year.[132] The study did randomise patients to the treatments but patients and doctors (not researchers) knew which medications they were taking. The authors argued that blinding would have meant obliging naltrexone patients to take pills three times a day (the required schedule for acamprosate) when just one a day would have been sufficient, eliminating one of the potential advantages of naltrexone in everyday practice. Other treatments were as close as possible to everyday practice and included consultations between patients and their psychiatrists and weekly abstinence-oriented supportive group therapy plus pharmacological supports as needed, including disulfiram to terminate relapse. Patients were required to have a stable family environment to aid compliance and in order to provide collateral information on the patient's progress. Families had to commit to attending the treatment centre with the patient throughout the study, a condition which meant that 30% of the candidate patients had to be excluded from

the study. Psychiatric co-morbidity and liver disease were exclusion criteria. All patients were men. Perhaps because of the study's requirements, the patients were only moderately severely dependent and nearly all were married and three-quarters in full-time employment. On average they had drunk on nearly 9 in 10 days over the past six months and consumed 12 UK units[133] on each of those days. 157 patients entered the study after completing detoxification. At least 10 days had elapsed between their last drink and the start of medication. Retention in the study was good and most therapy sessions were attended. Most patients in the study returned to drinking at some point during the year and naltrexone did not delay this any more than acamprosate, but naltrexone did further delay relapse to heavy drinking (63 days versus 42). The gaps between average time to first drink and to relapse suggest[134] that on acamprosate relapse typically quickly followed a lapse (three days average delay) but that often naltrexone patients tried a drink without relapsing into heavy drinking for several weeks (average delay 19 days). (This ability to prolong the lapse-relapse interval has been noted in other studies.[135 136]) By the end of the study 41% of naltrexone patients had not relapsed compared to just 17% on acamprosate.[137] During the last half the study twice as many naltrexone patients (54%) had maintained abstinence. In both groups, pre-treatment heavy drinking was virtually a daily occurrence. During the last half the study naltrexone patients had drunk heavily on a third of the days compared to over half the days among acamprosate patients. Perhaps most telling because of clear clinical significance are the facts that 13 acamprosate patients (16%) refused to continue in the study due to the severity of their relapse and that 52% had to be prescribed disulfiram to control relapses which were resistant to other interventions. On naltrexone the respective figures were 1 and 22%. In accounting for these findings the authors speculate that acamprosate might have done better with more severely dependent patients, especially perhaps those drinking to avoid negative states rather than (as may have typically been the case in the Spanish sample) to gain positive reinforcement. In their study population naltrexone reduced craving to a significantly greater degree than acamprosate.

See also section below.

Combining naltrexone and acamprosate

An Australian study[138] (following text is the study's abstract) "matched 236 patients across gender, age group, prior alcohol detoxification, and dependence severity and conducted a cohort comparison study of three medication groups (CBT+acamprosate, CBT+naltrexone, CBT+combined medication) which included 59 patients per group. Outcome measures included programme attendance, programme abstinence and for those who relapsed, cumulative abstinence duration (CAD) and days to first breach (DFB). Secondary analyses compared the remaining matched 59 subjects who declined medication with the pharmacotherapy groups. Results: Across medication groups, CBT+ combined medication produced the greatest improvement across all outcome measures. Although a trend favoured the CBT+ combined group, differences did not reach statistical significance. Programme attendance: CBT + Acamprosate group (66.1%), CBT + Naltrexone group (79.7%), and in the CBT + Combined group (83.1%). Abstinence rates were 50.8, 66.1, and 67.8%, respectively. For those that did not complete the programme abstinent, the average number of days abstinent (CAD)

were 45.07, 49.95, and 53.58 days, respectively. The average numbers of days to first breach (DFB) was 26.79, 26.7, and 37.32 days. When the focal group (CBT + combined) was compared with patients who declined medication (CBT-alone), significant differences were observed across all outcome indices. Withdrawal due to adverse medication effects was minimal. Conclusions: The addition of both medications (naltrexone and acamprosate) resulted in measurable benefit and was well tolerated. In this patient population naltrexone with CBT is as effective as combined medication with CBT, but the trend favours combination medication." Note that this was a study of sequential patient cohorts entering treatment when the normal drug regime was successively naltrexone, acamprosate or both. Patients could refuse any drug treatment and nearly half did so, registering distinctly worse outcomes presumably partly due to more motivated patients selecting the drug treatments. The accompanying cognitive-behavioural therapy was aimed at abstinence. The study used 50mg naltrexone doses daily. There were no placebos or blinding and no attempt was made to assess treatment leavers. Overall in terms of retention and abstinence during and at the end of treatment naltrexone was preferable to acamprosate but the two drugs together added little further benefit. The study did not report rates of return to heavy drinking.

In Germany (following text is the study's abstract) "after [inpatient] detoxification, 160 patients with alcoholism participated in a randomized, double-blind, placebo-controlled protocol.[139] Patients received [50mg] naltrexone, acamprosate, naltrexone plus acamprosate, or placebo for 12 weeks. Patients were assessed weekly by interview, self-report, questionnaires, and laboratory screening. Time to first drink, time to relapse, and the cumulative abstinence time were the primary outcome measures. Naltrexone, acamprosate, and the combined medication were significantly more effective than placebo. Comparing the course of nonrelapse rates between naltrexone and acamprosate, the naltrexone group showed a tendency for a better outcome regarding time to first drink and time to relapse. The combined medication was most effective with significantly lower relapse rates than placebo and acamprosate but not naltrexone." Note that most patients undergoing detoxification at the centre did not want to know about the study. Presumably only those interested in sustaining their abstinence and fearful of not being able to do so without assistance would have volunteered. Furthermore they had to have already sustained about two weeks without drinking, to not be using other drugs or have a history of opiate/cocaine abuse, to be free of serious medical/psychiatric conditions, and to not be homeless. The resulting caseload was mainly professionally trained men most of whom were working. They were however drinking on average nearly 32 UK units a day before detoxification. Medication was initiated about five days before they left the detoxification unit. Therapy was abstinence-oriented. Patients who returned to steady drinking (at least five days) or who drank heavily on a single day were considered relapsed and removed from the study, accounting for 68 patients. On no measure did naltrexone plus acamprosate significantly better naltrexone alone but on each there was a slight advantage for the combination at the cost of a heightened incidence of gastrointestinal adverse effects, none of which were serious. A later report of relapse outcomes at three months after the end of the trial (when patients could still take the medications but blinding was lifted) indicated that the combined treatment retained a non-significant advantage compared to the single drug regimes which were almost exactly equivalent.[140]

[1]Anton R.F. *et al*. "Combined pharmacotherapies and behavioral interventions for alcohol dependence. The COMBINE Study: a randomized controlled trial." *Journal of the American Medical Association*: 2006, 295, p. 2003–2017. Statements based on this report unless otherwise indicated.

2O'Malley S.S. *et al*. "Initial and maintenance naltrexone treatment for alcohol dependence using primary care vs specialty care." *Archives of Internal Medicine*: 2003, 163, p. 1695–1704.

[3]Rubio G. *et al*. "Naltrexone improves outcome of a controlled drinking program." *Journal of Substance Abuse Treatment*: 2002, 23, p. 361–366.

[4]Rubio G. *et al.* "Naltrexone versus acamprosate: one-year follow-up of alcohol dependence treatment." *Alcohol and Alcoholism*: 2001, 36(5), p. 419-425.

[5]Bohn M.J. *et al*. "Naltrexone and brief counselling to reduce heavy drinking." *American Journal on Addictions*: 1994, 3, p. 91-99.

[6]Kranzler H.R. *et al*. "Targeted naltrexone treatment of early problem drinkers." Addictive Behaviors: 1997, 22(3), p. 431–436.

[7]Monterosso J.R. *et al*. "Predicting treatment response to naltrexone: the influence of craving and family history." *American Journal on Addictions*: 2001, 10, p. 258–268.

[8]Feeney G.F.X. *et al*. "Combined acamprosate and naltrexone, with cognitive behavioural therapy is superior to either medication alone for alcohol abstinence: a single centre's experience with pharmacotherapy." *Alcohol and Alcoholism*: 2006, 41(3), p. 321–327.

[9] Kiefer F. *et al*. "Comparing and combining naltrexone and acamprosate in relapse prevention of alcoholism." *Archives of General Psychiatry*: 2003, 60, p. 92–99.

[10]Kiefer F. *et al*. "Combined therapy: what does acamprosate and naltrexone combination tell us?" *Alcohol & Alcoholism*: 2004, 39(6), p. 542–547.

[11]Rubio G. *et al.* "Naltrexone versus acamprosate: one-year follow-up of alcohol dependence treatment." *Alcohol and Alcoholism*: 2001, 36(5), p. 419-425.

[12]Feeney G.F.X. *et al*. "Combined acamprosate and naltrexone, with cognitive behavioural therapy is superior to either medication alone for alcohol abstinence: a single centre's experience with pharmacotherapy." *Alcohol and Alcoholism*: 2006, 41(3), p. 321–327.

[13] Kiefer F. *et al*. "Comparing and combining naltrexone and acamprosate in relapse prevention of alcoholism." *Archives of General Psychiatry*: 2003, 60, p. 92–99.

[14]O'Malley S. *et al*. ""Naltrexone and coping skills therapy for alcohol dependence." *Archives of General Psychiatry*: 1992, 49, p. 881–887.

[15]Anton R.F. *et al*. "Naltrexone and cognitive behavioral therapy for the treatment of outpatient alcoholics: results of a placebo-controlled trial." *American Journal of Psychiatry*: 1999, 156(11), p. 1758-64.

[16]Heinälä P. *et al*. "Targeted naltrexone with coping therapy for controlled drinking, without prior detoxification, is effective and particularly well tolerated: an 8-month controlled trial." *Alcoholism: Clinical and Experimental Research*: 2000, 24(5), p. 207A.

[17]Heinälä P. *et al*. "Targeted use of naltrexone without prior detoxification in the treatment of alcohol dependence: a factorial double-blind, placebo-controlled trial." *Journal of Clinical Psychopharmacology*: 2001, 21(3), p. 287-292.

[18] Balldin J. *et al*. "A 6-month controlled naltrexone study: combined effect with cognitive behavioral therapy in outpatient treatment of alcohol dependence." *Alcoholism: Clinical and Experimental Research*: 2003, 27(7), p. 1142–1149.

[19]Feeney G.F.X. *et al*. "Alcohol dependence: the impact of cognitive behaviour therapy with or without naltrexone on subjective health status." *Australian and New Zealand Journal of Psychiatry*: 2004, 38, p. 842–848.

[20]Chick J., *et al*. "A multicentre, randomized, double-blind, placebo-controlled trial of naltrexone in the treatment of alcohol dependence or abuse." *Alcohol and Alcoholism*: 2000, 35(6), p. 587–593.

[21]Chick J. *et al*. "United Kingdom Multicentre Acamprosate Study (UKMAS): a 6-month prospective study of acamprosate versus placebo in preventing relapse after withdrawal from alcohol." *Alcohol and Alcoholism*: 2000, 35(2), p. 176–187.

[22]Kranzler H.R. *et al*. "Efficacy of naltrexone and acamprosate for alcoholism treatment: a meta-analysis." *Alcoholism: Clinical and Experimental Research*: 2001, 25(9), p. 1335–1341.

[23]Mann K. *et al*. "The efficacy of acamprosate in the maintenance of abstinence in alcohol-dependent individuals: results of a meta-analysis." *Alcoholism: Clinical and Experimental Research*: 2004, 28(1), p. 51–63.

[24]Pettinati H.M., *et al*. "Improving naltrexone response: an intervention for medical practitioners to enhance medication compliance in alcohol dependent patients." *Journal of Addictive Diseases*: 2000, 19(1), p. 71–83.

[25]Personal communication from Dr Anton June 2006.

[26]COMBINE Study Research Group. "Testing combined pharmacotherapies and behavioral interventions in alcohol dependence: rationale and methods." *Alcoholism: Clinical and Experimental Research*: 2003, 27(7), p. 1107–1122.

[27]Pettinati H.M. *et al*. "A structured approach to medical management: a psychosocial intervention to support pharmacotherapy in the treatment of alcohol dependence." *Journal of Studies on Alcohol*: 2005 (suppl. 15), p. 170–178.

[28]Longabaugh R. *et al*. "Origins, issues and options in the development of the combined behavioral intervention." *Journal of Studies on Alcohol*: 2005 (suppl. 15), p. 179–187.

[29] Post-treatment about 8 in 10 returned to heavy drinking so more must have returned to some drinking at some stage.

[30]O'Malley S. *et al*. ""Naltrexone and coping skills therapy for alcohol dependence." *Archives of General Psychiatry*: 1992, 49, p. 881–887.

[31]Wang S-J. *et al*. "Short of complete abstinence: an analysis exploration of multiple drinking episodes in alcoholism treatment trials." *Alcoholism: Clinical and Experimental Research*: 2002, 26(12), p. 1803-1809.

[32]Morris P.L. *et al*. "Naltrexone for alcohol dependence: a randomized controlled trial." *Addiction*: 2001, 96, p. 1565–1573.

[33]Caputo F. *et al*. "Gamma-hydroxybutyric acid versus naltrexone in maintaining alcohol abstinence: an open randomized comparative study." *Drug and Alcohol Dependence*: 2003, 70(1), p. 85–91.

[34]Rubio G. *et al.* "Naltrexone versus acamprosate: one-year follow-up of alcohol dependence treatment." *Alcohol and Alcoholism*: 2001, 36(5), p. 419-425.

[35]Streeton C. *et al*. "Naltrexone, a relapse prevention maintenance treatment of alcohol dependence: a meta-analysis of randomized controlled trials." *Alcohol & Alcoholism*: 2001, 36(6), p. 544–552.

[36]Kranzler H.R. *et al*. "Efficacy of naltrexone and acamprosate for alcoholism treatment: a meta-analysis." *Alcoholism: Clinical and Experimental Research*: 2001, 25(9), p. 1335–1341.

[37]Carmen B. *et al*. "Efficacy and safety of naltrexone and acamprosate in the treatment of alcohol dependence: a systematic review." *Addiction*: 2004, 99, p. 811–828.

[38]Rohsenow D.J. "What place does naltrexone have in the treatment of alcoholism?" *CNS Drugs*: 2004, 18(9), p. 547–560.

[39]O'Malley S.S. *et al*. "Initial and maintenance naltrexone treatment for alcohol dependence using primary care vs specialty care." *Archives of Internal Medicine*: 2003, 163, p. 1695–1704.

[40]De Sousa A. *et al*. "A one-year pragmatic trial of naltrexone vs disulfiram in the treatment of alcohol dependence." *Alcohol & Alcoholism*: 2004, 39(6), p. 528-531.

[41]Monti P.M. *et al.* "Naltrexone and cue exposure with coping and communication skills training for alcoholics: treatment process and 1-year outcomes." *Alcoholism: Clinical and Experimental Research*: 2001, 25(11), p. 1634–1647.

[42]Monterosso J.R. *et al*. "Predicting treatment response to naltrexone: the influence of craving and family history." *American Journal on Addictions*: 2001, 10, p. 258–268.

[43]Chick J., *et al*. "A multicentre, randomized, double-blind, placebo-controlled trial of naltrexone in the treatment of alcohol dependence or abuse." *Alcohol and Alcoholism*: 2000, 35(6), p. 587–593.

[44]Rubio G. *et al*. "Clinical predictors of response to naltrexone in alcoholic patients: who benefits most from treatment with naltrexone?" *Alcohol and Alcoholism*: 2005, 40(3), p. 227–233.

[45]Kiefer F. *et al*. "Pharmacological Relapse Prevention of Alcoholism: Clinical Predictors of Outcome." European Addiction Research: 2005, 11, p. 83–91.

[46]Monterosso J.R. *et al*. "Predicting treatment response to naltrexone: the influence of craving and family history." *American Journal on Addictions*: 2001, 10, p. 258–268.

[47]Volpicelli J.R. *et al*. "Naltrexone in the treatment of alcoholism: predicting response to naltrexone." *Journal of Clinical Psychiatry*: 1995, 56, p. 39–44. Cited in: Monterosso J.R. *et al*. "Predicting treatment response to naltrexone: the influence of craving and family history." *American Journal on Addictions*: 2001, 10, p. 258–268.

[48]Jaffe A. J. *et al*. "Naltrexone, relapse prevention, and supportive therapy with alcoholics: an analysis of patient-treatment matching." *Journal of Consulting and Clinical Psychology*: 1996, 64, p. 1044–1053. Cited in: Monterosso J.R. *et al*. "Predicting treatment response to naltrexone: the influence of craving and family history." *American Journal on Addictions*: 2001, 10, p. 258–268 and: Rohsenow D.J. "What place does naltrexone have in the treatment of alcoholism?" *CNS Drugs*: 2004, 18(9), p. 547–560.

[49]Killeen T.K. *et al*. "Effectiveness of naltrexone in a community treatment program." *Alcoholism: Clinical and Experimental Research*: 2004, 28(11), p. 1710-1717.

[50]Heinälä P. *et al*. "Use of naltrexone in the treatment of alcohol dependence – a double-blind Finnish trial." *Alcohol and Alcoholism*: 1999, 34(3), p. 433.

[51]Heinälä P. *et al*. "Targeted use of naltrexone without prior detoxification in the treatment of alcohol dependence: a factorial doubleblind, placebocontrolled trial." *Journal of Clinical Psychopharmacology*: 2001, 21(3), p. 287-292.

[52]*Revia Package Insert*. DuPont Merck Pharmaceutical Company, 1999.

[53]O'Malley S.S. *et al*. "Naltrexoneinduced nausea in patients treated for alcohol dependence: clinical predictors and evidence for opioidmediated effects." *Journal of Clinical Psychopharmacology*: 2000, 20(1), p. 69–76.

[54]Rohsenow D.J., *et al*. "Predictors of compliance with naltrexone." *Alcoholism: Clinical and Experimental Research*: 2000, 24(10), p. 1542–1549.

[55]Croop R.S., *et al*. "The safety profile of naltrexone in the treatment of alcoholism. Results from a multicenter usage study." *Archives of General Psychiatry*: 1997, 54, p. 1130–1135.

[56]Salloum I.M, *et al*. "Naltrexone utility in depressed alcoholics." *Psychopharmacology Bulletin*: 1998, 34(1), p. 111–115.

[57]Kranzler H.R. *et al*. "Naltrexone vs. nefazodone for treatment of alcohol dependence. A placebo-controlled trial." *Neuropsychopharmacology*: 2000, 22(5), p. 493–503.

[58]Salloum I.M, *et al*. "Naltrexone utility in depressed alcoholics." *Psychopharmacology Bulletin*: 1998, 34(1), p. 111–115.

[59]Croop R.S., *et al*. "The safety profile of naltrexone in the treatment of alcoholism. Results from a multicenter usage study." *Archives of General Psychiatry*: 1997, 54, p. 1130–1135.

[60] COMBINE Study Research Group. "Testing combined pharmacotherapies and behavioral interventions in alcohol dependence: rationale and methods." *Alcoholism: Clinical and Experimental Research*: 2003, 27(7), p. 1107–1122.

[61]Monterosso J.R. *et al*. "Predicting treatment response to naltrexone: the influence of craving and family history." *American Journal on Addictions*: 2001, 10, p. 258–268.

[62]Streeton C. *et al*. "Naltrexone, a relapse prevention maintenance treatment of alcohol dependence: a meta-analysis of randomized controlled trials." *Alcohol & Alcoholism*: 2001, 36(6), p. 544–552.

[63]Kranzler H.R. *et al*. "Efficacy of naltrexone and acamprosate for alcoholism treatment: a meta-analysis." *Alcoholism: Clinical and Experimental Research*: 2001, 25(9), p. 1335–1341.

[64]Rubio G. *et al.* "Naltrexone versus acamprosate: one-year follow-up of alcohol dependence treatment." *Alcohol and Alcoholism*: 2001, 36(5), p. 419-425.

[65]Annemans L. *et al*. "Economic evaluation of Campral (acamprosate) compared to placebo in maintaining abstinence in alcohol-dependent patients." *European Addiction Research*: 2000, 6=, p. 71–78.

[66]Palmer A.J., *et al*. "The long-term cost-effectiveness of improving alcohol abstinence with adjuvant

acamprosate." *Alcohol and Alcoholism*: 2000, 35(5), p. 478–492.

[67]Carmen B. *et al*. "Efficacy and safety of naltrexone and acamprosate in the treatment of alcohol dependence: a systematic review." *Addiction*: 2004, 99, p. 811–828.

[68]Mann K. *et al*. "The efficacy of acamprosate in the maintenance of abstinence in alcohol-dependent individuals: results of a meta-analysis." *Alcoholism: Clinical and Experimental Research*: 2004, 28(1), p. 51–63.

[69]Streeton C. *et al*. "Naltrexone, a relapse prevention maintenance treatment of alcohol dependence: a meta-analysis of randomized controlled trials." *Alcohol & Alcoholism*: 2001, 36(6), p. 544–552.

[70]Kranzler H.R. *et al*. "Efficacy of naltrexone and acamprosate for alcoholism treatment: a meta-analysis." *Alcoholism: Clinical and Experimental Research*: 2001, 25(9), p. 1335–1341.

[71]Excludes retention measure.

[72]O'Malley S. *et al*. ""Naltrexone and coping skills therapy for alcohol dependence." *Archives of General Psychiatry*: 1992, 49, p. 881–887.

[73]O'Malley S. *et al*. "Six-month follow-up of naltrexone and psychotherapy for alcohol dependence." *Archives of General Psychiatry*: 1996, 53, p. 217–224.

[74]16 out of 19 coping skills, all 15 supportive.

[75]9 out of 16 coping skills, 13 out of 15 supportive.

[76]This finding was not subjected to statistical testing in the source paper.

[77]Anton R.F. *et al*. "Naltrexone and cognitive behavioral therapy for the treatment of outpatient alcoholics: results of a placebo-controlled trial." *American Journal of Psychiatry*: 1999, 156(11), p. 1758-64.

[78]Heinälä P. *et al*. "Targeted naltrexone with coping therapy for controlled drinking, without prior detoxification, is effective and particularly well tolerated: an 8-month controlled trial." *Alcoholism: Clinical and Experimental Research*: 2000, 24(5), p. 207A.

[79]Heinälä P. *et al*. "Use of naltrexone in the treatment of alcohol dependence – a double-blind Finnish trial." *Alcohol and Alcoholism*: 1999, 34(3), p. 433.

[80]Heinälä P. *et al*. "Targeted use of naltrexone without prior detoxification in the treatment of alcohol dependence: a factorial double-blind, placebo-controlled trial." *Journal of Clinical Psychopharmacology*: 2001, 21(3), p. 287-292.

[81]Sinclair J.D. "Evidence about the use of naltrexone and for different ways of using it in the treatment of alcoholism." *Alcohol and Alcoholism*: 2001, 36(1), p. 2–10.

[82]7.5 UK units or more at one sitting or drinking at least five times in a week or turning up for therapy or research interviews intoxicated.

[83]Sinclair J.D. "Evidence about the use of naltrexone and for different ways of using it in the treatment of alcoholism." *Alcohol and Alcoholism*: 2001, 36(1), p. 2–10.

[84] Balldin J. *et al*. "A 6-month controlled naltrexone study: combined effect with cognitive behavioral therapy in outpatient treatment of alcohol dependence." *Alcoholism: Clinical and Experimental Research*: 2003, 27(7), p. 1142–1149.

[85]Månsson M. *et al*. "Six-month follow-up of interaction effect between naltrexone and coping skills therapy in outpatient alcoholism treatment." *Alcohol and Alcoholism*: 1999, 34(3), p. 454.

[86]Feeney G.F.X. *et al*. "Alcohol dependence: the impact of cognitive behaviour therapy with or without naltrexone on subjective health status." *Australian and New Zealand Journal of Psychiatry*: 2004, 38, p. 842–848.

[87]Chick J., *et al*. "A multicentre, randomized, double-blind, placebo-controlled trial of naltrexone in the treatment of alcohol dependence or abuse." *Alcohol and Alcoholism*: 2000, 35(6), p. 587–593.

[88]Just over 10 US drinks each of 13mg.

[89]West S.L., *et al*. *Pharmacotherapy for alcohol dependence*. Agency for Health Care Policy and Research, US Department of Health and Human Services, 1999.

[90]O'Malley S. *Naltrexone and alcoholism treatment*. Treatment Improvement Protocol (TIP) Series 28. US Department of Health and Human Services, 1998.

[91]Rohsenow D.J., *et al*. "Predictors of compliance with naltrexone." *Alcoholism: Clinical and Experimental Research*: 2000, 24(10), p. 1542–1549.

[92]Chick J. *et al*. "United Kingdom Multicentre Acamprosate Study (UKMAS): a 6-month prospective study of acamprosate versus placebo in preventing relapse after withdrawal from alcohol." *Alcohol and Alcoholism*: 2000, 35(2), p. 176–187.

[93]12% and 11% abstinent plus 3% and 6% controlled drinking = 15% and 17% one or the other = 85% and 83% presumed or known uncontrolled drinking.

[94]West S.L., *et al*. *Pharmacotherapy for alcohol dependence*. Agency for Health Care Policy and Research, US Department of Health and Human Services, 1999.

[95]155 + 33 for whom no data and assumed to be drinking. p. 185.

[96]West S.L., *et al*. *Pharmacotherapy for alcohol dependence*. Agency for Health Care Policy and Research, US Department of Health and Human Services, 1999.

[97]O'Malley S.S. *et al*. "Initial and maintenance naltrexone treatment for alcohol dependence using primary care vs specialty care." *Archives of Internal Medicine*: 2003, 163, p. 1695–1704. Document 4046 3.9 6.8 6.7

[98]Though the analysis is based on the 190 patients who actually started counselling and medication.

[99]59 of 97.

[100]43 of 93.

[101]At least those who had also taken at least 60% of their pills in the last four week - this excluded 8 of the primary care management patients and 3 of the CBT patients.

[102]The extended recruitment period (five years) and the fact that just 190 of the 425 adult alcohol dependent contacts who contacted the study actually started treatment suggests that they may be a highly selected and perhaps atypical population. They had to have abstained for at least five days before entry and to have no major comorbidity or other drug problems. The study offered no assurance of continuing to receive an active medication, of a particular kind or intensity of therapy, or of continuing care at the research clinic. Patients prepared to accept these conditions were overwhelmingly white, nearly half were married, and they were relatively well educated and over three-quarters were in employment. They abstained on nearly 4 out of 10 days in the run-up to entering treatment but when they did drink drank heavily, on average about 16 UK units. During the initial 10 weeks of treatment they were reasonably compliant, two-thirds completing treatment and the whole sample on average taking their pills on 7 out of 10 days.

[103]The cognitive behavioural approach specifically excluded strategies for preventing lapses developing into relapses.

[104]Rubio G. *et al*. "Naltrexone improves outcome of a controlled drinking program." *Journal of Substance Abuse Treatment*: 2002, 23, p. 361–366.

[105]Rubio G. *et al.* "Naltrexone versus acamprosate: one-year follow-up of alcohol dependence treatment." *Alcohol and Alcoholism*: 2001, 36(5), p. 419-425.

[106]Rubio G. *et al*. "Naltrexone improves outcome of a controlled drinking program." *Journal of Substance Abuse Treatment*: 2002, 23, p. 361–366.

[107]Rubio G. *et al.* "Naltrexone versus acamprosate: one-year follow-up of alcohol dependence treatment." *Alcohol and Alcoholism*: 2001, 36(5), p. 419-425.

[108]Bohn M.J. *et al*. "Naltrexone and brief counselling to reduce heavy drinking." *American Journal on Addictions*: 1994, 3, p. 91-99.

[109]Kranzler H.R. *et al*. "Targeted naltrexone treatment of early problem drinkers." Addictive Behaviors: 1997, 22(3), p. 431–436.

[110]Davidson D. "Naltrexone and brief counseling to reduce heavy drinking in hazardous drinkers".Addictive Behaviors: 2004, 29(6), p. 1253-1258.

[111] Babor T.F. *et al. AUDIT. The Alcohol Use Disorders Identification Test. Guidelines for use in primary care*. 2nd edition. World Health Organization, 2001. 3295 6.1ns.

[112]Monterosso J.R. *et al*. "Predicting treatment response to naltrexone: the influence of craving and family history." *American Journal on Addictions*: 2001, 10, p. 258–268.

[113]Rubio G. *et al*. "Naltrexone improves outcome of a controlled drinking program." *Journal of Substance Abuse Treatment*: 2002, 23, p. 361–366.

[114] Kiefer F. *et al*. "Comparing and combining naltrexone and acamprosate in relapse prevention of alcoholism." *Archives of General Psychiatry*: 2003, 60, p. 92–99.

[115] Kiefer F. *et al*. "Comparing and combining naltrexone and acamprosate in relapse prevention of alcoholism." *Archives of General Psychiatry*: 2003, 60, p. 92–99.

[116]Monti P.M. *et al.* "Naltrexone and cue exposure with coping and communication skills training for alcoholics: treatment process and 1-year outcomes." *Alcoholism: Clinical and Experimental Research*: 2001, 25(11), p. 1634–1647.

[117]O'Malley S. *et al*. "Naltrexone and coping skills therapy for alcohol dependence." *Archives of General Psychiatry*: 1992, 49, p. 881–887.

[118]Anton R.F. *et al*. "Naltrexone and cognitive behavioral therapy for the treatment of outpatient alcoholics: results of a placebo-controlled trial." *American Journal of Psychiatry*: 1999, 156(11), p. 1758-64.

[119]Streeton C. *et al*. "Naltrexone, a relapse prevention maintenance treatment of alcohol dependence: a meta-analysis of randomized controlled trials." *Alcohol & Alcoholism*: 2001, 36(6), p. 544–552.

[120]Heinälä P. *et al*. "Targeted naltrexone with coping therapy for controlled drinking, without prior detoxification, is effective and particularly well tolerated: an 8-month controlled trial." *Alcoholism: Clinical and Experimental Research*: 2000, 24(5), p. 207A.

[121]O'Malley S. *et al*. "Six-month follow-up of naltrexone and psychotherapy for alcohol dependence." *Archives of General Psychiatry*: 1996, 53, p. 217–224.

[122] Kranzler H.R. *et al*. "Efficacy of naltrexone and acamprosate for alcoholism treatment: a meta-analysis." *Alcoholism: Clinical and Experimental Research*: 2001, 25(9), p. 1335–1341.

[123]Streeton C. *et al*. "Naltrexone, a relapse prevention maintenance treatment of alcohol dependence: a meta-analysis of randomized controlled trials." *Alcohol & Alcoholism*: 2001, 36(6), p. 544–552.

[124]Pettinati H.M., *et al*. "Improving naltrexone response: an intervention for medical practitioners to enhance medication compliance in alcohol,dependent patients." *Journal of Addictive Diseases*: 2000, 19(1), p. 71–83.

[125]Monterosso J.R. *et al*. "Predicting treatment response to naltrexone: the influence of craving and family history." *American Journal on Addictions*: 2001, 10, p. 258–268.

[126]Salloum I.M, *et al*. "Naltrexone utility in depressed alcoholics." *Psychopharmacology Bulletin*: 1998, 34(1), p. 111–115.

[127]Maxwell S. *et al*. "Use of naltrexone in the treatment of alcohol use disorders in patients with concomitant major mental illness." *Journal of Addictive Diseases*: 2000, 19(3), p. 61-69.

[128]Morris P.L. *et al*. "Naltrexone for alcohol dependence: a randomized controlled trial." *Addiction*: 2001, 96, p. 1565–1573.

[129]Krystal J.H. et al. "Naltrexone in the treatment of alcohol dependence." *New England Journal of Medicine*: 2001, 345, p. 1734–1739.

[130]Chick J., *et al*. "A multicentre, randomized, double-blind, placebo-controlled trial of naltrexone in the treatment of alcohol dependence or abuse." *Alcohol and Alcoholism*: 2000, 35(6), p. 587–593.

[131]Modesto-Lowe V. et al. "Clinical uses of naltrexone: a review of the evidence." *Experimental and Clinical Psychopharmacology*: 2002, 10(3), p. 213–227.

[132]Rubio G. *et al.* "Naltrexone versus acamprosate: one-year follow-up of alcohol dependence treatment." *Alcohol and Alcoholism*: 2001, 36(5), p. 419-425.

[133]In the article the term 'drinks' is used but (see p. 420) this was equivalent to 8 gm alcohol.

[134]This cannot be established since an average may be composed of widely varying figures but the scope for this is constrained by the fact that the delay cannot have been less than zero.

[135]Morris P.L. *et al*. "Naltrexone for alcohol dependence: a randomized controlled trial." *Addiction*: 2001, 96, p. 1565–1573.

[136]O'Malley S. *et al*. ""Naltrexone and coping skills therapy for alcohol dependence." *Archives of General Psychiatry*: 1992, 49, p. 881–887.

[137]There is a mistake in table 2 of the source article which assigns these figures to a measure of subjects who did relapse rather than those who did not.

[138]Feeney G.F.X. *et al*. "Combined acamprosate and naltrexone, with cognitive behavioural therapy is superior to either medication alone for alcohol abstinence: a single centre's experience with pharmacotherapy." *Alcohol and Alcoholism*: 2006, 41(3), p. 321–327.

[139] Kiefer F. *et al*. "Comparing and combining naltrexone and acamprosate in relapse prevention of alcoholism." *Archives of General Psychiatry*: 2003, 60, p. 92–99.

[140]Kiefer F. *et al*. "Combined therapy: what does acamprosate and naltrexone combination tell us?" *Alcohol & Alcoholism*: 2004, 39(6), p. 542–547.