THE UNIVERSITY OF ADELAIDE
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SUB CRUCE LUMEN

USING GENOTYPING TO IMPROVE THE EFFECTIVENESS OF NALTREXONE

FINAL REPORT

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EXECUTIVE SUMMARY

Naltrexone is an effective treatment for alcohol dependence, with studies showing that it reduces alcohol consumption and craving, prevents relapse and promotes abstinence. However not all drinkers experience benefits. The primary objective of this study was to carry out a prospective study to determine whether a simple genetic test could predict those people who would respond best to naltrexone. Specifically, it was hypothesized that participants homozygous (A/G) or heterozygous (G/G) for the variant allele of the mu opioid receptor would show greater reductions in alcohol consumption and would remain in naltrexone treatment for a longer time period before relapse than those homozygous for the wildtype allele (A/A).

In addition, this study examined other patient characteristics and treatment factors that may be associated with improved outcomes. Identifying these could optimize the clinical usefulness of the medication, resulting in naltrexone being used in those for whom it is likely to be most effective.

A total of 100 alcohol-dependent participants were prescribed naltrexone and offered cognitive-behavioural therapy for 12 weeks. Comparisons were made according to genetic status, referral source and pre-treatment abstinence. Outcome measures included changes in self-reported and objective (GGT and MCV) indicators of alcohol use, time to first relapse and craving.

Overall, naltrexone treatment produced significant decreases in self-reported and objective indicators of alcohol use and craving from baseline, particularly during the first two months of treatment. Participants remained in treatment for an average of 10 weeks. Side-effects were minor and resolved quickly. Self-reported alcohol use decreased from 1085 grams/week to 45 at the end of treatment. MCV decreased from 95 to 93 femtolitres, and GGT from 70 to 48 units/litre. Moreover, the proportion of participants with MCV and GGT levels above the normal range decreased significantly over the treatment period, from 24% to 13% for MCV and from 55% to 37% for GGT.

There was no evidence of a significant association between genotype and treatment success. Better outcomes were observed in participants who commenced treatment after a period of detoxification in an inpatient clinic, including significant decreases in self-reported and objective measures of alcohol consumption and time to first relapse. Moreover, participants in this group who specified a goal of abstinence were significantly more likely to achieve their goal than those referred from other sources. A greater number of days abstinent prior to treatment was also associated with better outcomes.

The results of this study indicate that naltrexone is an effective treatment for alcohol dependence, with high levels of treatment retention, as well as significant decreases in self-reported and objective indicators of alcohol use. Genotype was not a predictor of success, but pre-treatment abstinence did show an association.

INTRODUCTION

Alcohol misuse, with or without dependence, is an extremely important health issue facing Australia. Based on the results of the 2007 National Drug Strategy Household Survey (AIHW, 2008), 83% of the population aged 14 years and over had consumed alcohol in the last 12 months, while 50% reported drinking at least once per week. In 2003, an estimated 2% of the total burden of disease in Australia was attributable to excessive alcohol consumption (AIHW, 2007), with the net impact comprising almost 1,100 deaths and over 61,000 years lost to disability or premature death. Alcohol was the most common principal drug of concern for which treatment was sought in 2005–06, accounting for 39% of closed treatment episodes, as well as 49% of all hospital separations (AIHW, 2007).

Management of Alcohol Dependence

There are a number of treatments available for problematic or dependent alcohol use. These include management of withdrawal (detoxification), residential programs such as therapeutic communities, outpatient treatment that may include cognitive behavioural therapy and social support, and self help groups such as Alcoholics Anonymous. While disulfiram (Antabuse) has been available as a pharmacotherapy for a number of years, it is only appropriate for a small sub-group of those who are alcohol-dependent. More recently, two pharmacotherapies have become available and are being increasingly utilised for the treatment of alcohol dependence. Acamprosate is a compound that acts mainly to reduce the protracted withdrawal syndrome that occurs following cessation of alcohol use, while naltrexone is an opioid antagonist that acts to reduce or block the opioid-mediated effects of alcohol. Recent evidence suggests that naltrexone may be more effective in reducing alcohol consumption and craving (Richardson et al., 2008; Anton et al., 2006), and that it may have use for a wider proportion of the population with alcohol-related problems rather than only for those with high levels of dependence (Morley et al., 2006; Rubio et al., 2001).

Naltrexone as a Pharmacotherapy

The most widely accepted hypothesis concerning the action of naltrexone is that opioid antagonism blocks alcohol-stimulated increases in endogenous opioid peptide activity, resulting in a decrease in some of the positive reinforcing properties of alcohol (see reviews by Gianoulakis et al., 1993; Volpicelli et al., 1994). The endogenous opioid peptides include the enkephalins, beta-endorphin, dynorphin and endomorphins. They act through the three opioid receptors: mu, kappa and delta. The mu opioid receptor (OPRM1) is the major binding target site for most opioid drugs such as morphine and naltrexone, and is a major modulator of reward pathways in the brain.

Studies have shown that treatment with naltrexone promotes abstinence, prevents relapse, and reduces alcohol consumption and craving (Anton et al., 1999; Volpicelli et al., 1992; O'Malley et al., 1996), and there is evidence of increased efficacy when craving is high (Richardson et al., 2008). When taken regularly by alcohol-dependent patients, naltrexone results in attenuation of the subjective high experienced when alcohol is consumed (McCaul et al., 2000; Volpicelli et al. 1995). Moreover, there is evidence that naltrexone is effective in treating non-dependent heavy drinkers seeking to reduce their use rather than achieve abstinence (Bohn et al., 1994; Davidson et al., 1996; Kranzler et al., 1997). Naltrexone has also been shown to block the reinforcing and physiological effects of opioids (Resnick et al., 1974; Walsh et al., 1996; Sullivan et al., 2006), and has been used as an adjunctive relapse prevention therapy for ex-opioid users. Recent meta-analyses have confirmed its effectiveness in reducing alcohol consumption and relapse episodes, and increasing the likelihood of achieving abstinence (Kranzler and Van Kirk, 2001; Streeton and Whelan, 2001; Srisurapanont and Jarusuraisin, 2005). However, the overall therapeutic effect was modest, with one review reporting that outcomes for participants treated with naltrexone were only 12-19% better than for those treated with placebo (Kranzler and Van Kirk, 2001), and another concluding that naltrexone is best suited for short to medium term treatment (Srisurapanont and Jarusuraisin, 2005). In addition, some doubt has been cast on its use in all dependent drinkers and while effective overall, many do not experience benefit from naltrexone. A large multi-centre randomised controlled trial carried out by Krystal et al. (2001) raised questions about its efficacy,

although nearly all participants were males with chronic severe alcohol dependence. Chick et al. (2000) found no evidence that naltrexone was more effective than placebo on drinking outcomes, although further analyses using a subset of highly compliant participants revealed that those treated with naltrexone had significantly lower craving scores and drank significantly less. Pettinati et al. (2006), carried out a review comparing randomised controlled trials measuring reductions in heavy drinking with those measuring abstinence. It was found that 70% of those measuring reductions in use showed increased efficacy of naltrexone over placebo, while only 36% of those measuring abstinence had outcomes that favoured the naltrexone group. These findings suggest that naltrexone may be most useful as a harm reduction treatment rather than as a means of achieving abstinence.

Pharmacogenetics of response to naltrexone

While studies have shown that naltrexone treatment is associated with decreased alcohol consumption and craving, there is substantial inter-individual variability in both response and side-effects experienced. Whereas age, disease (renal and hepatic dysfunctions), drug-drug and drug-food interactions have traditionally been the source of such differences, these mainly impact on pharmacokinetic variables. There is increasing recognition that genetic factors play an important role (Roden and George, 2002), and it has been estimated that these account for up to 95% of variability in drug response; and specifically for around 50% of ethanol elimination rates (Kalow et al., 1998).

One such genetic component is polymorphism in the CYP2D6 gene that directly affects drug metabolism (Weinshilboum, 2003). There is now evidence that an additional and important pharmacogenetic determinant of inter-individual variability in drug response is that of genetic polymorphism in drug receptors, particularly G-protein coupled receptors, such as the opioid receptors, the target sites of naltrexone (Evans and McLeod, 2003). This has resulted in the development of genetic tests that enable prediction of the likely effects of a drug on an individual.

More than 40 sequence variants in the human mu opioid receptor gene have been described (Hoehe et al., 2000) and reviewed (Lee and Smith, 2002). The major variants involve Single Nucleotide Polymorphisms (SNPs) at C17T (T allele frequency ~ 5%) and in exon 1 at A118G (G allele frequency ~12%). The latter is the most extensively studied in terms of incidence and function. It involves an asparagine to aspartic acid substitution at amino acid 40 (N40D), resulting in the loss of a putative glycosylation site in the N-terminal region of the receptor that could potentially modify receptor expression (Befort et al., 2001). There are differences in the frequency of this G variant between ethnic groups (Gelernter Kranzler and Cubells, 1999) and studies have also shown it is more common among heroin-dependent individuals (Szeto et al., 2001), suggesting that it may play a role in the predisposition to heroin dependence. In contrast, others have found no association between mu opioid receptor variants and alcohol dependence (Bergen et al., 1997). However, while beta endorphin binding affinity to the variant receptor is 3.5-fold higher and with greater potency in signal transduction than the wildtype receptor, morphine binding was not different (Bond et al., 1998). The difference in beta endorphin affinity and potency associated with the A118G variant could have important implications for its role in alcohol dependence and the effects of naltrexone.

There is substantial evidence that the A118G variant allele alters the pharmacological and therapeutic effects of opioids (Höllt, 2002), with participants homozygous or heterozygous for the variant (A/G or G/G) requiring higher doses of opioids to achieve an effect than those with the homozygous wildtype (A/A) (Caraco et al., 2001; Holthe et al., 2002). Lötsch and coworkers (Lötsch et al., 2002; Skarke et al., 2003) studied homozygous wildtype, heterozygous and homozygous variant participants, all of whom received IV morphine and its active metabolite MG6 on two separate occasions, with measurements made of pupil diameter and plasma concentrations. The calculated morphine and M6G concentrations at the effect site for 50% maximum effect significantly increased across the genotype groups, such that those who were homozygous variant required almost double the concentration to produce the same effect as those homozygous wildtype. In addition, participants with the variant allele reported less side-effects after

morphine administration. These data support the hypothesis that the A118G variant is associated with a reduced response to opioid agonists such as morphine.

Of particular relevance in the treatment of alcohol dependence, it appears that the *opposite effect* occurs with opioid antagonists. Participants with the A118G variant were found to have altered hypothalamic-pituitary-adrenal axis activation induced by opioid receptor blockade with naloxone; that is, a higher plasma cortisol was found in those with the G variant (Wand et al., 2002).

More striking results were obtained with naltrexone responses in alcohol-dependent participants (Oslin et al., 2003). This study obtained genotype data from three clinical trials and compared 82 participants treated with 100 mg naltrexone and 59 treated with placebo. The association between A118G genotype and drinking outcomes was assessed over 12 weeks of treatment. Participants homozygous or heterozygous for the G variant who were treated with naltrexone had a significantly lower rate of relapse and a longer time to return to heavy drinking than those with the homozygous wildtype, although there were no significant differences in relapse rates to any drinking. After 12 weeks, less than 20% of the A/G and G/G groups had relapsed compared with 55% for the A/A and placebo groups. However, these findings must be interpreted with some caution. Sample sizes were relatively small, and results were based on a retrospective analysis of case notes using participants from different studies, which were not originally designed to examine the effects of genotype on treatment success.

More recently, Anton et al. (2008) found consistent results in a large randomised controlled trial. Participants were given 100 mg naltrexone or placebo for 16 weeks, and comparisons were made according to genotype group. Those homozygous or heterozygous for the G variant showed a better response if treated with naltrexone than with placebo, with an increased percentage in days abstinent and a decreased percentage of heavy drinking days. In contrast, participants with the homozygous wildtype showed no significant difference in outcome between groups. Furthermore, looking only at participants treated with naltrexone, those with the G variant had significantly better drinking outcomes than those with the wildtype (87% vs 55%). However, the association between genotype and naltrexone was not significant when a cognitive-behavioural intervention was provided in addition to naltrexone treatment.

In contrast, a study by Gelernter et al (2007) looked at the relationship between genotype and risk of relapse to heavy drinking by reanalysing a subset of an earlier randomised controlled trial (Krystal et al. 2001), using 215 alcohol-dependent male participants who provided genetic information. While 50 mg naltrexone was effective in increasing time to heavy drinking, there were no significant differences between genotype groups. However, it is important to note that this was the only outcome measure used.

Other factors associated with increased response to naltrexone

Several studies have identified potential predictors of treatment success. Participants with high baseline craving for alcohol (Richardson et al. 2008; Jaffe et al. 1996), early age of onset of problem drinking (Rubio et al. 2005) and family antecedents of alcohol dependence (Monterosso et al. 2001; King et al. 1997; Rubio et al. 2005) were found to benefit most from naltrexone treatment.

Other factors have been identified that relate to the treatment program itself. Participants with high levels of compliance demonstrate better outcomes (Chick et al. 2000; Volipicelli et al. 1997), and there is consistent evidence that adjunctive counselling, specifically cognitive behavioural therapy, produces better outcomes than medication alone (Anton et al. 2005; Oslin et al. 2008). There is also some evidence that a patient's goal prior to commencing treatment may contribute to the effectiveness of naltrexone. For example, O'Malley et al. (1992) found that the combination of naltrexone and counselling improved abstinence rates where a clear goal of abstinence was stated.

A requirement of nearly all studies looking at the efficacy of naltrexone is a period of abstinence from alcohol prior to commencing treatment. In order to investigate the possible impact of pre-entry

abstinence on outcomes, O'Malley et al (2007) reanalysed a subgroup from a study carried out by Garbutt et al. (2005) which used a criterion of at least four alcohol-free days. It was found that participants with at least seven days of pre-treatment abstinence had longer periods of prolonged abstinence throughout the study, as well as a significantly lower number of drinking days and heavy drinking days. The results of this study suggest that an extended period of abstinence prior to commencing treatment was associated with better outcomes.

The primary objective of this study was to carry out a prospective study to determine whether a simple genetic test could predict those people who would respond best to naltrexone. Specifically, it was hypothesized that participants homozygous (A/G) or heterozygous (G/G) for the variant allele of the mu opioid receptor would show greater reductions in alcohol consumption and would remain in naltrexone treatment for a longer time period before relapse than those homozygous for the wildtype allele (A/A).

In addition, this study examined other patient characteristics and treatment factors that may be associated with improved outcomes. Identifying these could optimize the clinical usefulness of the medication, resulting in naltrexone being used in those for whom it is likely to be most effective.

METHODS

Participants

A total of 100 alcohol-dependent participants were involved in this study between March 2006 and May 2008. Participants were recruited from two populations: firstly, alcohol-dependent patients treated in an inpatient unit for alcohol withdrawal prior to commencing the study (n=54); and secondly, a sample accessed through referrals from general practitioners (GPs), community health centres and advertisements (n=46). It was expected that this group would include people with a range of alcohol consumption levels, whereas those from the inpatient unit would have higher levels of alcohol dependence.

Participants were screened by the medical officer and informed consent was obtained prior to enrolment in the study. Participants were eligible if they fulfilled DSM IV criteria for alcohol dependence, but could not be dependent on other drugs (excluding nicotine). In addition, participants were excluded if they showed any significant clinical or laboratory evidence of hepatic and renal impairment or had any significant medical condition that would preclude the prescription of naltrexone. Pregnant or lactating females were also ineligible, as well as participants who had taken naltrexone in the previous six months.

Design

Ethics approval was obtained from the Royal Adelaide Hospital Research Ethics Committee. Each participant was initially screened by the medical officer. During the assessment, a complete medical history was taken, including the age of onset of drinking, family history of drinking, pattern and level of consumption, degree of craving for alcohol as well as physical dependence. A blood sample was collected to test for hepatic and renal function, as well as obtain markers to be used as objective indicators of alcohol consumption: Carbohydrate Deficient Transferrin (CDT); Mean Corpuscular Volume (MCV); and Gammaglutamyl Transferase (GGT).

Following screening, eligible participants were treated for 12 weeks with daily administration of 50 mg naltrexone, and were assessed monthly by the medical officer and weekly by research staff. They also received up to five cognitive behavioural therapy sessions focusing on motivation to use the medication and relapse prevention strategies.

A final appointment with the medical officer occurred after 12 weeks of treatment, where blood samples were collected for analysis, and participants were referred back to their GP for ongoing prescription of naltrexone if requested.

Genotyping

Samples were genotyped to identify participants carrying the A118G SNP of the *OPRM1* gene encoding for the mu opioid receptor. Genomic DNA was isolated from blood samples using a QIAamp® DNA mini kit according to the manufacturer's instructions (QIAGEN Pty Ltd, Doncaster, Australia). Purity and concentration of the genomic DNA was quantified using a standard spectrophotometric method. All samples were of acceptable purity and concentration. The A118G SNP assay used is an allele-specific assay based on that used by Jorm et al. (2002). Briefly, this involved 2 polymerase chain reactions (PCRs) per sample, one to detect the wild-type and one to detect the variant gene sequence. PCR products were then run on a 4% 2:1 Omnigel Sieve Agarose:Agarose I gel stained with ethidium bromide and visualised under UV exposure. All assays contained a known homozygous wild-type and homozygous variant sample to ensure assay was free of non-specific amplification and a DNA template-free control to ensure the assay was free of potential contaminants.

It was expected that approximately 30 of the 100 participants would have at least one copy of the G allele and 70 would be homozygous for the A allele. The genotype assay has been established and validated in a sample of 83 normal healthy controls, and 31% had at least one copy of the variant G allele. In the present study, a total of 65 participants were homozygous (A/A) and 35 had at least one copy of the variant allele (34 with A/G and 1 with G/G).

Measures

The main performance indicator in this study was the determination of a statistically and clinically significant difference in measures of alcohol consumption over the study period between the two genotype groups. Data were collected without knowledge of participants' genetic status, with comparisons made between groups at the end of the study period. Outcome measures included:

1. Self-reported alcohol use;
2. Objective indicators of alcohol use (CDT, GGT and MCV);
3. Proportion of participants at baseline and at month 3 with GGT levels above the normal range;
4. Proportion of participants at baseline and at month 3 with MCV levels above the normal range;
5. Proportion of participants who achieved their treatment goal (controlled drinking or abstinence);
6. Time to first relapse, with relapse defined as consuming five or more drinks in a single day for men and four or more drinks for women, or drinking on five or more days per week;
7. Self-reported number of days alcohol was used during the study;
8. Degree of craving for alcohol;
9. Duration of treatment.

For participants seeking controlled drinking, achievement of treatment goal was based on NH&MRC drinking guidelines (2001), allowing consumption of up to 280 grams/week for men and 140 grams/week for women. For participants seeking abstinence, achievement of treatment goal was defined by not consuming alcohol in the week prior to each monthly assessment.

Secondary outcomes included a comparison of above outcomes according to:

1. Referral source (participants recruited from the detoxification unit compared with those recruited from the community);
2. Number of abstinent days prior to commencing treatment (participants with at least four alcohol-free days compared with 0-3).

Descriptive analyses included overall demographic and drug treatment history, and the attribution of positive outcome, that is, whether participants perceived treatment success to be due to naltrexone or to other factors.

Data analyses

To test for differences between groups (defined by genotype, referral source and pre-treatment abstinence) and over time, linear regression models were fitted to the data. Linear mixed effects models incorporating a random patient ID effect were used to analyse continuous outcome data (self-reported and objective alcohol use, craving, deviation from treatment goal), while log binomial GEE regression models were used to analyse binary outcome data (alcohol use during the trial, proportion of MCV/GGT values above the normal range, proportion who achieved treatment goal). All continuous outcomes were examined for normality and transformed where necessary. In all models, group, time, and the interaction between group and time were entered as predictor variables. Where the interaction effect between group and time was found to be non-significant, a second model excluding the interaction term was fitted so that the main effects of group and time could be interpreted. Secondary analyses were also performed in which 'family history of alcohol dependence' and 'age of first regular use of alcohol' were included as covariates.

Several outcomes were compared between groups that were not measured over time. These include the proportion of participants who relapsed at day 7 and at day 28 (modelled using log binomial models), the number of days alcohol was used alcohol during the trial (modelled using a negative binomial model) and time to first relapse (modelled using the Kaplan-Meier or product-limit estimate of the survivor function).

All calculations were performed using SAS Version 9.1 (SAS Institute Inc., Cary, NC, USA). Descriptive data were analysed using SPSS for Windows (version 16.0).

RESULTS

Section 1: Effects of Genotype on Outcomes

Characteristics of Sample

Table 1 presents baseline characteristics of the sample, including measures of alcohol consumption. Over half of participants were male (57%), with a mean age of 42.5 years (± 8.8 years). Participants started problematic alcohol use at a mean age of 26.7 years (± 8.6 years). Just under half (45%) were unemployed or on a disability pension, 15% had tertiary qualifications, and nearly all (92%) had received prior treatment for alcohol dependence. Only 37% were married, although 70% had children. The majority (76%) reported a family history of alcohol dependence. Just over half were referred from inpatient detoxification, and 68% were seeking abstinence as their treatment goal.

Median self-reported alcohol use at baseline was 1085 grams over the previous week, equivalent to 155 grams (or 15.5 standard drinks) per day. Note that this denotes average weekly use over the three months prior to commencing treatment to ensure that it was an accurate reflection of usual consumption. This is particularly important for those who were referred from the inpatient detoxification clinic, as the standard length of stay is four days. This is further highlighted by participants reporting an average of nearly five alcohol-free days prior to commencing the study.

Median GGT at baseline was 69 units/litre, which was above the normal cut-off of 50 units/litre. Mean MCV was 95 fl, which was just within the normal range of 80-98 fl. Baseline craving for alcohol was low, with a median of 12 (maximum possible was 100).

Table 1: Overall Sample

Variable	***N*=100**
% male	57
Mean age (years) *	42.5 (8.8)
Mean age began regular or daily use (years) *	26.7 (8.6)
% university education	15
% currently unemployed/disability pension	45
% currently married/*de facto*	37
% with children	70
% with family history[1] of alcohol dependence/abuse	76
% previous treatment for alcohol dependence	92
% referred through inpatient detoxification clinic	54
% seeking abstinence as goal of treatment	68
Mean no. CBT sessions during study*	1.9 (1.6)
Mean no. alcohol free days prior to first tablet*	4.8 (7.0)
Median self-reported alcohol use at baseline (total grams in previous week)	1085
Median GGT at baseline (units/litre)	69
Mean MCV at baseline (fl)	95
Median craving at baseline (mm)	12

* Standard deviations in brackets

[1] Based on self-report; defined as parents, grandparents or siblings

There were 65 participants (65%) homozygous for the Asn40 genotype (A/A) and 35 (35%) with at least one copy of the Asp40 allele (34 A/G and 1 G/G). Table 2 compares the two groups at baseline.

Table 2: Comparisons according to Genotype

Variable	A/A (*n*=65)	A/G or G/G (*n*=35)
% male	57	57
Mean age (years) *	42.8 (8.9)	41.9 (8.7)
Mean age began regular or daily use (years) *	27.8 (9.0)	24.6 (7.5)
% university education	17	11
% currently unemployed/disability pension	48	40
% currently married/*de facto*	39	34
% with children	71	69
% with family history of alcohol dependence/abuse	74	80
% previous treatment for alcohol dependence	92	91
% referred through inpatient detoxification clinic	62	40
% seeking abstinence as goal of treatment	71	63
Mean no. CBT sessions during study*	1.9 (1.6)	1.9 (1.5)
Mean no. alcohol free days prior to first tablet*	3.9 (3.6)	6.5 (10.6)
Estimated median self-reported alcohol use at baseline (total grams in previous week)	1086	1064
Estimated median GGT at baseline (units/litre)	70	60
Mean MCV at baseline (fl)	96	95
Estimated median craving at baseline (mm)	14	10

* Standard deviations in brackets

There were no significant differences according to genotype on any baseline measures. Genotype groups were then compared on a range of drinking outcomes over the course of treatment.

Self-Reported Alcohol Use

As the distribution of self-reported alcohol use was right skewed, data were log transformed and the relationship between alcohol use and genotype was modelled using a linear mixed effects model.

Figures 1 and 2 show a decrease in alcohol consumption for both groups between baseline and the end of treatment, and these changes over time were statistically significant ($p<0.0001$). However, there were no differences according to genotype ($p=0.782$).

Post-hoc tests carried out on the data found that in both groups, baseline alcohol use was significantly higher than at all subsequent time points ($p<0.0001$). Although use at month 3 was significantly higher than at month 1 ($p=0.021$) and at month 2 ($p=0.011$), consumption did not return to baseline levels.

Figure 1: Estimated Median Self-Reported Alcohol Use according to Genotype[2]

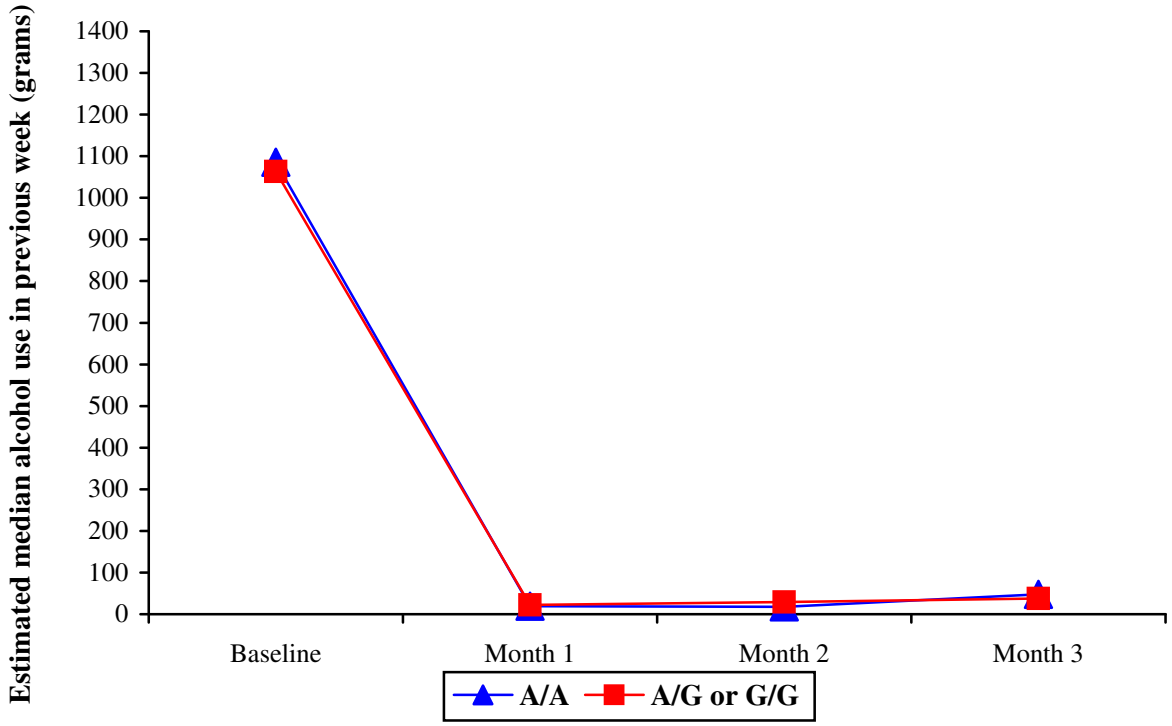
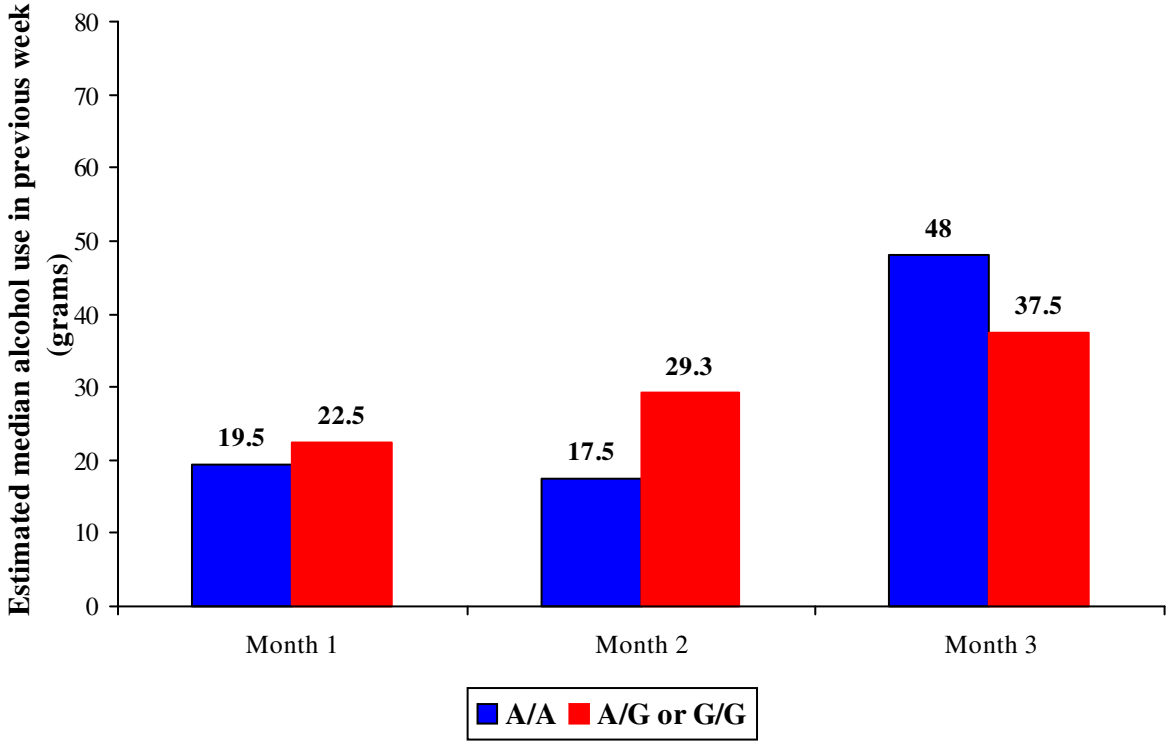


Figure 2: Estimated Median Self-Reported Alcohol Use during Treatment Period Only[2]



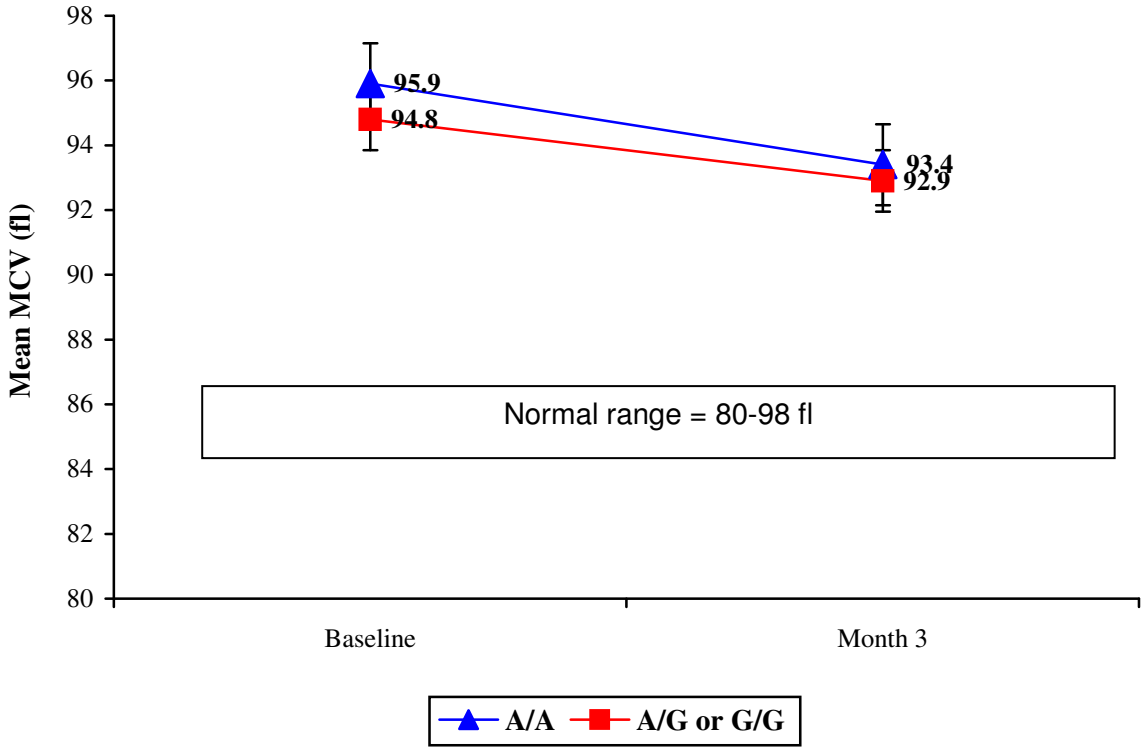
[2] Median values refer to those estimated in the linear mixed effects model

Objective Measures of Alcohol Use

Mean Corpuscular Volume (MCV)

The distribution of MCV was approximately normal, and the relationship between MCV and genotype was modelled using a linear mixed effects model. Figure 3 shows a trend consistent with self-reported alcohol use, with significant decreases in MCV levels over time (p<0.0001). Again, differences between genotype groups were not significant (p=0.538).

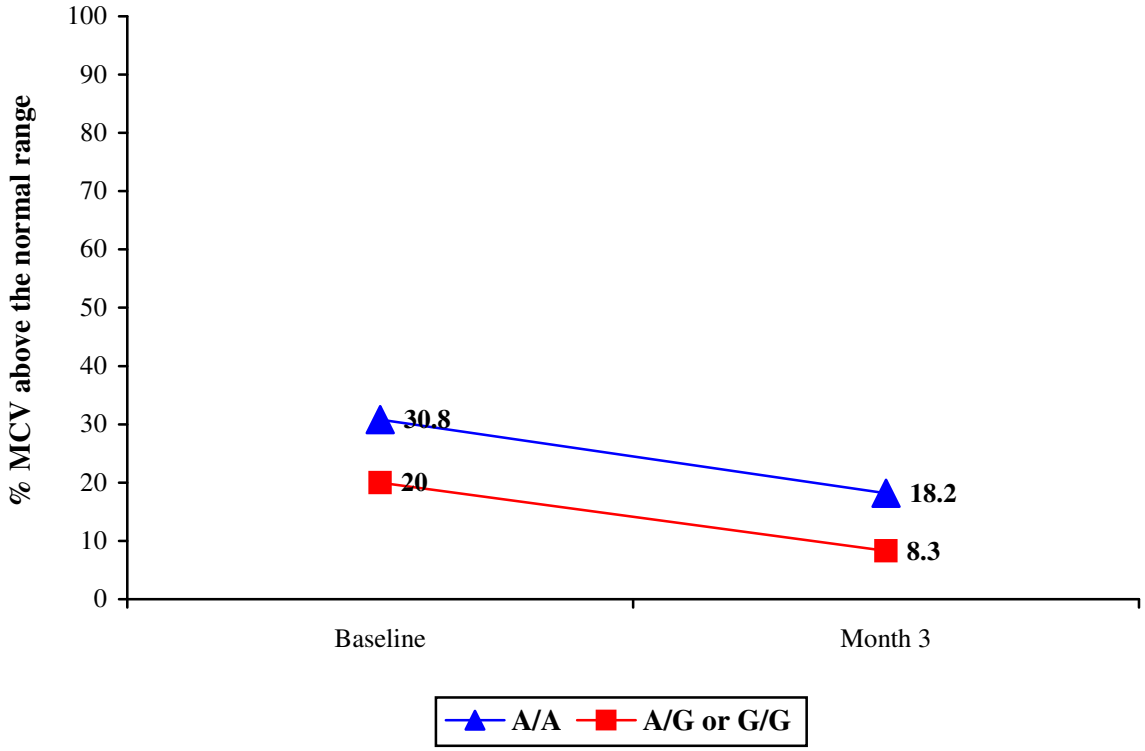
Figure 3: MCV according to Genotype



The effects of naltrexone on MCV were investigated further by looking at the percentage of participants with levels above the normal range over the treatment period. Results were analysed using log binomial models, and Figure 4 presents the results according to genotype group.

There were significant decreases in the percentage of participants with MCV levels above the normal range from baseline to month 3 (p=0.050) but no differences between groups (p=0.114).

Figure 4: % Participants with MCV above the Normal Range according to Genotype



Gammaglutamyl Transferase (GGT)

As with self-reported alcohol use, the distribution of GGT was right skewed, so data were log transformed and the relationship between GGT and genotype was modelled using a linear mixed effects model.

Again, Figure 5 shows significant decreases in GGT over time (p<0.001) but no differences between groups (p=0.782).

Participants' changes in GGT over time were also analysed using log binomial models as the percentage with levels above the normal range. Figure 6 shows that results were almost identical for both groups, and although there was a significant decrease in the percentage of participants with GGT levels above the normal range over time (p=0.020) there were no differences between groups (p=0.964).

Figure 5: Estimated Median GGT according to Genotype[3]

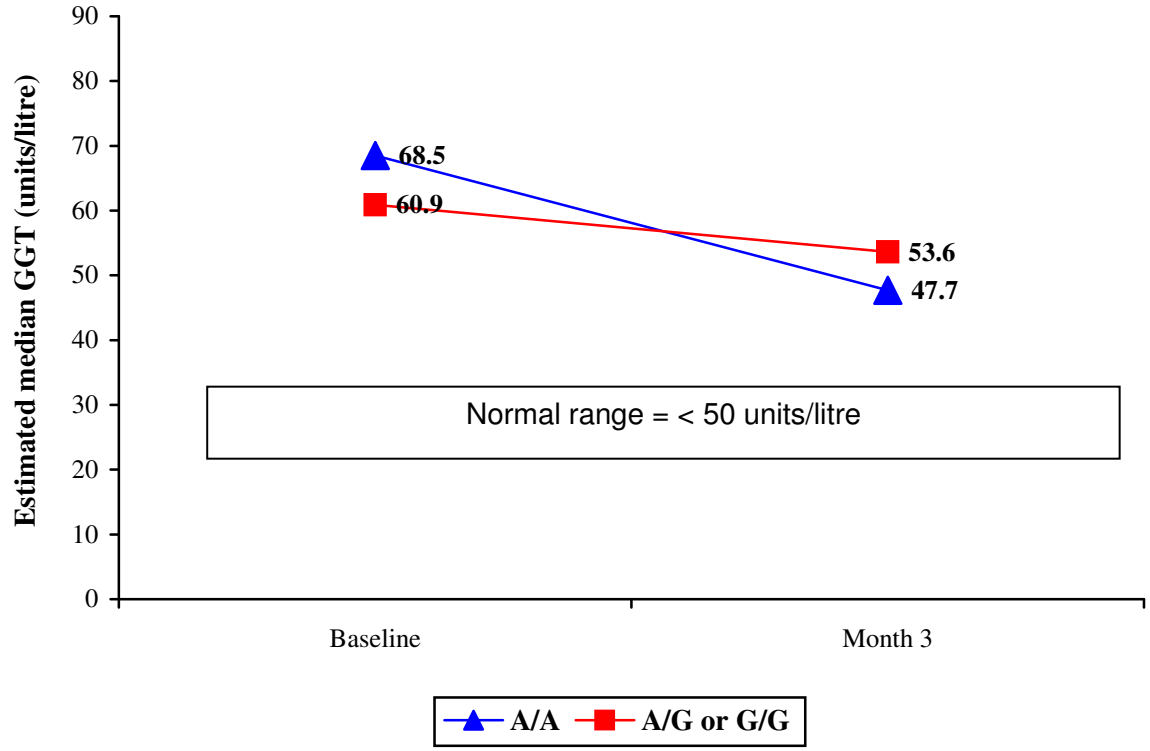
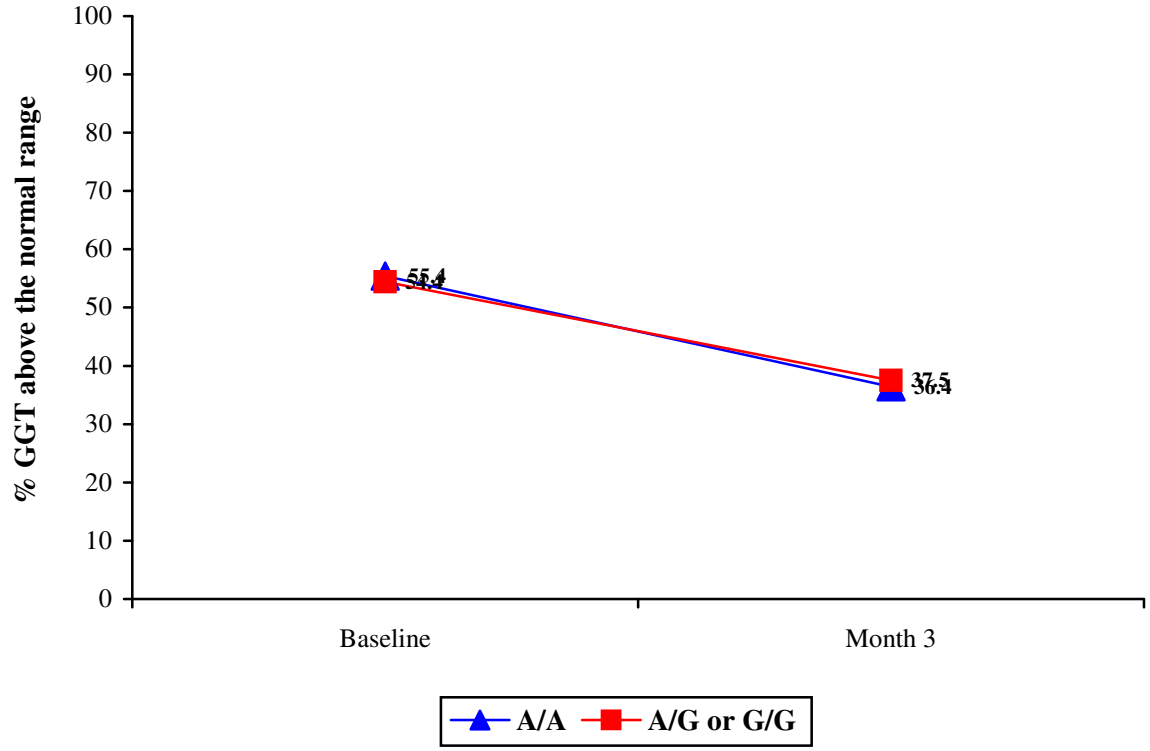


Figure 6: % Participants with GGT above the Normal Range according to Genotype



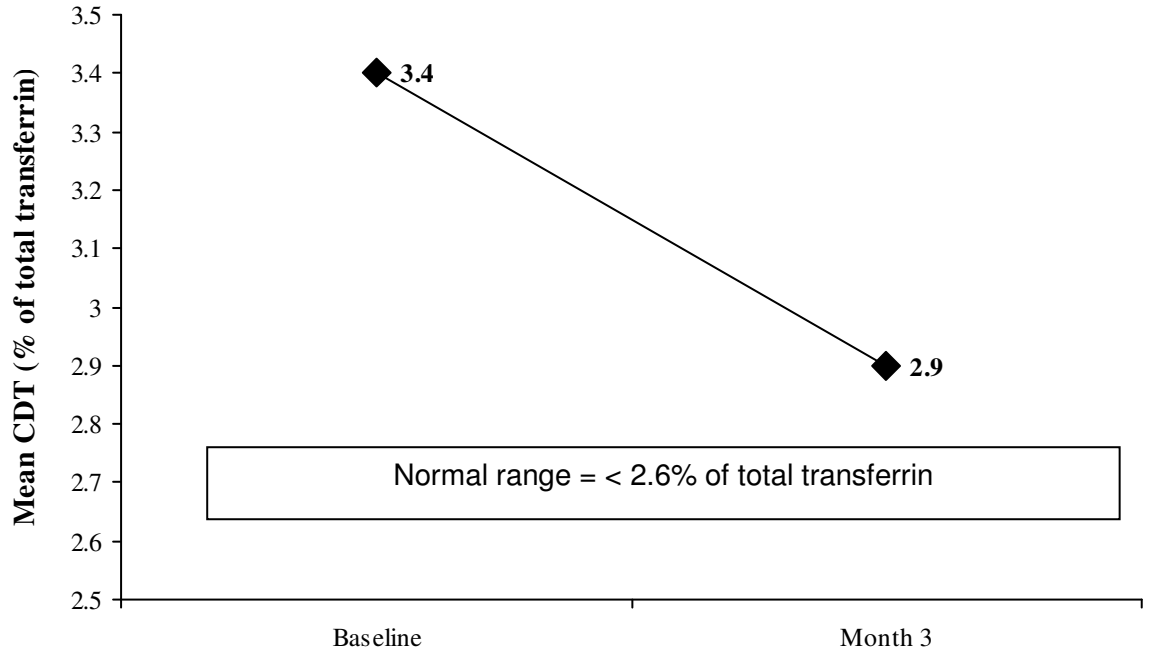
[3] Median values refer to those estimated in the linear mixed effects model

Carbohydrate Deficient Transferrin (CDT)

Due to problems with the blood sample analyses, complete data were only available for 39 participants. We were therefore unable to look at comparisons between genotype groups.

The distribution of CDT was right skewed, so data were log transformed and results were modelled using a linear mixed effects model. Figure 7 shows there was a significant reduction in CDT from baseline to month 3 (p=0.042).

Figure 7: CDT over Time[4]



Time to First Relapse

Overall, 46% of participants had their first relapse within the first week and 68% within the first month. The number of days to first relapse was compared between genotype groups, with no significant difference found. Participants homozygous for the Asn40 genotype (A/A) had a median number of 11 days before their first relapse, compared with 10 days for those with one or two copies of the variant allele (A/G or G/G).

Chi-square analyses were performed to compare the proportion of participants who had relapsed by day 7 and by day 28. Again, there were no differences according to genotype group (p=0.966 and p=0.318, respectively).

[4] Median values refer to those estimated in the linear mixed effects model

Alcohol Use during Trial

This measure was based on self-report data, and was modelled using a negative binomial model with the log of the number of days of participation included as an offset to compare the proportion of days alcohol was used. Participants with the Asn40 genotype reported a mean of 17.6 days of alcohol use throughout the trial, compared with 21.9 days for those with the Asp40 variant. A chi-square analysis found no significant difference between genotype groups (p=0.561).

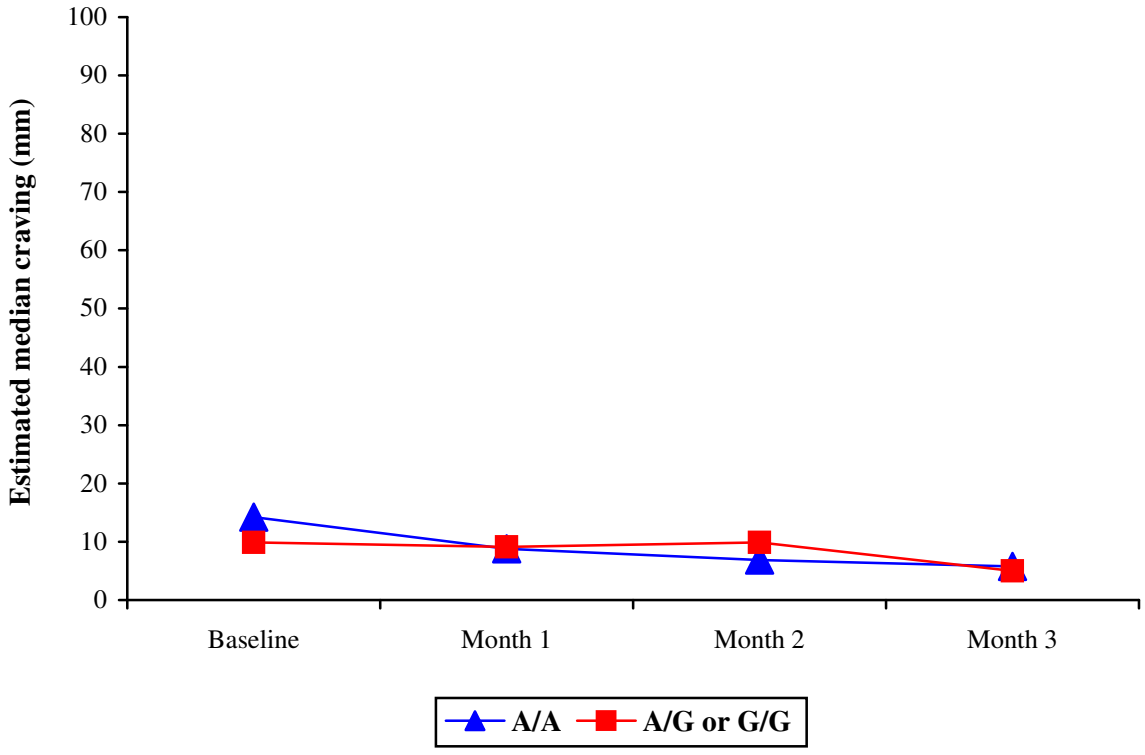
Craving for Alcohol

Craving was measured using a visual analogue scale, where participants had to record their *current* level of craving by drawing a vertical line on a continuum from 0 "no craving" to 100 "maximum experienced".

The distribution of craving scores was right skewed, so data were log transformed and the relationship between craving and genotype was modelled using a linear mixed effects model. Overall, Figure 8 shows that participants' baseline craving for alcohol was low, with a median score of 12. However, there were consistent decreases in craving over the treatment period, which were statistically significant (p=0.017) but there were no differences according to genotype (p=0.918).

Post-hoc tests were carried out, which found that in both groups, baseline craving was significantly higher than at all subsequent time points (month 1 p=0.041; month 2 p=0.032; month 3 p<0.001). Moreover, craving at month 3 was significantly lower than at month 1 (p=0.039).

Figure 8: Estimated Median Craving for Alcohol according to Genotype[5]



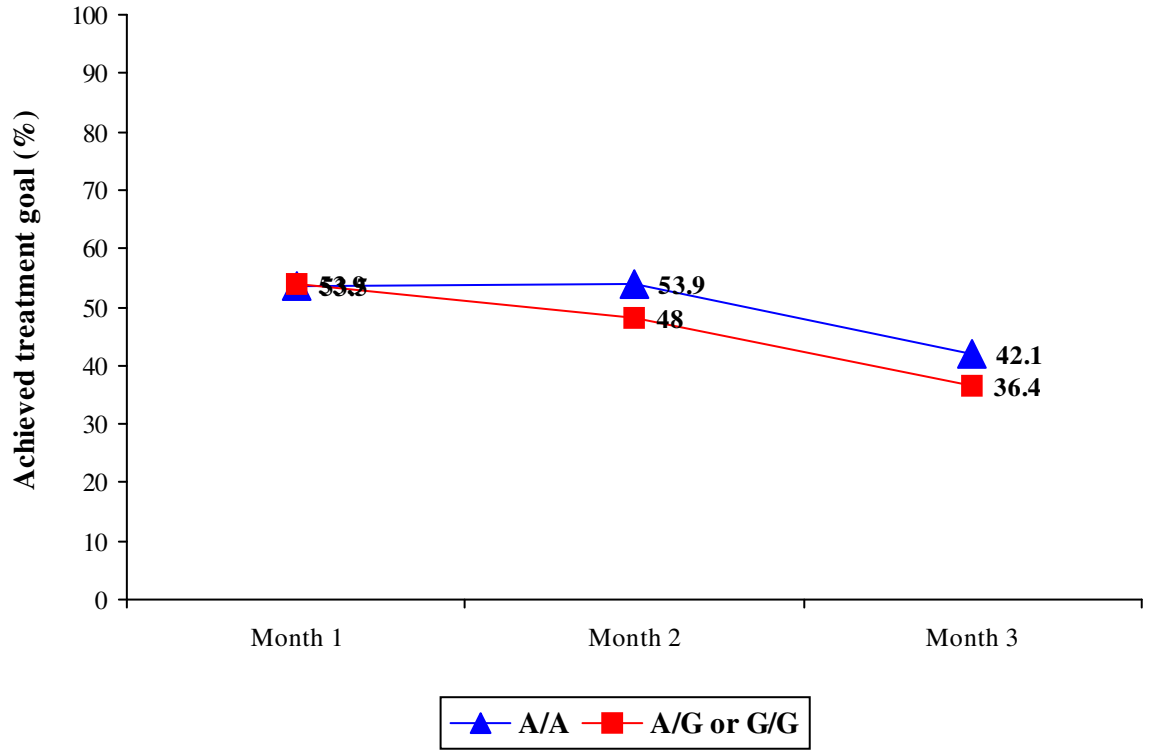
[5] Median values refer to those estimated in the linear mixed effects model

Goal of Treatment

Participants were asked during their counselling sessions to state their main goal in commencing treatment. Of the 71 participants who specified a goal, 48 (68%) were seeking abstinence and 23 (32%) a reduction in use/controlled drinking. In order to examine the potential impact of genotype on treatment goal, a new variable was created measuring the proportion of participants who achieved their goal after each month of treatment. For those seeking abstinence, "achieving goal" was defined as no alcohol consumption in the week prior to assessment, and for those seeking controlled drinking, "achieving goal" was based on consumption of alcohol within the NH&MRC drinking guidelines for safe drinking.

Figure 9 shows that the proportion of participants who achieved their treatment goal was similar between genotype groups, and was around 53% after month 1, falling to 42% at the end of treatment for those homozygous for the Asn40 genotype and to 36% for those with at least one copy of the Asp40 allele. Changes over time in the proportion of participants who achieved their treatment goal were not significant (p=0.226) and there were no differences between groups (p=0.646). Further analyses looking at each treatment goal separately found consistent results, although for controlled drinkers, there was a trend to an increased percentage of those homozygous for the Asn40 genotype achieving their goal over the treatment period (56% vs 34%; p=0.099).

Figure 9: % Achieved Treatment Goal according to Genotype



Duration of Treatment

Participants homozygous for the Asn40 genotype (n=65) remained in treatment for a mean of 9.6 weeks (SD=3.9) compared with 10.3 weeks for those with at least one copy of the Asp40 allele (SD=3.1). This difference was not statistically significant (p=0.928).

Side-Effects

Participants were asked to record any side-effects experienced in the first week of treatment. Nearly 45% of those homozygous for the Asn40 genotype reported no side-effects, 44.6% reported one and the remaining 11% reported two or more. These included nausea (*n*=14), fatigue (*n*=4), headaches (*n*=4) and abdominal cramps (*n*=3).

In comparison, 34% of participants with at least one copy of the Asp40 allele did not report side-effects, while 54% reported one and 12% two or more. Side-effects among this group included nausea (*n*=4), fatigue (*n*=3) and headaches (*n*=3).

Using a chi-square analysis, there was no difference between genotype groups in the proportion who reported side-effects in the first week of treatment (p=0.314).

Completers vs Non-Completers

Analyses were performed on a sub-group who completed the 12 weeks of treatment (*n*=68). This group comprised 44 homozygous for the Asn40 genotype and 24 with at least one copy of the Asp40 allele. Results were consistent with those reported for the sample as a whole; that is, there was no significant association between genotype group on any of the outcomes measured (self-report and objective measures of alcohol use, time to first relapse or craving). However, there was still a significant decrease over time in both self-reported and objective measures of alcohol use (p<0.001) and craving (p=0.050).

A chi-square analysis also revealed no significant difference in the proportion of completers and non-completers reporting side-effects in the first week of treatment (p=0.131).

In summary, while treatment with naltrexone and cognitive-behavioural therapy was effective in reducing alcohol consumption and craving, there was no evidence that genotype was a significant factor in improving outcomes. In order to examine whether other factors may have contributed to treatment success, the sample was divided into groups according to (1) source of referral; and (2) pre-treatment abstinence. Results are presented in the following sections.

Section 2: Community Referrals vs Inpatient Detoxification

Participants were divided into two groups according to their referral source: either from an inpatient detoxification unit (*n*=54) or from the community, primarily through GPs (*n*=46). Groups were compared on measures of alcohol consumption and craving using the same statistical models as for the genotype analyses.

Characteristics of Sample

Table 3: Sample Characteristics

Variable	Community Referrals (*n*=46)	Inpatient Unit (*n*=54)
% male	67	48
Mean age (years)*	41.8 (9.2)	43.1 (8.4)
Mean age began daily use (years)*	25.1 (8.0)	28.0 (8.9)
% university education	15	15
% currently unemployed/disability pension	37	52
% currently married/*de facto*	39	33
% with children	63	76
% with family history[6] of alcohol dependence/abuse	80	72
% previous treatment for alcohol dependence	89	94
% seeking abstinence as treatment goal	51 **	83
Mean no. weeks in study*	10.0 (3.5)	9.8 (3.7)
Mean no. CBT sessions during study*	2.0 (1.7)	1.8 (1.4)
Mean no. alcohol free days prior to first tablet*	4.2 (9.6) **	5.3 (3.5)
Estimated median self-reported alcohol use at baseline (total grams in previous week)	737	1490
Estimated median GGT at baseline (units/litre)	49 #	97
Mean MCV at baseline (fl)	94 #	97
Estimated median craving at baseline (mm)	11	14

* Standard deviations in brackets
** Statistically significant $p<0.01$

Table 3 shows that there were several significant differences between groups at baseline. As expected, participants recruited from inpatients had a significantly higher number of alcohol-free days compared with those recruited from other sources. In addition, 83% of the inpatient group stated abstinence as their treatment goal compared with 51% of the community sample. This difference was statistically significant. The inpatient group also had significantly higher MCV and GGT levels at baseline.

[6] Based on self-report; defined as parents, grandparents or siblings

Self-Reported Alcohol Use

Figure 10: Estimated Median Self-Reported Alcohol Use according to Referral Source[7]

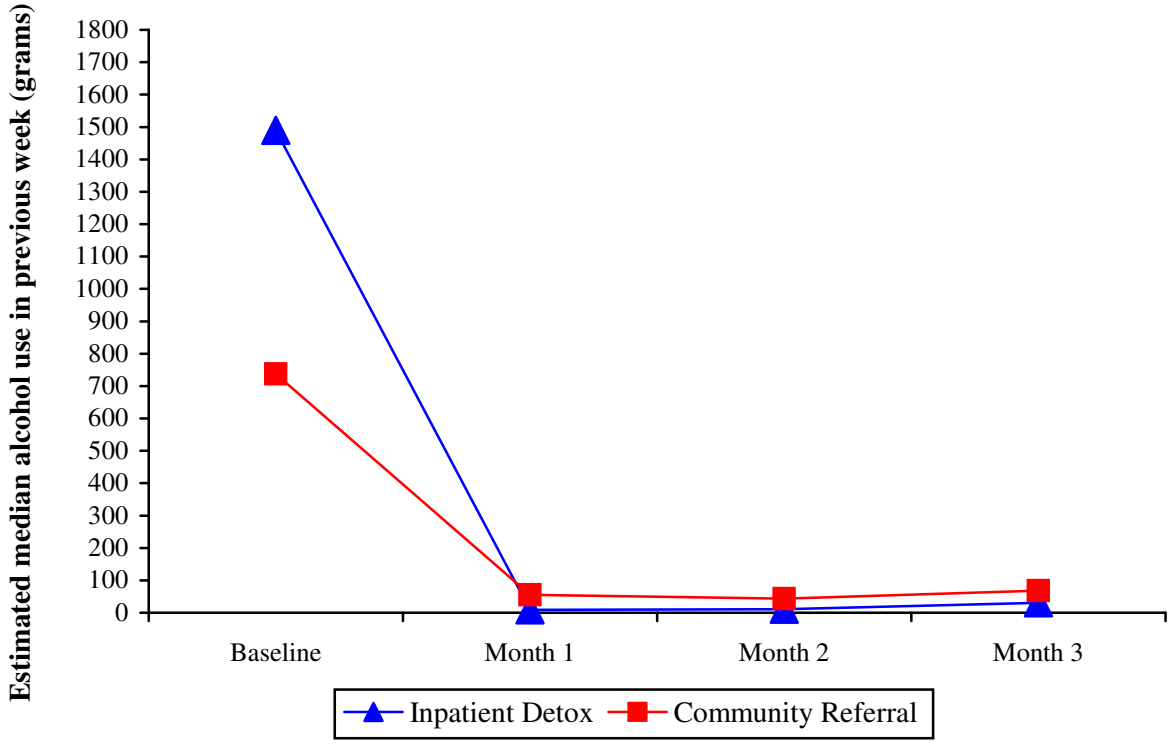
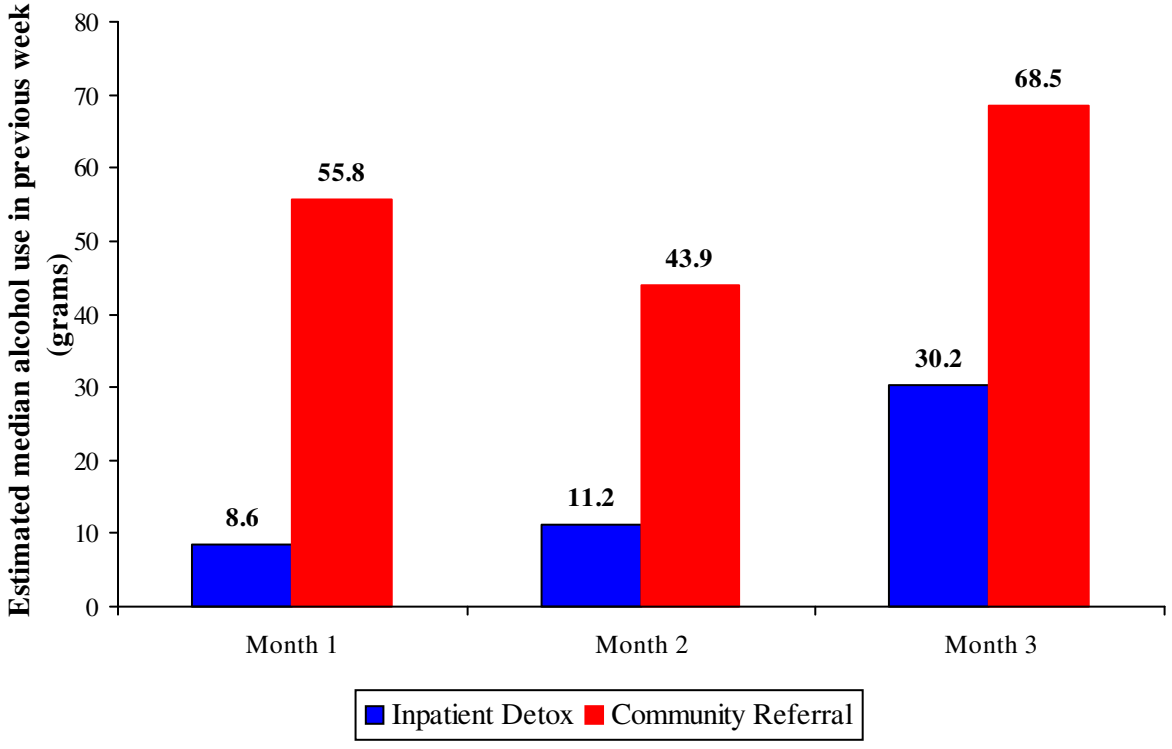


Figure 11: Estimated Median Self-Reported Alcohol Use during Treatment Period Only[7]



[7] Median values refer to those estimated in the linear mixed effects model

Figures 10 and 11 present changes in alcohol consumption for each group. There was a statistically significant effect over time, with decreases in use over the treatment period (p<0.0001). Both inpatient and community-referred samples showed significant reductions in alcohol use between baseline and all subsequent time points (p<0.0001). In addition, within the inpatient sample alcohol use at month 3 was significantly higher than at month 1 and at month 2 (p=0.005 and p=0.011 respectively), although consumption did not return to baseline levels.

A significant group by time interaction was also found (p<0.0001), where self-reported alcohol use at months 1 and 2 was significantly lower in the inpatient group (p<0.001 and p=0.007 respectively).

Objective Measures of Alcohol Use

Mean Corpuscular Volume (MCV)

Figure 12: MCV according to Referral Source

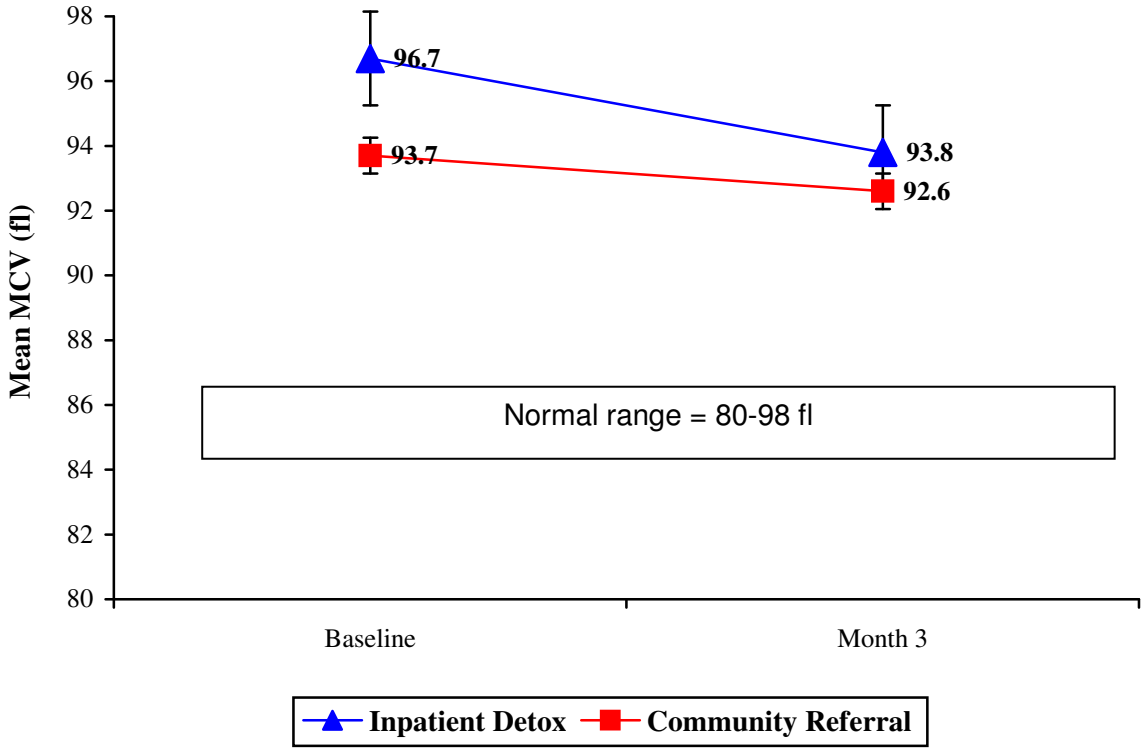
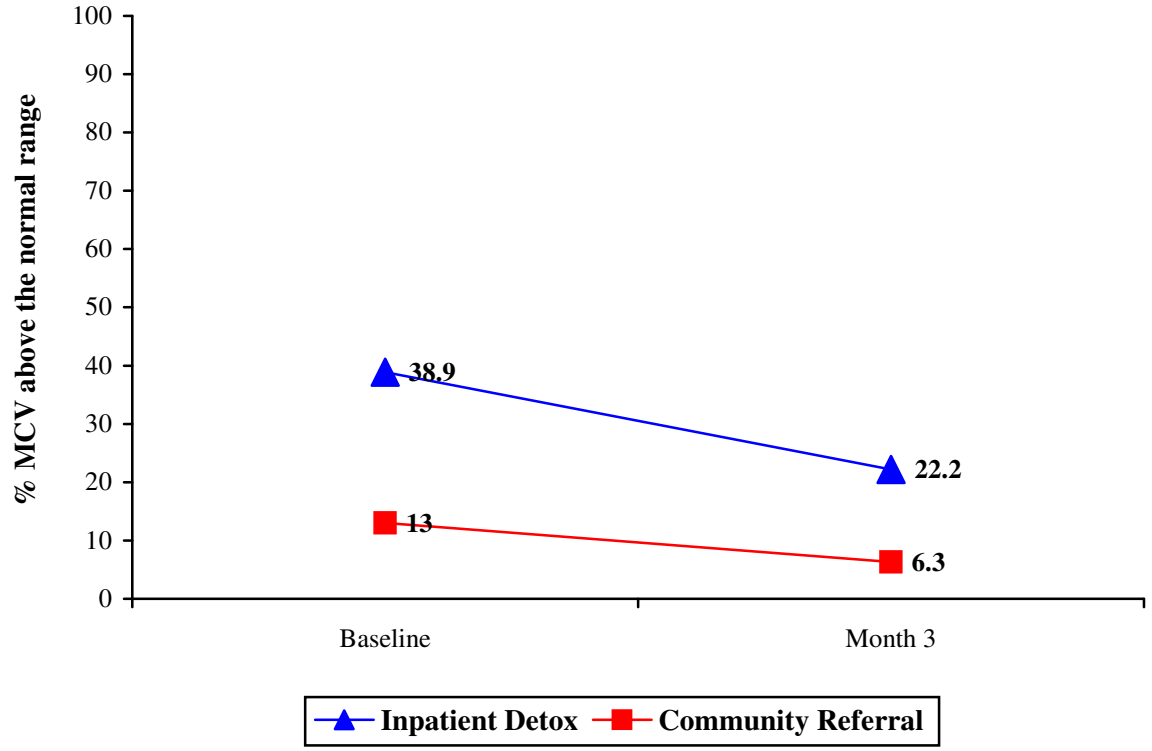


Figure 12 shows that MCV levels decreased between baseline and month 3 for both groups, a difference which was statistically significant (p<0.0001) A significant group by time interaction effect was reported (p=0.014), with MCV levels among participants recruited from inpatients showing a greater reduction over time.

As with genotype comparisons, the effects of naltrexone on MCV were investigated further by looking at the percentage of participants with levels above the normal range over the treatment period. Figure 13 presents the results according to referral source.

There were significant decreases in the percentage of participants with MCV levels above the normal range from baseline to month 3 (p=0.052). There were also significant differences between groups, with a higher percentage of participants referred from inpatients having MCV levels above the normal range over the treatment period (29% vs 9%; p<0.001). Note that baseline MCV was significantly higher among this group (see Table 3).

Figure 13: % Participants with MCV above the Normal Range according to Referral Source



Gammaglutamyl Transferase (GGT)

As with MCV, Figure 14 shows that GGT levels decreased between baseline and month 3 for both groups. This difference was statistically significant ($p<0.001$). A group by time interaction effect was also reported, indicating that the change in GGT from baseline to month 3 was significantly different between the groups ($p=0.035$). Figure 14 clearly shows that GGT levels decreased more over time among participants referred from inpatients.

In Figure 15, GGT results are presented for each group as the percentage of participants with levels above the normal range over the treatment period. Again, there was a significant decrease in GGT over time for both groups ($p=0.001$). There was also a significant difference between groups, where a higher proportion of participants referred from inpatients had levels above the normal range (54% vs 34%; $p=0.006$). As with MCV, baseline GGT was significantly higher among the inpatient group (Table 3). However, there was no evidence of an interaction effect; that is, the change in the proportion of participants with GGT above the normal range over time did not differ between groups.

Figure 14: Estimated Median GGT according to Referral Source[8]

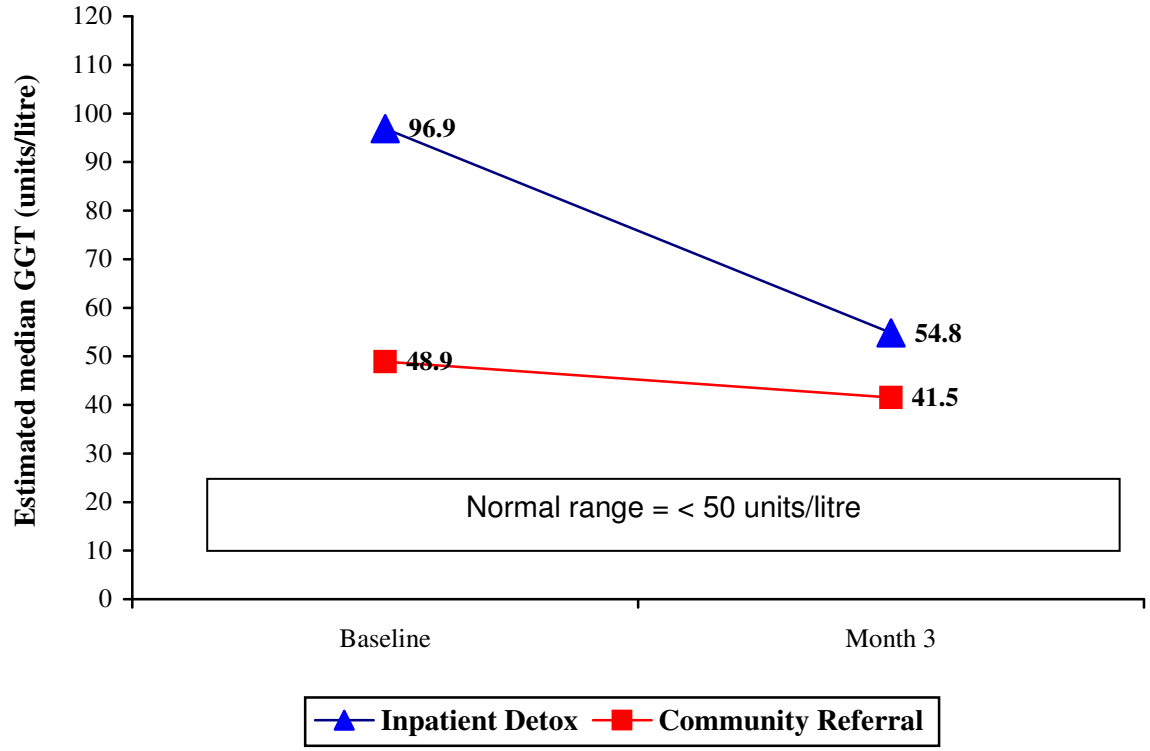
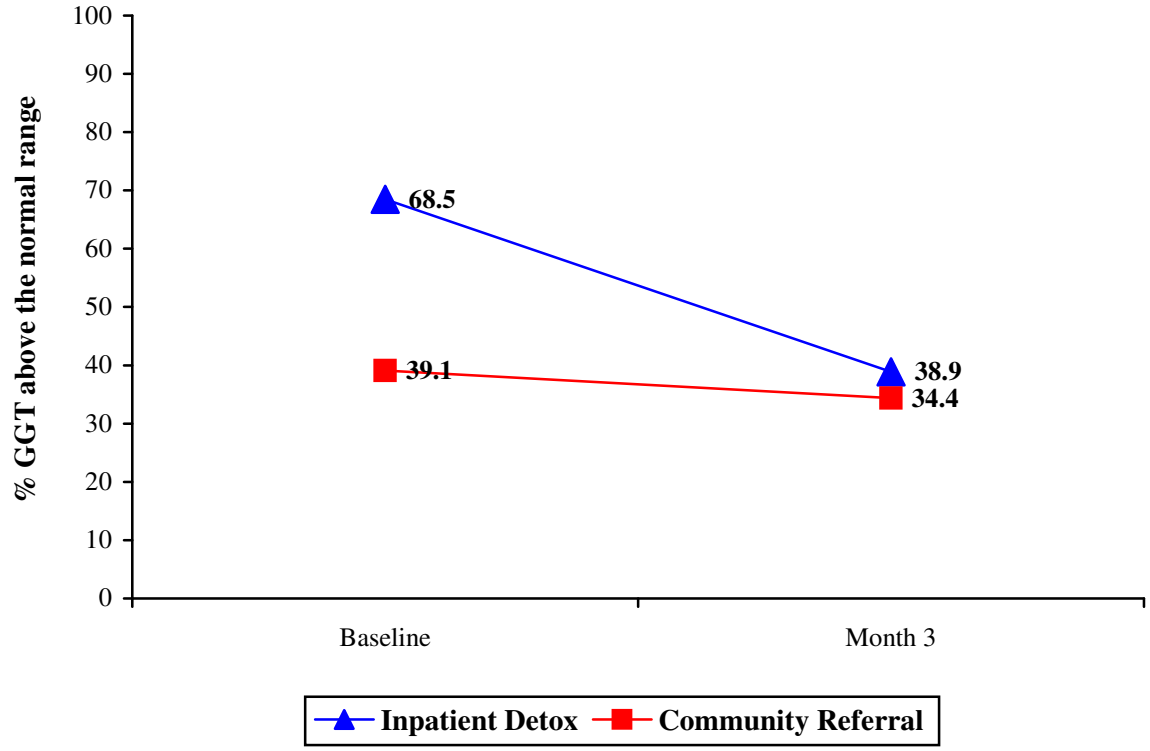


Figure 15: % Participants with GGT above the Normal Range according to Referral Source



Time to First Relapse

[8] Median values refer to those estimated in the linear mixed effects model

The number of days to first relapse was compared between groups, with those referred from inpatient detoxification remaining abstinent for a significantly higher number of days (median 26.5 days compared with 4.0: $p<0.001$).

Chi-square analyses were also performed to compare the proportion of participants who had relapsed by day 7 and by day 28. A significantly lower proportion of those referred from inpatients had relapsed ($p=0.006$ and $p<0.001$, respectively).

Alcohol Use during Trial

A chi-square analysis found that participants referred from inpatient detoxification reported a significantly lower number of days in which alcohol was used compared with those referred from the community (12.7 days compared with 26.7 days, respectively: $p=0.004$).

Craving for Alcohol

Figure 17: Estimated Median Craving for Alcohol according to Referral Source[9]

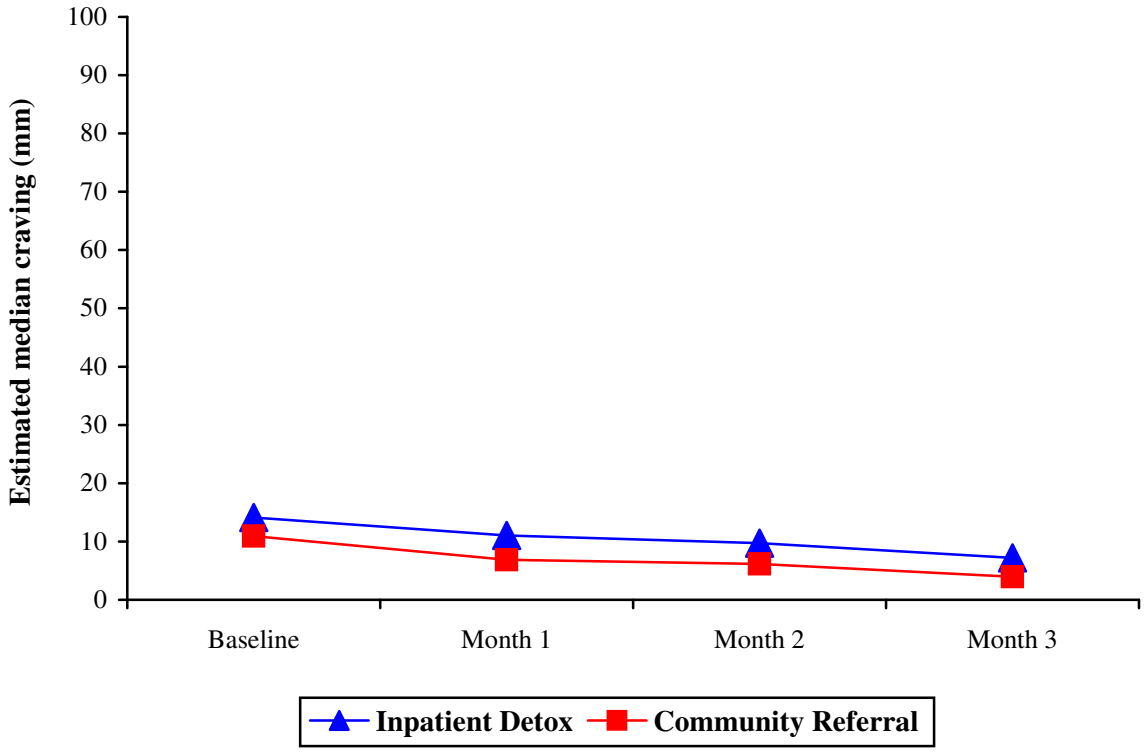


Figure 17 shows craving for alcohol over the treatment period according to referral source. While participants within each group demonstrated significant reductions over time ($p=0.008$), there were no differences between groups ($p=0.112$).

Post-hoc tests found that baseline craving was significantly higher than at all subsequent time points (month 1 $p=0.040$; month 2 $p=0.031$; month 3 $p<0.001$). In addition, craving at month 3 was significantly lower than at month 1 ($p=0.040$).

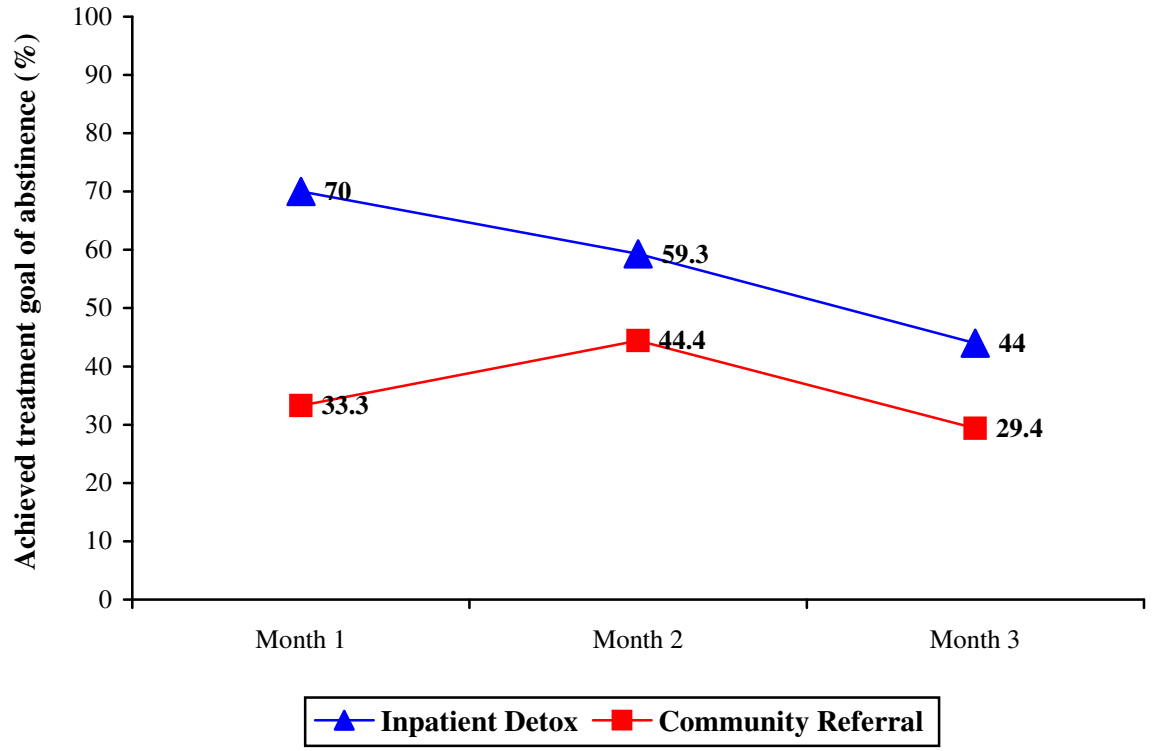
Goal of Treatment

As was done for genotype, the proportion of participants who achieved their treatment goal was compared over time according to referral source. Changes over time were not significantly different

[9] Median values refer to those estimated in the linear mixed effects model

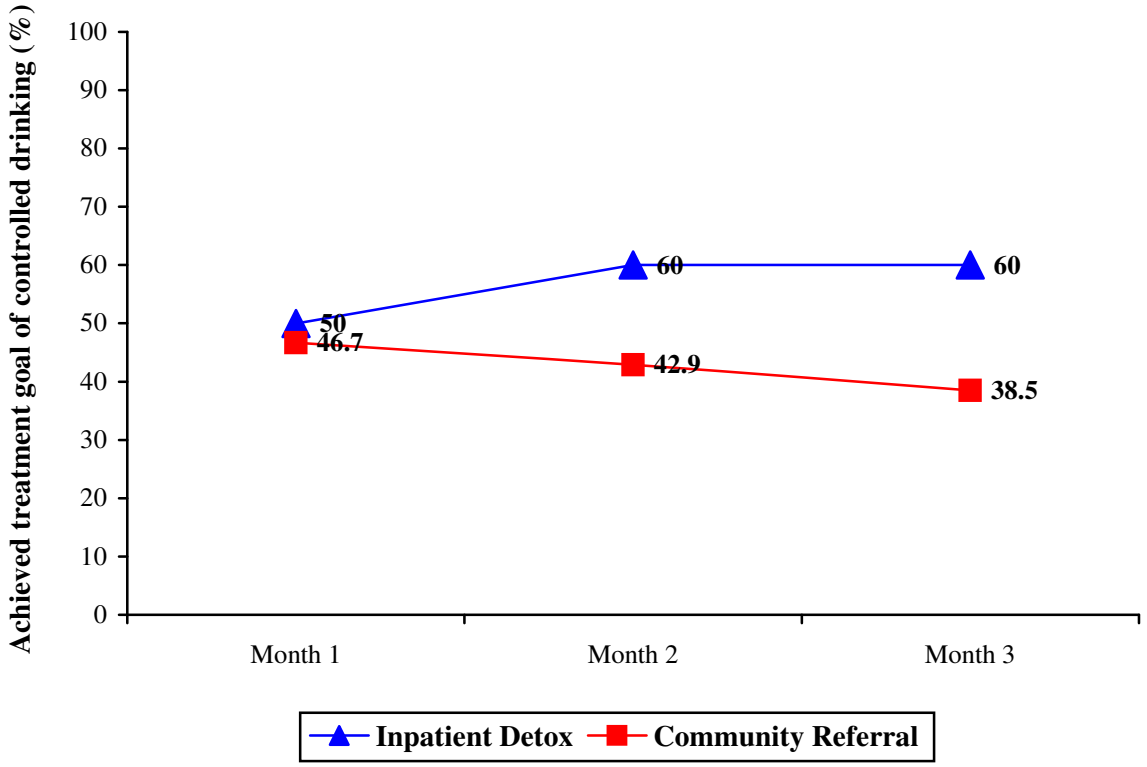
(p=0.226) but there was a difference between groups, with a higher proportion of participants referred from inpatients achieving their goal (57% vs 38%; p=0.006). However, this may be confounded by imbalances between the two referral groups on this variable: at baseline, a significantly higher proportion of participants referred from inpatients stated abstinence as their treatment goal (see Table 3). Consequently, further analyses were carried out to control for this, which involved examining the proportion that met their treatment goal *separately* for the goals of abstinence and controlled drinking. For each group, we then examined whether there was an effect of referral source on the achievement of that goal. By matching participants according to their goal of treatment one can control for its effect.

Figure 18: % Achieved Treatment Goal of Abstinence according to Referral Source



For the goal of abstinence (Figure 18), although there was a trend to decreases in the proportion who achieved their treatment goal over time, changes within each group were not significant (p=0.154). Moreover, Figure 18 shows that a consistently higher proportion of participants referred from inpatients achieved their treatment goal from month 1 to month 3, a difference which was significant (57% vs 35%; p=0.008).

Figure 19: % Achieved Treatment Goal of Controlled Drinking according to Referral Source



Looking at participants with a goal of controlled drinking, although a higher proportion of those referred from inpatients achieved their goal, which also increased slightly over time, differences were not statistically significant either within (p=0.984) or between groups (p=0.365).

Duration of Treatment

Participants referred from inpatient detoxification remained in treatment for a mean of 9.8 weeks (SD=3.7) compared with 10.0 weeks for those referred from the community (SD=3.5). This difference was not statistically significant (p=0.757).

Side-Effects

Fifty percent of participants referred from inpatient detoxification reported at least one side-effect in the first week of treatment, compared with 70% of those referred from the community. A chi-square analysis found that this difference was statistically significant (p=0.046).

Section 3: Effects of Pre-Treatment Abstinence on Outcomes

There was variation between participants in the number of alcohol-free days (AFDs) they reported prior to commencing treatment. The mean number was 4.8 days, with a median of 4 days.

Participants were divided into two groups: those with four or more alcohol-free days prior to commencing (*n*=56) and those with less than four days (*n*=44). Groups were compared on measures of alcohol consumption and craving. Note that the same statistical models were used as for the genotype and referral source analyses.

Characteristics of Sample

Table 4: Sample Characteristics

Variable	≥ 4 days (*n*=56)	0-3 days (*n*=44)
% male	54	61
Mean age (years)*	42.7 (8.5)	42.2 (9.3)
Mean age began daily use (years)*	26.8 (8.4)	26.5 (8.9)
% university education	11	21
% currently unemployed/disability pension	52	36
% currently married/*de facto*	29	34
% with children	75	64
% with family history[10] of alcohol dependence/abuse	75	77
% previous treatment for alcohol dependence	93	91
% referred through inpatient detoxification clinic	84**	16
Mean no. weeks in study*	9.5 (3.8)	10.3 (3.3)
Mean no. CBT sessions during study*	1.7 (1.6)	2.2 (1.6)
% seeking abstinence as treatment goal	85**	51
Estimated median self-reported alcohol use at baseline (total grams in previous week)	1407	768
Estimated median GGT at baseline (units/litre)	87	55
Mean MCV at baseline (fl)	96	94
Estimated median craving at baseline (mm)	13	12

* Standard deviations in brackets
** Statistically significant $p<0.01$

Table 4 shows that participants with at least four days of pre-treatment abstinence were significantly more likely to have been referred from inpatient detoxification, as well as have an abstinence-based treatment goal.

[10] Based on self-report; defined as parents, grandparents or siblings

Self-Reported Alcohol Use

Figure 20: Estimated Median Self-Reported Alcohol Use according to Days of Abstinence[11]

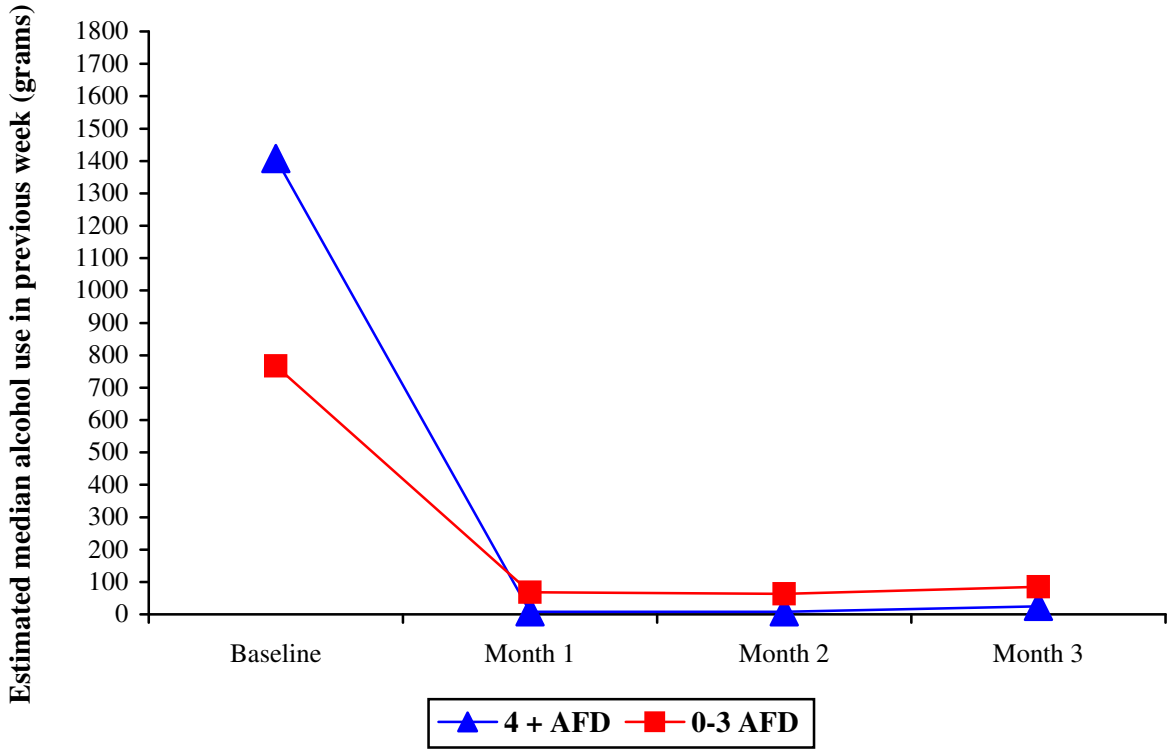
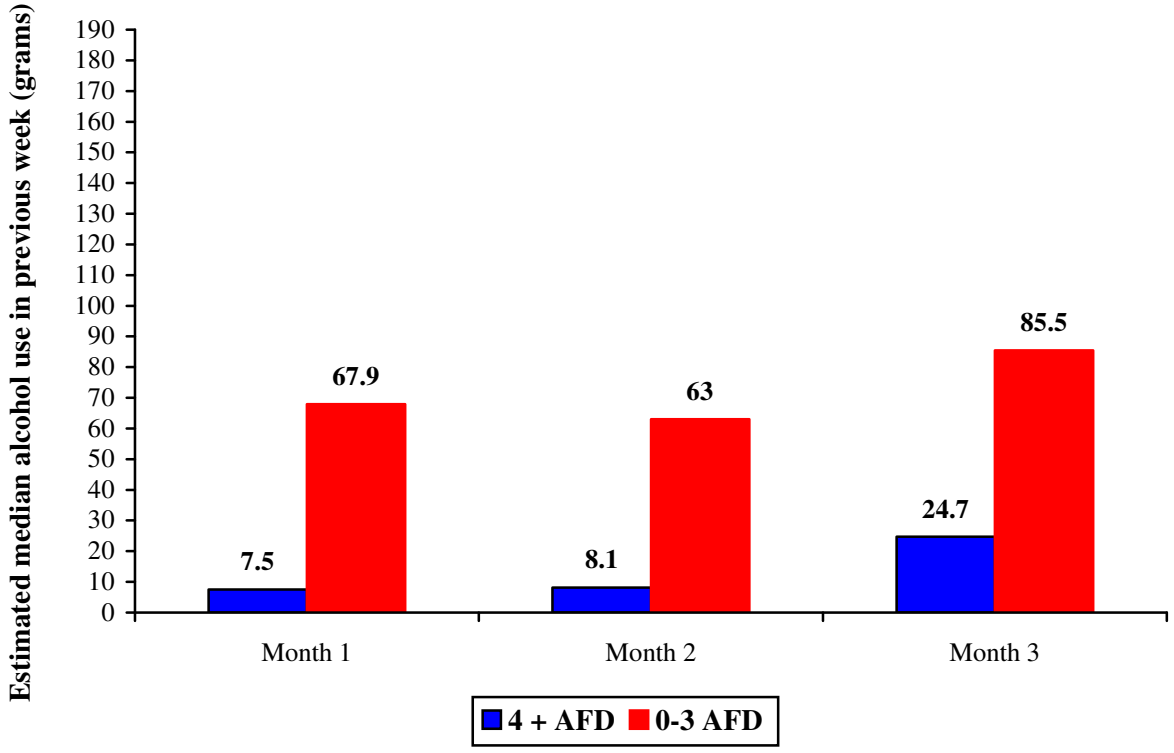


Figure 21: Estimated Median Self-Reported Alcohol Use during Treatment Period Only[11]



[11] Median values refer to those estimated in the linear mixed effects model

Figures 20 and 21 present changes in alcohol consumption for each group. There was a statistically significant effect over time, with decreases in use over the treatment period (p<0.0001). Post-hoc tests revealed that in both groups, self-reported alcohol use was significantly higher at baseline compared with all subsequent time points. In addition, for the group with higher pre-treatment abstinence, self-reported alcohol use at month 3 was significantly higher than at months 1 and 2 (p<0.001), although consumption did not return to baseline levels.

There was also a significant group by time interaction (p<0.0001), indicating that self-reported alcohol use at months 1-3 was significantly lower in the group with more days of pre-treatment abstinence (p<0.0001, p<0.0001 and p=0.014 respectively).

Objective Measures of Alcohol Use

Mean Corpuscular Volume (MCV)

Figure 22: MCV according to Days of Abstinence

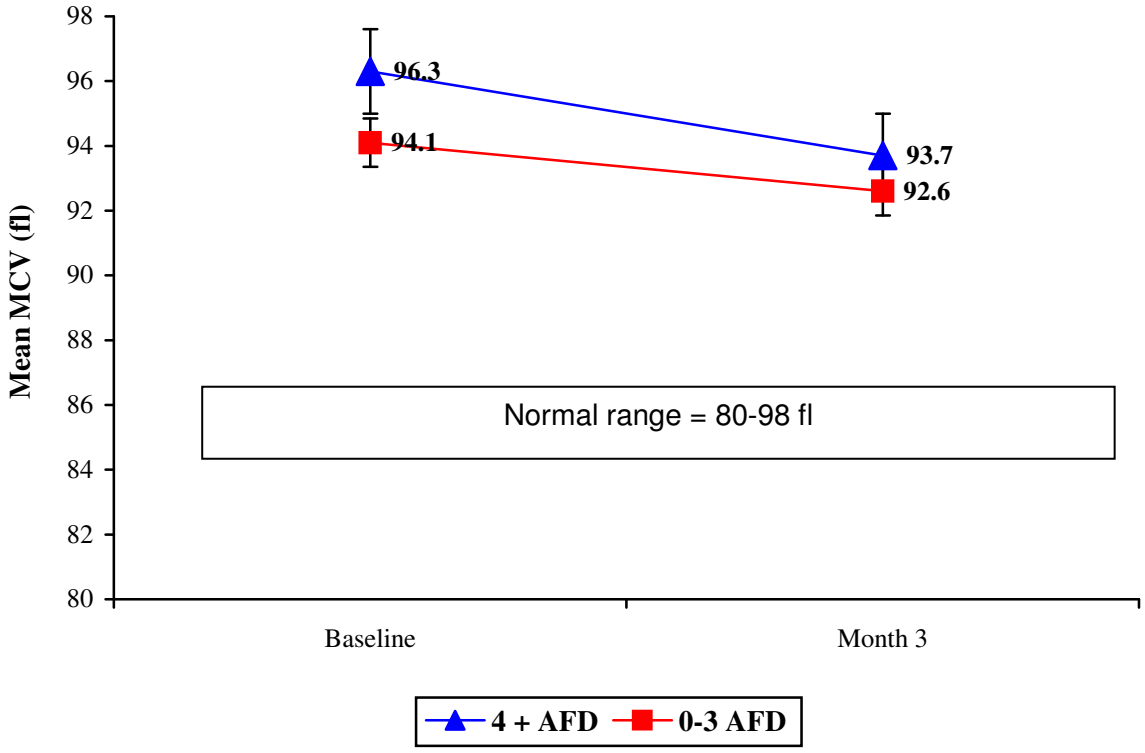
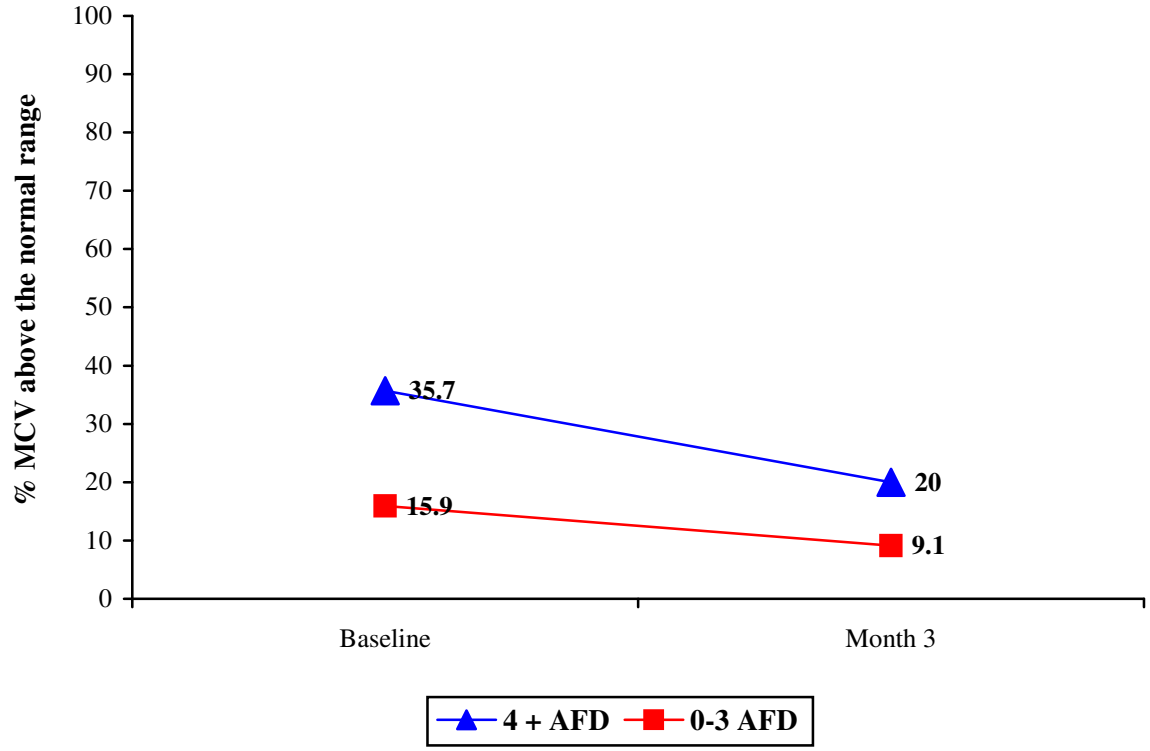


Figure 22 shows there was a decrease in MCV levels over time in both groups, which was statistically significant (p<0.0001). Differences between groups were not significant (p=0.072).

As was done in previous sections, the effects of naltrexone on MCV were investigated further by looking at the percentage of participants with levels above the normal range over the treatment period. Figure 23 presents the results according to the level of pre-treatment abstinence. Changes over time approached significance for both groups (p=0.064), and there was a significant difference between groups, with higher levels of pre-entry abstinence associated with higher overall MCV levels above the normal range (50% vs 39%; p=0.009).

Figure 23: % Participants with MCV above the Normal Range according to Days of Abstinence



Gammaglutamyl Transferase (GGT)

Consistent with MCV levels, Figure 24 shows that there was a decrease in GGT levels over time for both groups, which was statistically significant ($p<0.001$). In addition, the group x time interaction was significant ($p=0.019$), indicating a greater reduction in GGT levels over time for the group with more days of pre-treatment abstinence.

In Figure 25, there was a significant decrease in the proportion of participants in both groups with GGT levels above the normal range ($p=0.015$) but no differences between groups ($p=0.108$).

Figure 24: GGT according to Days of Abstinence[12]

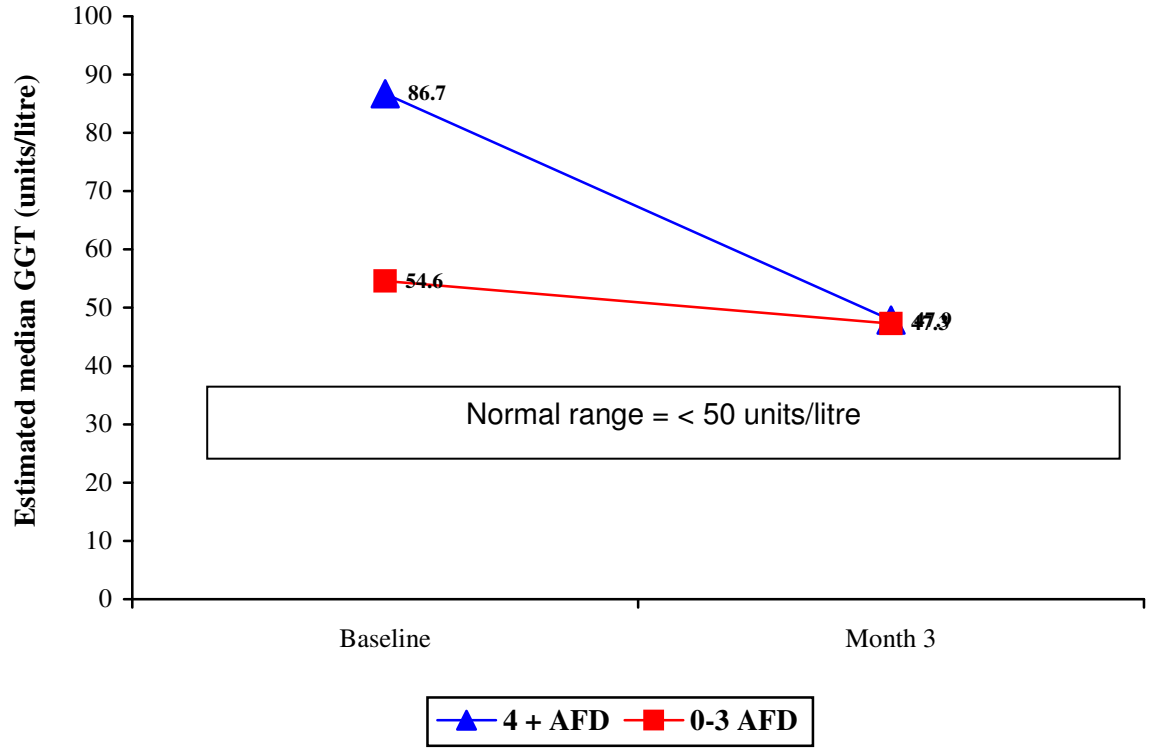
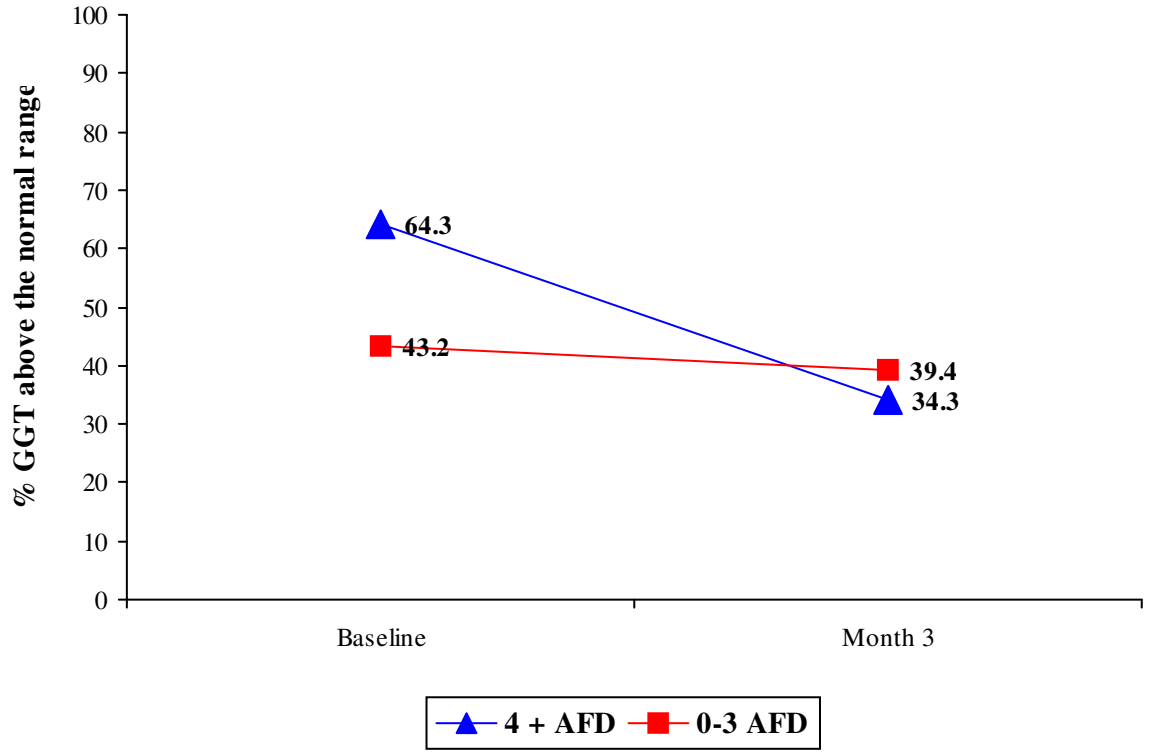


Figure 25: % Participants with GGT above the Normal Range according to Days of Abstinence



[12] Median values refer to those estimated in the linear mixed effects model

Time to First Relapse

The number of days to first relapse was compared between groups, with those having four or more says of pre-treatment abstinence remaining alcohol-free for a significantly higher number of days (median of 27.5 days compared with 3.5 for those seeking controlled drinking: $p<0.0001$).

Chi-square analyses were also performed to compare the proportion of participants who had relapsed by day 7 and by day 28. Again, a significantly lower proportion of those with more pre-treatment abstinence had relapsed within the first month ($p<0.0001$).

Alcohol Use during Trial

A chi-square analysis found that participants with at least four days of pre-treatment abstinence reported a significantly lower number of days in which alcohol was used compared with those having less than four alcohol-free days prior to commencing (10.6 days compared with 29.9 days, respectively: $p<0.0001$).

Craving for Alcohol

Figure 26: Craving for Alcohol according to Days of Abstinence[13]

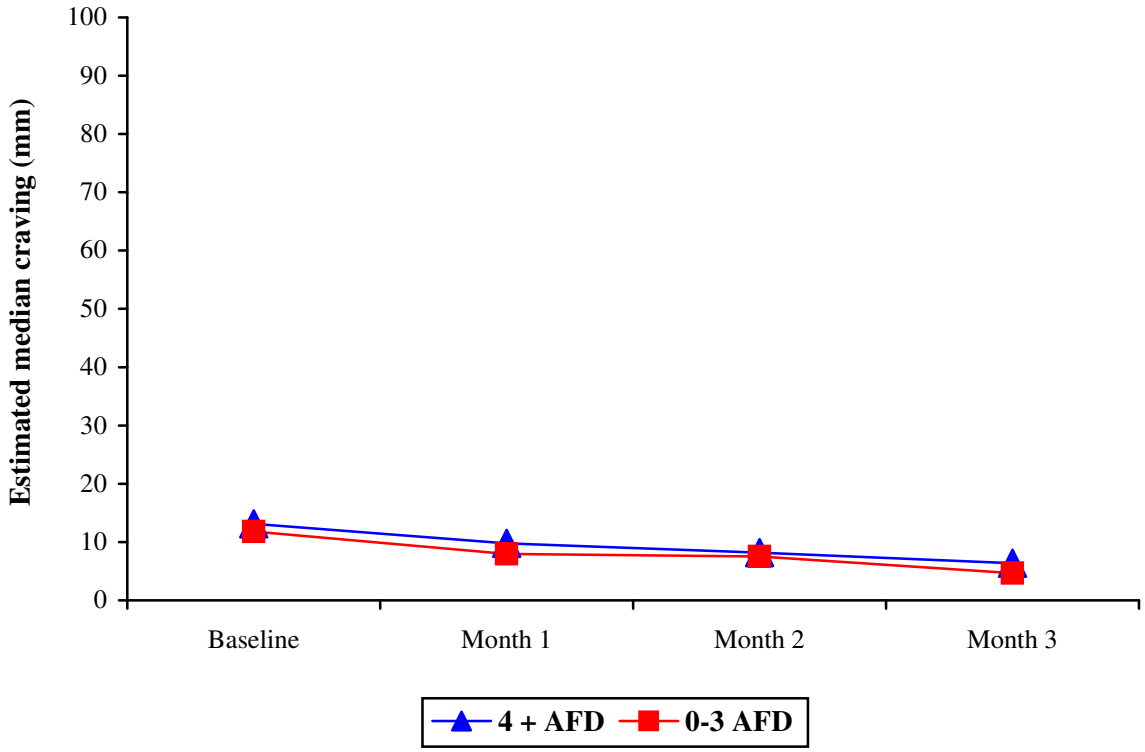


Figure 26 shows that craving for alcohol was similar between groups, and decreased significantly over time ($p=0.008$). However, there were no differences between groups ($p=0.514$). Post-hoc tests carried out at specific time points found that baseline craving was significantly higher than at all subsequent time points ($p=0.040$ at month 1; $p=0.032$ at month 2; $p<0.001$ at month 3). In addition, craving at month 3 was significantly higher than at month 1 ($p=0.041$).

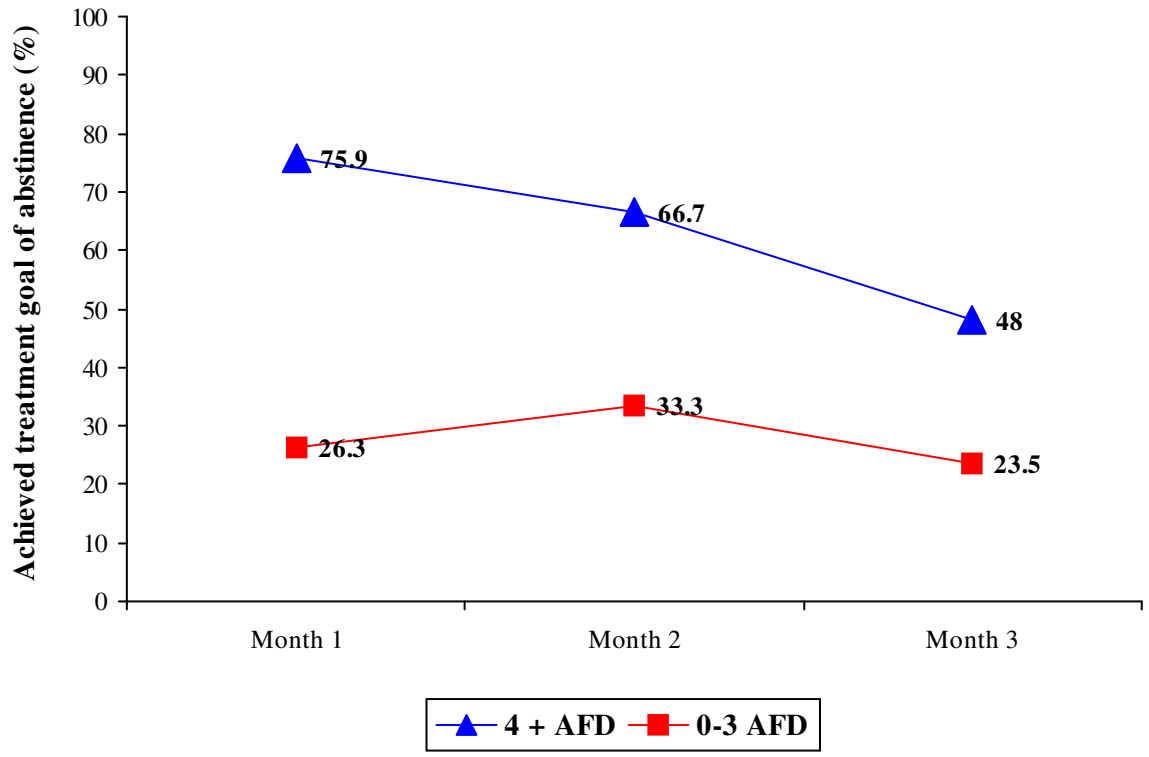
[13] Median values refer to those estimated in the linear mixed effects model

Goal of Treatment

As was done for genotype and referral source, the proportion of participants who achieved their treatment goal was compared over time according to referral source. Changes over time were not significantly different (p=0.182) but there was a difference between groups, with a higher proportion of participants with at least four days of pre-treatment abstinence achieving their goal over the treatment period (63% vs 34%; p<0.0001). However, this may again be confounded by imbalances between the two groups on this variable: at baseline, a significantly higher proportion of participants with four or more alcohol-free days prior to commencing stated abstinence as their treatment goal (see Table 4). Consequently, Figures 27 and 28 present results separately for the goals of abstinence and controlled drinking, respectively.

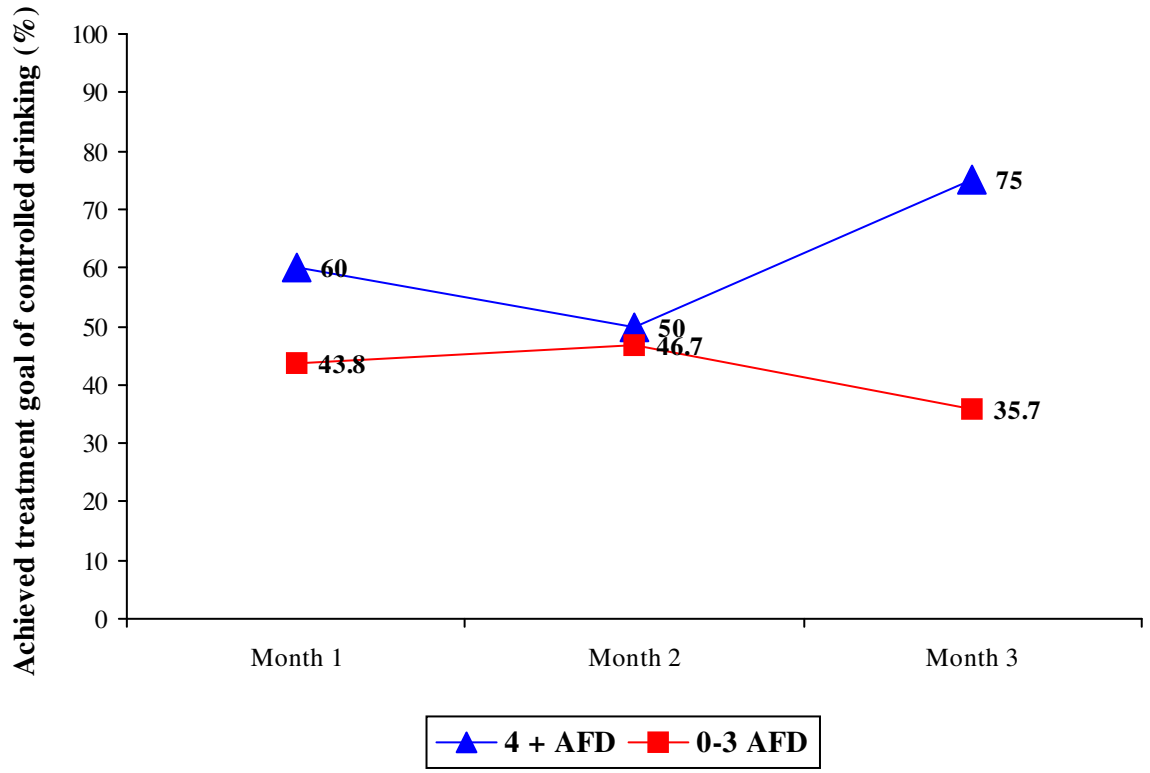
For the goal of abstinence (Figure 27), although there was a trend to decreases in the proportion who achieved their treatment goal over time, changes within each group were not significant (p=0.105). Moreover, Figure 27 shows that a consistently higher proportion of participants with four or more alcohol-free days achieved their treatment goal from month 1 to month 3, a difference which was significant (63% vs 27%; p<0.0001).

Figure 27: % Achieved Treatment Goal of Abstinence according to Days of Abstinence



Looking at participants with a goal of controlled drinking (Figure 28), although a higher proportion of those with at least four days of pre-treatment abstinence achieved their goal, particularly at the end of treatment, differences were not statistically significant either within (p=0.998) or between groups (p=0.225).

Figure 28: % Achieved Treatment Goal of Controlled Drinking according to Days of Abstinence



Side-Effects

Fifty-four percent of participants with four or more days of pre-treatment abstinence reported at least one side-effect in the first week of treatment, compared with 66% of those with less than four days abstinence. A chi-square analysis found that this difference was not statistically significant (p=0.212).

Duration of Treatment

Participants with at least four days of pre-treatment abstinence (n=56) remained in treatment for a mean of 9.5 weeks (SD=3.8) compared with 10.3 weeks for those with less than four days abstinence (SD=3.3). This difference was not statistically significant (p=0.315).

Attribution of Outcome

Participants who attended counselling were asked whether they attributed any treatment effects to naltrexone. Data were only available for 53% of the sample, as 25 did not attend any sessions and a further 22 did not provide any information. Details are in Table 6 below.

Table 6: Attribution of Outcome

Attribution	N
Naltrexone helping	21
Naltrexone not helping	11
Naltrexone helping a bit	5
Naltrexone as well as internalizing abilities re achieving/maintaining abstinence	3
Not sure if Naltrexone helping	2
Not sure, but effects of alcohol are less pleasurable	1
Not sure, but feels Naltrexone causes less intense need for alcohol	1
Naltrexone helping but also ultimatum from partner	1
Naltrexone helping but "overrides" it when decides to drink	1
Naltrexone, but also attending AA and seeing comorbidity counsellor	1
Alcohol tastes horrible, can't enjoy it: may be due to Naltrexone	1
Concern for health effects of alcohol	1
Cost of alcohol as a deterrent	1
Did not like Naltrexone; exacerbated side effects already experiencing from other problems	1
Head cold	1
Made up my mind	1

DISCUSSION/IMPLICATIONS

Naltrexone is one of the two most effective pharmacotherapies for treating alcohol problems. However, use is still limited in Australia and effectiveness of alcohol interventions could be enhanced by more widespread naltrexone prescribing. One factor leading to this underutilisation may be lack of confidence in the effectiveness of the drug. While research trials show an overall positive outcome, many patients do not benefit from naltrexone treatment and would be better diverted to other types of alcohol interventions.

This study was designed to explore previously reported findings of an association between genotype and improved outcomes with naltrexone treatment (Oslin et al., 2003; Anton et al., 2008). Although the findings of this earlier research were not replicated in our study, the results reinforce the notion that naltrexone is an effective treatment, and provide support for its use in general practice.

Overall, naltrexone combined with cognitive-behavioural therapy produced large and statistically significant decreases in alcohol consumption and craving over the three months of treatment. In addition, treatment retention was high and no serious adverse effects were reported. Although genotype was not a predictor of treatment success, there was a significant association between pre-entry abstinence and improved outcomes, suggesting the study had sufficient power to detect a difference according to genotype if one existed.

The results of this study do not support the use of genotyping to identify patients who might respond best to naltrexone. This avoids costly tests…other factors that are better…

The results of this study will be disseminated via presentations at international conferences, including APSAD in November 2008 for which an abstract has been submitted.

- Publications in scientific/clinical journals
- Direct presentation to general practitioner and other prescriber groups

Recommendations for prescribing naltrexone in clinical practice based on our findings

- Naltrexone works in combination with CBT
- May be more effective as a post-detoxification treatment

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