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INQUIRY INTO DRUG AND ALCOHOL TREATMENT

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Statement to the NSW Parliamentary Enquiry into Drug Treatment

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At the heart of the process of trying to close the naltrexone programs both here and elsewhere is an agenda driven by a few to want to decriminalise drugs and to install methadone as the only treatment option that should be available. They do not want to accept any suggestion or evidence that there might be a better more effective option. The spread of methadone in Australia and now into the Asian nations where there are several million dependent on heroin is only in the interests of the pharmaceutical companies who market methadone as a major strategy to combat HIV spread by injecting drug use. There is no evidence to support this claim (See the attached papers: " The Use of Methadone or Naltrexone for Treatment of Opiate Dependence: An Ethical Approach" and "How effective is Methadone: What does the research say?").

This campaign to legalise or decriminalise drugs is misguided as it is well accepted that to make any drug more accessible, available or acceptable increases the use of that drug. The legalisation and regulation of nicotine has led to a massive use of this dangerous and addictive substance, which has accounted for some 20,000 deaths each year. The heart of the anti-smoking campaign is built on the basis of reducing its attractiveness and availability. The war on cigarette smoking is slowly being won.

Those who advocate dispensing with deterrents, reducing the cost and making heroin and other addictive drugs easier to obtain would be horrified if we threw the strategies to reduce alcohol, nicotine or prescription drug misuse into reverse.

We have the proof of the effect of such a mistaken policy if we look at the situation in Sydney in the late 1990s. During a time when Police turned a blind eye to drug dealing in Cabramatta, the price went down, the selling became open (and many young people went there believing they would not be troubled if they wanted to try the drug for the first time and developed a habit), the use of the drug exploded as did the death rate. With increased law enforcement and interdiction heroin use and overdose deaths declined dramatically.

It is also suggested by this drug legalization group, including their experts, that detoxification is not effective. Without detoxification no-one would ever be able to be drug free. It is also suggested that abstinence is impossible for the addicted drug user as it is a 'chronic relapsing disease". Both of these positions that are used to rationalise the lifetime use of methadone are both false. While some addictions may be difficult to overcome and a small group will not respond to treatment, the vast majority of those who were addicted to a substance will become abstinent with or without assistance. Hundreds of thousands of addicts' are now living normal lives.

While it is very sad for anyone to die, especially the young, it is a fact that death rates for people using opiates is some ten times higher than for their peers. Death rates for methadone are documented to be 0.7 to 0.8% each year (compared to just over 1% for heroin) That's some 300 methadone deaths every year. A Cochrane study by Mattick et al.,(2009) comparing methadone to no treatment shows only marginal benefit in that methadone is only better in terms of retention in treatment and injection rates. It is no better in terms of mortality or criminal activity. Many of those on the no-treatment side of the study were abstinent. None of those on methadone were abstinent. If every methadone doctor who had a patient die (or their children die) were charged as I have for say apparently not assessing people properly, the Medical Tribunal would be overflowing (See the paper "How effective is Methadone: What does the research say?").

At the same time as prohibitions need to be kept in place (as they are for all drugs) effective treatment that affords some choice, should be an option that is readily available.

We have treated some 2000 people (quite modest compared to Dr O'Neill's 8000) and many have done very well and not returned to opiate use. See the research documented in the attached paper "Open Label Trial of Naltrexone Implants: Measuring Blood Serum Levels of Naltrexone". You also need to ask why Dr O'Neill gets over $1m each year from the WA Govt and has done so for 14 years. Are they deluded; is it the terrible treatment others would have us believe? And what is their agenda? What is different there compared to the Eastern states where naltrexone are being closed down.

Naltrexone has an important role to play in the treatment of opiate and alcohol dependence. The research has shown this, but to acknowledge this by some sectors is not in their interests despite the overwhelming evidence from RCTs (see the paper "Open Label Trial of Naltrexone Implants: Measuring Blood Serum Levels of Naltrexone") .

The coroner recently found that three patients treated by Psych n Soul were not suitable as they should have been given methadone as it was the only evidence-based treatment currently available. At the end of the day the Coroner found no definite link between the treatment and the deaths of the three people that occurred over 12 years of treating opiate dependent people, where the evidence shows that most become drug free and return to a normal life. Apart from criticism that staffing and training was inadequate, although it complied with the relevant Guidelines at the time, the finding was that they would have been better off on methadone. The fact is that they were all on methadone and it had failed them and they wanted to be rid of it. The facts are that some 4000 deaths were attributable to methadone over 9 years and that the promoted benefits are not supported by the research (see paper "How effective is Methadone: What does the research say?") .

People need to understand that people seek naltrexone treatment because they had made a decision they did not want to have the life of an addict. The vast majority of addicts come to that decision at some time and they need an alternative to methadone so they can be free of it. Research shows that 80% of those being dosed with methadone want to be free of it. Naltrexone is undoubtedly an effective way to do that, albeit with some risk, but much less, in the short term (See research of deaths linked to induction onto methadone , which is described as unacceptable by NDARC researchers) and especially in the long term, compared to staying on heroin or methadone.

As part of my submission I have attached a number of papers I have researched and written.

The paper "How effective is Methadone: What does the research say?" was written in response to the findings of the Coroner. It shows that methadone has little evidence to support its continued funding as the benefits are few and the negative consequences of long term use of methadone makes it more damaging than heroin.

The paper "Open Label Trial of Naltrexone Implants: Measuring Blood Serum Levels of Naltrexone" has been accepted for publication in an international peer reviewed scientific journal. It was based on the research shows that, while effective the usefulness of oral naltrexone has been limited by compliance. Mmore recent research shows that sub-cutaneous sustained release naltrexone implants can offer a solution to this problem and improve long-term outcomes. The aim of the study was to compare levels

of blood serum naltrexone of patients who had received a naltrexone implant after detoxification to a number of dependent variables of interest. These dependent variables included drug use including urine screens of each patient, any adverse response to the implant, subjective evaluation of self-esteem, quality of relationships and changes in social functioning. Sixty (66) patients received an implant, and they were surveyed, urine and blood samples taken at around 1, 3, and 6 months after implantation. Patients were compared on gender, age, and length of time since detoxification. Naltrexone levels were on average above 1 ng/ml at 6 months after insertion and patients showed significant improvements on all dependent variables The preliminary evidence indicates that implants can improve compliance rates and outcomes.

The next paper, ” The Use of Methadone or Naltrexone for Treatment of Opiate Dependence: An Ethical Approach” is a review of the use of methadone and compares it to the use of naltrexone from an ethical perspective. It has been published in an International peer reviewed Journal. The paper contends that the policy of Harm Reduction was adapted and implemented by the Australian health establishment in response to a rising epidemic of opiate use, dependency and death from overdose and fears of the spread of AIDs and Hepatitis C throughout the intravenous drug-using population in the 1980s. The Harm Reduction movement procured funding for the methadone treatment program, needle exchanges, education about safe use of drugs, a harm reduction approach by police, a safe injecting room in Sydney and continues to call for drug trials of heroin for maintenance purposes. This is despite the lack of evidence that these measures result in disease prevention, reductions in drug use and/or criminality, or that health is significantly improved. On the other hand, naltrexone has been shown to be non-toxic, safe with no significant side-effects, highly effective in providing high rates of detoxification, and helpful in improving long term drug free status. Being drug free significantly reduces all risks associated with drug addiction. In Australia, since the year 2000, recent major reductions in the numbers of individuals using opiates and dying of overdose indicate that the enforcement of legal penalties and reduction in supply, has resulted in a reduction in demand and a greatly reduced rate of mortality. It seems these policies need to be part of a broad-based and coherent policy on preventing harm from drug use. This

also applies to abstinence-based treatment approaches. Opiate dependent people have a right to the best form of treatment available and the right to choose to be drug-free and that includes naltrexone treatment incorporating those components which maximise effectiveness and safety.

How Effective is Methadone: What Does the research Say?

Ross Colquhoun

According to the report of the New South Wales Chief Health Officer, “Health-related behaviours: Methadone/buprenorphine program use” methadone maintenance is declared to be an effective treatment for opioid dependence. Further, it is claimed that while methadone is the major treatment used in Australia, the risk of overdose death is substantially reduced in opiate-dependent people who are enrolled in methadone treatment (Warner-Smith at al., 2000) and that a recent study based on court appearance records in NSW shows that methadone maintenance programs are effective at controlling crime (Lind et al, 2004).

However, recent research shows that these claims are not supported. Mattick, Breen, Kimber and Davoli (2009) in a review of the research literature, stated that while methadone maintenance remains the most researched treatment for this problem, and despite the widespread use of methadone maintenance treatment for opioid dependence in many countries, it remains a controversial treatment whose effectiveness has been disputed.

The results of the study comparing methadone recpients to no treatment groups, showed that “methadone appeared statistically significantly more effective than non-pharmacological approaches in retaining patients in treatment and suppressing of heroin use as measured by self report and urine/hair analysis but not statistically different in criminal activity or mortality” (Mattick et al., 2009).

Moreover, of those in the methadone treatment group 37% tested positive to other opiates. None of this group tested negative for opioids although some were involved in out-patient rehabilitation programs. Included in the no-treatment group were those who were treated with placebo medication, withdrawal or detoxification, drug-free rehabilitation and no treatment or wait-list controls. It would be expected that those receiving no-treatment would continue to use opiates and yet 25% of this group who were not receiving replacement treatment (methadone) were opiate free. The conclusion to be drawn is that even if minimal treatment is available many more are able to become drug free compared to the very few when maintained on methadone even after many years of treatment and the inclusion of other interventions.

In this Cochrane review of the clinical research of Mattick and colleagues (2009) reported that “Methadone can cause death in overdosage, like other similar medications such as morphine, and for this reason it is a treatment which is dispensed under medical supervision and relatively strict rules”. However, there is a large blackmarket for methadone and a lack of adherence by practitioners to the Guidelines for Prescribing Methadone severely compromises the safety of those who are put on this treatment. Recent coroners reports trend to confirm these fears (Bucci, N., 2012; Lowe, A., 2011)

They conclude that “evidence on reduction of criminal activity and mortality from clinical trials is lacking” and that “a number of measures (e.g., of other drug use, physical health, and psychological health) were too infrequently and irregularly reported in the literature to be usefully integrated in the quantitative review.”

Further they concede that “the effects of methadone may be modest, if they are judged by unrealistic expectations of patients can easily achieve enduring abstinence from opioid drugs. Methadone nonetheless attracts and retains more patients than alternative treatments, and it does produce better outcomes amongst those **who complete treatment**. Methadone maintenance appears to provide better outcomes than simple detoxification programs, where the evidence suggests that **short-term** detoxification has no enduring effect on drug use” (my emphasis).

It is quite clear from the published research that the claims made for methadone have been overstated. As it is estimated to cost some $4000 each year to maintain some 46,000 people on opiate substitute therapy (at a cost of the order of $150m) is hard to justify.

The poor treatment outcomes for people on methadone maintenance programs is supported by a Glasgow University’s Centre for Drug Misuse Research government-funded study. They found a failure of the methadone program as “only 3% of addicts kick the habit” (Womersley, 2006).

According to McKeganey’s study, addicts treated in residential rehabilitation centres were far more likely to kick the habit. Almost 30% were drug-free three years later.

They conclude that the way forward if “we are serious about reducing drug addiction in Scotland and helping to keep more people off drugs, is to expand rehabilitation facilities”.

A 2008 study of older people on methadone maintenance warned of the dangers of long-term methadone dependence. As individuals aged 40-50 are the largest cohort receiving methadone maintenance treatment for heroin use (representing 27.5% of that group) those dependent on opioids are known to be at risk of adverse health conditions and mortality: “substance related syndromes” (including methadone dependence) “are known to harm every organ system” and the long term physical effects include liver and kidney diseases and increased susceptibility to infectious diseases (Rosen, Smith and Reynolds, 2008).

Among older methadone patients 76.4% were found to continue to use illegal drugs while on methadone although frequency was reduced. Co-morbid mental health disorders and chronic physical health conditions (arthritis and hypertension) and overall health functioning were worse for the older methadone group compared to populations norms for their own age group and older cohorts. While it appears that an older group who still actively use illegal drugs whether on methadone or not have poorer mental and physical health, those older addicts who no longer use illegal substances and are not in methadone maintenance have better health outcomes (Rosen, Smith and Reynolds, 2008).

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Moreover, opioid use increases the risk of premature mortality due to drug overdose, suicide, trauma (MVAs, homicide and other injuries) and HIV and the longer people remain dependent on opioids the greater the risk. The mean length of time dependent on opiates for those who never enter opioid substation treatment is 5.5 years, whereas many on methadone have been dependent for 30 to 40 years and they tend to inject for many more years. Not only is the risk of harm increased by being dependent on methadone for prolonged periods, the usefulness of methadone in reducing the spread of HIV is questionable as any increase in mortality of HIV among drug users is only the case where HIV is already prevalent among people who inject drugs. In countries where prevalence is low, it appears that injecting drug use does not increase the risk of spread of HIV infection. Further to this, while HIV has remained low the prevalence of Hep C infection is very high (74% among IV drug users).

Degenhardt and colleagues (2009) found that over an average of 9.2 years person years in treatment there have been nearly 4000 recorded methadone deaths over 20 years. Based on these figures it is estimated that there are over 200 deaths annually attributed to methadone compared to some 400 heroin-related deaths. This is over ten times higher for someone dependent on methadone compared to the general population. Another paper based on Coroner's reports in Victoria estimates methadone deaths at .833% per annum. That equates to about 383 deaths per year for 46,000 on methadone in Australia in 2012. As there are reported some 400 heroin related deaths each year in Australia the figures tend to confirm a similar or higher death rate for methadone users depending on the numbers of heroin users (Pilgrim, McDonough & Drummer, 2013).

Degenhardt reported that average length of time in the methadone program is 198 days with some 50% dropping out of treatment within 6 months and returning to illegal opiate use. People tend to cycle in and out of treatment and are exposed to higher mortality rates during induction (35 times the general population) and in the period following cessation. They state that as there is evidence of increased overdose death on induction onto the methadone treatment there is the need for alternative treatments, including alternative pharmacotherapy such as buprenorphine and conclude that those entering treatment have an "unacceptably elevated mortality rate". The Mattick Cochrane review found no difference in mortality rates for this group compared to a no-treatment group (Mattick et al., 2009) and no other advantages for people who do not complete treatment. Moreover, it states that there are no RCTs that include HIV as a variable and hence no reliable data that shows protection from HIV, despite their claims.

Mattick et al (2009) further reported that the conditions associated with the clinical trials would produce more favourable results for methadone as higher doses are used compared to outside the studies (in the real world) and subjects also receive ancillary services such as counselling within the trials, but not often in practice.

When this is coupled with the annual death rate it appears that methadone treatment is not effective, it kills people at a similar rate to heroin and it costs the tax payer a substantial sum.

However, it gets much worse as, to quote Mattick et al.: 'it (methadone) retains people in treatment longer compared to no treatment'. This is not suprising given the addictive nature of the drug and that it is relatively more difficult to detox from (as reported by McKeganey's study). Now instead of being a virtue, retention in treatment adds up to many more years dependent on the drug, with many more years of injecting (at a lower annual rate) and more deaths, more morbidity and a much lower quality of life, compared to an addict who NEVER goes into a ORT, as the average time a person stays on heroin is about 5.5 years compared to many more years for methadone.

Moreover, if people had been treated in abstinence-based settings more people would have been able to become drug-free and as a consequence mortality among those who have ceased opioid use would be much lower.

Methadone is associated with continued injection of heroin and other drugs, as the overall median duration of injecting is longer for those who start methadone compared to those who don't. For those who do not start methadone treatment, the medium time of injecting around 5 years (with nearly 30% ceasing within a year) compared to a prolongation of opiate use, and injecting for some 20 years for those who do start substitution treatment This means that if injecting drugs is 4 times as long the associated risks are higher. It is therefore estimated that because people stay on opioid substitution for many years they are dependent for much longer once they enter methadone treatment and inject drugs for many more years, compared to those addicts who never used methadone, the overall death rate is higher.

On the other hand, the evidence demonstrating the effectiveness of naltrexone treatment is beyond dispute. A number of randomised controlled trials have found statistically significant results, including comparing naltrexone implants to oral naltrexone and placebo. A recent NIDA press release states that sustained release naltrexone is not only effective but safe when used to treat opiate dependence (Colquhoun 2010, 2012, 2013).

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Abstract

The usefulness of oral naltrexone has been limited by compliance. Sub-cutaneous implants would seem to offer a solution to this problem and improve long-term outcomes. The aim of the present study was to compare levels of blood serum naltrexone of patients who had received a naltrexone implant after detoxification to a number of dependent variables of interest. These dependent variables included drug use including urine screens of each patient, any adverse response to the implant, subjective evaluation of self-esteem, quality of relationships and changes in social functioning. Sixty (66) patients received an implant, and they were surveyed, urine and blood samples taken at around 1, 3, and 6 months after implantation. Patients were compared on gender, age, and length of time since detoxification. Naltrexone levels were on average above 1 ng/ml at 6 months after insertion and patients showed significant improvements on all dependent variables The preliminary evidence indicates that implants can improve compliance rates and outcomes.

Keywords: Naltrexone, Implant, Social-support, Compliance, and Opiate addiction.

Open Label Trial of Naltrexone Implants: Measuring Blood Serum Levels of Naltrexone

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1. Introduction

Naltrexone, a potent opiate antagonist, has been shown to have valuable properties for the treatment of addiction to opiates such as heroin and methadone. The most important property is its ability to completely block the effects of heroin and methadone (Tennant, Rawson, Cohen, & Mann, 1984), making relapse to regular opiate use almost impossible while it is being taken. Research has shown that a dose of 50-100mg of oral naltrexone provides effective protection against heroin for 2-3 days, and with chronic dosing, no accumulation of naltrexone or its metabolites have been observed (Meyer, Straugn, Lo, Schary, & Whitney, 1984, Colquhoun 2003a). Naltrexone is non-toxic (Volavka, Resnick, Kestenbaum, & Freedman, 1976; Meyer et al., 1984) However, the manufacturers warn against use of the medication among patients who have renal impairment and state that it is contraindicated in patients who have acute Hepatitis C or liver failure as doses at five times the recommended dose of 50 mg/day over five to eight weeks may cause elevations in liver enzyme levels. Further, caution should be exercised when taking other medication and unprescribed drugs and when the patient is pregnant or lactating (Orphan, 1999). Contrary to these warnings, recent studies have indicated that naltrexone does not cause hepotoxicity or exacerbate pre-existing serious liver disease and there are no indications of naltrexone interacting harmfully

with other medications (Brewer & Wong, 2004; Comer et al., 2002)and produces no clinically important side-effects (Volavka et al., 1976; Meyer et al., 1984; King, Volpicelli, Gunduz, O'Brien, & Kreek, 1997; Perez & Wall, 1980). Before the introduction of implants the main factor restricting naltrexones' widespread use in opiate dependency treatment was non-compliance rates (Anton, Hogan, Jalali, Riordan, & Kleber, 1981; Azarian, Papiasvilli, & Joseph, 1994; Bell, Young, Masterman, Morris, Mattick, & Bammer, 1999; Hulse & Basso, 2000; Wodak, Saunders, Mattick and Hall, 2001).

The ability to resist and ignore drug-misusing cues is not easy. Indeed 50% of clients who left a 3-week in-patient opiate detoxification programme had misused opiates within several days, (Gossop, Green & Phillips, 1987). This early relapse undermines any chance of success, as it does not allow the user the chance to implement new opiate-free behaviours and thoughts. Naltrexone use offers no (immediate) reinforcement and the discontinuation of naltrexone produces no adverse effects, and this makes it easy to cease taking it. This contrasts against heroin use, which offers strong reinforcement immediately after use, and adverse withdrawal effects upon cessation, and for persons stabilized on methadone, methadone may give mild reinforcement upon ingestion and prevent sometimes severe and prolonged opiate withdrawal symptoms (Comer, Collin, Kleber, Nuwayser, Kerrigan and Fischman, 2002). Non-compliance to naltrexone-based treatment is a particular concern, because after a period of abstinence from opiate use, tolerance is reduced and as such patients who relapse are at an increased risk of overdose and death (Caplehorn, Dalton, Haldar, Petranus, and Nisbet, 1996).

Poor outcomes in the treatment of opiate dependency using naltrexone relates to the shortened time in treatment; time in treatment has been related to better long-term outcomes (Delucchi, Masson, Rosen, Clark, Robilliard, Banys, and Hall, 2000; Simpson, 1979). Moreover, with no after-care counselling, compliance strategy or social support in place, studies have shown

predictably poor long-term outcomes (Bell et al., 1999; Rawson, McCann, Shoptaw, Miotto, Frosch, Obert and Ling, 2001; BMJ Editorial, 1997). However, when naltrexone is combined with an effective after-care program and social support to enhance compliance, results have been promising (Shufman, Porat, Wiztum, Gandacu, Bar-Hamburger, & Ginath, 1994, Colquhoun, 1999). This view has been supported empirically for other drug addiction treatment services (Woody, Luborsky, Mclellan, O'Brien, Beck, Blaine, Herman & Hole, 1983: Ziedonis & Kosten, 1991).

The current strategy to overcome the issue of non-compliance to naltrexone has been the development and use for some 10 years of sub-cutaneous naltrexone implants. The latest development with the implants enables a slow release into the body at a rate of 8 to 10 mg/day (Hulse, Arnold-Reed, O'Neil, Chan and Hansson, 2004; Colquhoun, Tan & Hull, 2005; Colquhoun, 2010). Naltrexone implants have been shown to effectively block the effects of opiates for between 180 and 240 days thus allowing an extended drug free period to deal with social and psychological problems that would otherwise lead to early relapse and risk of overdose (Hulse, et la., 2009; Colquhoun, Tan & Hull, 2005). This frees the patient of the mental battle they face when trying to remain compliant to oral naltrexone use, and the need to sustain a support person relationship as part of a compliance strategy. Several studies have indicated the excellent bio-availability of naltrexone in subcutaneous form (Comer et al.,2002; Perez and Wall, 1980).

Trials of slow-release naltrexone have shown very promising outcomes, although more studies appear warranted. Our paper published in 2005 comparing 42 and 41 patients either taking oral naltrexone or having a naltrexone implant respectively showed much better outcomes for the latter group (Colquhoun, Tan & Hull, 2005). Follow-up showed that 19 of the 42 individuals taking oral naltrexone (45%) relapsed to opiate use or were non-contactable

at twelve months, while only eight out of 41 individuals (19%) were using opiates (or non-contactable) after receiving an implant at six months. This advantaged was maintained for the implant group at twelve months with relapse rates at 61% and 40% respectively. That is, at twelve months 61% of the implant group were abstinent, while 40% were abstinent in the oral group. Since then two randomised controlled trails have been published that also demonstrate the efficacy of the implant. In a Norwegian study 56 abstinence-oriented patients after detoxification were randomly and openly assigned to receive either a 6-month naltrexone implant or their usual aftercare. The results showed that patients who received a naltrexone implant had on average 45 days less heroin use and 60 days less opioid use than controls in the 180-day period (both $p<0.05$) and naltrexone serum blood levels stayed above 1 ng/ml for the duration of the 6 months. They concluded that naltrexone implant treatment was safe and significantly reduced opioid use in a motivated population of patients (Kunøe, et al. 2009). In the second study 70 patients (35 in each group) were randomised to active a naltrexone implant (2.3g of NTX) and placebo naltrexone tablets or placebo implant and 50mg oral naltrexone each day. At 6 month follow up more implant than oral patients had levels above 2ng/ml ($p<0.001$); more oral patients returned to regular heroin use at 6 months ($p<0.003$) and at an earlier stage (115 vs 158 days). They concluded that the naltrexone implant effectively reduced relapse to regular heroin use compared with oral naltrexone and was not associated with major adverse events. (Hulse, 2009).

More recently studies have shown similar results. In 2011 Krupitsky and colleagues published results of a RCT trial of a monthly injectable formulation of naltrexone approved by the US Food and Drug Administration for preventing relapse to opioid dependence in 2010. The percentage of opioid-free weeks was significantly higher in the injectable naltrexone group than the placebo group ($p=0{\cdot}0002$), Total abstinence was reported in 36% of patients in the former group compared with 23% in the placebo group ($p=0{\cdot}0224$).

In summary, clinical studies of patients recovering from opiate addiction indicate that patients who have receive a naltrexone implant have better outcomes than those who receive placebo naltrexone or oral naltrexone. The issue of compliance has been largely resolved with the use of naltrexone implants. There are still unanswered questions and these mainly concern the reliability of the implant, particularly consistency of release rates. It has been established that serum blood levels above 1 ng.ml are sufficient to block a normal street dose of heroin and to proptect against overdose (Brewer and Streel, 2010; Hulse, et al., 2004; Kunoe, et al. 2009; Foster & Brewer, 1998), although higher doses tend to be only partially blocked and patients report some sensation they associate with opiate use.

The aim of the study was to investigate the reliability of release of an effective dose of naltrexone over the life of the implant and to investigate adverse responses. It was hypothesised that the blood serum levels of naltrexone implants on average remain above 1 ng/ml for a period of 6 months. As a consequence it was also hypothesised that there would be commensurate improvements in drug use and social functioning among the group receiving the implant.

2. Method

2.1 Participants

As part of an open-label trickle-inclusion study 66 patients with each patient receiving a 6 month naltrexone implant. All participants had completed detoxification and the initial data collection coincided with them having the implant and underwent a naloxone challenge prior to implantation. All participants had signed and had witnessed consent forms to participate in

the study and each completed medical checks including liver function, thyroid and full blood counts. All patients had a urine drug screen and then completed a questionnaire. Patients were asked to return to the clinic to complete follow up questionnaires, do Urine Drug Screens and provide blood to be analysed for naltrexone levels at one month, three months and six months after receiving the naltrexone implant

2.2 Implant

Implants produced by Civil Life Scientific Company in Shenzhen, China were used. Each implant was 3.47g total mass and designed to contain approximately 1.85 grams naltrexone base that had an *in vitro* release rate ranging from 0.2-0.8% of its residual mass per day. The naltrexone was encapsulated in poly-DL-lactide (a polymer similar to that used in dissolvable surgical sutures and screws) microspheres compressed into pellets. Each implant consisted of 10 pellets. Subjects were given a single (10 pellets; 185gr naltrexone) implant, which was surgically inserted into the subcutaneous tissues on the right or left side of the lower abdomen, in the fat tissue below the waist line. The length of time the implant was expected to release therapeutic doses of naltrexone was 6 months (approx. 180 days).

2.3 Procedure

Prior to detoxification, all patients underwent a psychosocial assessment to determine whether or not they were suitable for the program. Suitability was determined by the client's motivation to be opiate free, their level of social support, any serious psychiatric diagnoses of mental illness and any medical issues that were considered to be contraindications that might compromise safety.

Part of the psychosocial assessment also entailed the completion of a questionnaire. This included questions relating to any adverse effects of the implant, subjective level of craving for opiates, legal and health history, days of using heroin in the previous month and use of illcit and licit drugs. All participants were asked to rate their self-esteem and the quality of their primary relationships on a 0 – 10 Likert scale both before and after treatment. Participants were also required to provide blood samples scheduled at 1 month, 3 months and 6 months post- implantation, to be analysed to determine serum levels of naltrexone and its major metabolite, 6-beta-naltrexol and a urine sample to indicate the presence of opiates and other illicit drugs, including, amphetamines, methamphetamines, cocaine, cannabis and benzodiazepines

All patients were told prior to receiving the implant that there were other forms of treatment available including agonist replacement therapy, the costs and benefits of the naltrexone implants and each signed informed consent forms prior to inserting the implant in accordance with the Helsinki Declaration of 1975. One of the consent forms included permission to release the data collected for research purposes and included other information relating to the nature and risks attached to use of naltrexone. Use of the implant was authorised under the Special Access Scheme of the Therapeutic Goods Administration. The trial had received approval from an Ethics Committee that conformed with the National Regulations on the Ethical Conduct of Human Research and the Therapeutic Goods Administration approved the trial under the Clinical Trial Notification provisions (CTN 2010/0510, Protocol No., A10) in accordance with Item 3 of Schedule 5A of the Therapeutic Goods Regulations.

2.4 Analysis

The survey data, blood samples and urine was collected over a period of 20 months. Blood serum levels of naltrexone were analysed by the Royal Prince Alfred Hospital Blood Analysis Laboratory and the Western Australian Chemistry Centre. Data was compared for significant differences using two-tailed t-tests with alpha level set at 0.05.

3. Results

The characteristics of the patients were recorded at their first interview, prior to having the implant. Table 1 shows the means and standard deviations on a number of characteristics, including gender, age, total time they had been using opiates (heroin), the amount of heroin being used at the time of the interview (any methadone users had relapsed to heroin before entering the program), the year they left school, whether they were employed and whether they used other drugs.

Table 1. Characteristics of subjects prior to detoxification from opiates.

Patient Characteristics	**Means**
Male (%)	59 (92%)
Age (Standard Deviation)	29.56 (8.07)
Mean Years using Opiates	6.29 (SD 5.88)
Mean Years of Schooling	10.6
Employed (%)	37 (58%)
Mean Heroin	0.41g (SD 0.24)
Mean Counselling Sessions	8.5 (SD 2.7) (2 months)
Drug Related Convictions	38 (60%)
Poly drug use	77.4%

Table 2. Mean self ratings of self-esteem and general relationship quality at pre-detox and at 1, 3 and 6 months post-detox (range)

	Self Esteem (sig p<0.05)	**Relationships (non-sign)**
Pre-detox	3.65 (2-5)	5.5 (0-10)

One month	7.1 (4-10)	8.4 (7-10)
Three months	7.66 (4-8)	8.8 (6-10)
Six months	7.6 (2-10)	8.4 (6-10)

T tests were conducted to determine if the differences over time were statistically significant. Subjective reports using a lickert scale (0 -Disastrous to 10, Excellent) showed that ratings of self esteem improved over the 6 months of the trial, while ratings of relationship quality was not significant it did indicate improvements in this area. At 6 months the differences since detoxification was significant for self-esteem with an alpha level of 0.05 ($p=0.018$), while the relationship ratings, approached significance ($p=0.085$). The lack of significance was due in part to a number of participants rating their relationship highly (10) despite their drug problem at the first interview. The differences between the two areas of social function that were measured when ratings were compared in the period from 1 to 6 months were all non-significant, indicating that improvements in self esteem and relationships tended to be maintained.

Self ratings of craving, before detoxification, while detoxing and at one, three and six months were recorded. Participants were also asked to indicate if they had used heroin in the previous month and how many days they had used in that month. Urine Drug Screens (UDS) were used to verify these reports, although they could not determine if a person had used some days before testing in the previous month or how often they may have used. The presence of other drugs was tested for and it was found that self report was consistent with the UDS results, although there was a tendency to under report stimulant use.

Altogether 108 urine samples were taken. Forty six samples indicated that people were using more than one drug, mostly stimulants, cannabis and/or benzodiazepines. At one month, of

the 31 tests completed, 5 tested negative for all drugs, 19 tested positive for stimulants, 17 for benzodiazepines, 16 for cannabis and 6 positive for opiates. Of the 48 that were taken at 6 months 23 indicated no illicit drug use, 13 tested positive to cannabis, 15 tested positive for amphetamines or methamphetamines, 19 for benzodiazepines (most would have been prescribed) and six had positive results for opiates. Of the remaining samples taken between 1 and 6 months the pattern remained the same with high levels of poly drug use, including one positive test for cocaine, although 16 were negative to all drugs and only three tested positive to opiates over this time.

Table 3 lists the type of drug tested for and the numbers who tested positive at 1, 3 and 6 months post implant.

Drug	1 month (n=31)	3 months (n=29)	6 months (n=48)
Amphetamine	11 (35%)	9 (31%)	7 (15%)
Methamphetamine	8 (25%)	9 (31%)	8 (17%)
Opiates	6 (19%)	3 (10%)	6 (12%)
Benzodioazepines	17 (55%)	11 (37%)	19 (40%)
Cannabis	16 (52%)	8 (27%)	13 (27%)
Cocaine	0 (0%)	1 (3%)	0 (0%)

The most obvious result was the sharp decline in opiate use despite some providing urine samples well after the implant was due to run out. Other drug use also tended to declined over the 6 months.

Table 4. Number of drugs used over the research period.

No of drugs	1 month	3 months	6 months
No drug use	5 (16%)	8 (28%)	21 (44%)
One	5 (16%)	8 (28%)	11 (23%)
Two to four	19 (61%)	12 (41%)	16 (33%)
Four or more	2 (6%)	1 (3%)	0 (0%)

The number of participants using no drugs rose over the 6 months to 44% of the sample compared to 16% at one month. Of those using 2 to 4 other drugs the number fell from 77.4% pre-implant to 61% at one month to 33% at 6 months. The results show a trend toward less use of drugs quite apart from opiate use.

Table 5. Days using during the previous month at baseline, 1 month, 3 months and 6 months (range).

Days Using – Pre-detox	**Days Using – 1 month**	**Days Using - 3 months**	**Days Using – 6 months**
28.8 (24-30)	0.2 (0-2)	2.1 (0-30)	5.34 (0-30)

Table 6. Mean self rating of craving while using, during detoxification and 1 month,3 months and 6 months post implant (range) All sig $p<0.05$

Craving while Using	Craving during detox	Craving- 1mth post implant	Craving - 3 mth post implant	Craving – 6mth post implant
6.7 (3-10)	7.36 (5-10)	1.36 (0-8)	1.4 (0-7)	1.4(0-7)

The main aim of the research was to determine the consistency of release of naltrexone and if, on average, levels of over 1 ng/ml were maintained over the claimed 6 month life of the

implant. The tables 7 to 9 show serum blood levels approximately 1 (30.2 days), 3 (88.6 days) and 6 months (191.2 days).

Table 7. Serum Blood Levels at 1 month

	Days	Naltrexone (ng/ml)	Naltrexol (ng/ml)
Mean	30.2	5.2	9.1
Standard Deviation	4.5	3.2	6.0

At around 1 month, 33 blood samples were taken over a range of 21 to 37 days from 35 subjects. By this time 2 had refused to participate and one had been jailed.

Table 8. Serum Blood Levels at 3 months

	Days	Naltrexone (ng/ml)	Naltrexol (ng/ml)
Mean	88.6	5.4	10.7
Standard Deviation	28.1	4.1	11.1

51 blood samples, of which 8 first samples, were taken over a range of 42 to 139 days from 43 subjects.

By this time 2 had refused to participate, 3 had been jailed, 3 were non-contactable, 5 had gone overseas and 1 interstate, one had a MVA and 2 implants extruded due to an allergic reaction.

Table 9. Serum Blood Levels at 6 months

	Days	Naltrexone (ng/ml)	Naltrexol (ng/ml)
Mean	191.2	0.9	3.5
Standard Deviation	40.0	3.2	3.14

The time over which samples were taken ranged between 140 to 322 days and 53 blood samples were taken (5 of which were first samples) from 48 participants.

Of the 66 who commenced the trial 18 participants were eventually lost to follow up: 2 refused to take part, 3 were jailed, 3 extruded the implant due to an allergic response and relapsed to heroin, 1 had a MVA and had implant removed and was stable on methadone at 6 months, 6 travelled overseas or interstate and 3 were non-contactable

The chart below plots naltrexone levels in ng/ml over time. There were two samples that indicated levels of naltrexone of 39.5 and 43.2 ng/ml respectively. These were considered to be outliers that would have distorted the trend shown in the graph and were omitted. Overall the graph indicates that mean levels of naltrexone, as shown by the trend line, stayed above 1 ng/ml for over 180 days. Chart 2 shows a similar trend for the major active metabolite of naltrexone, 6 beta-naltrexol. Again outliers of 121.3 and 125.1 ng/ml were not included.

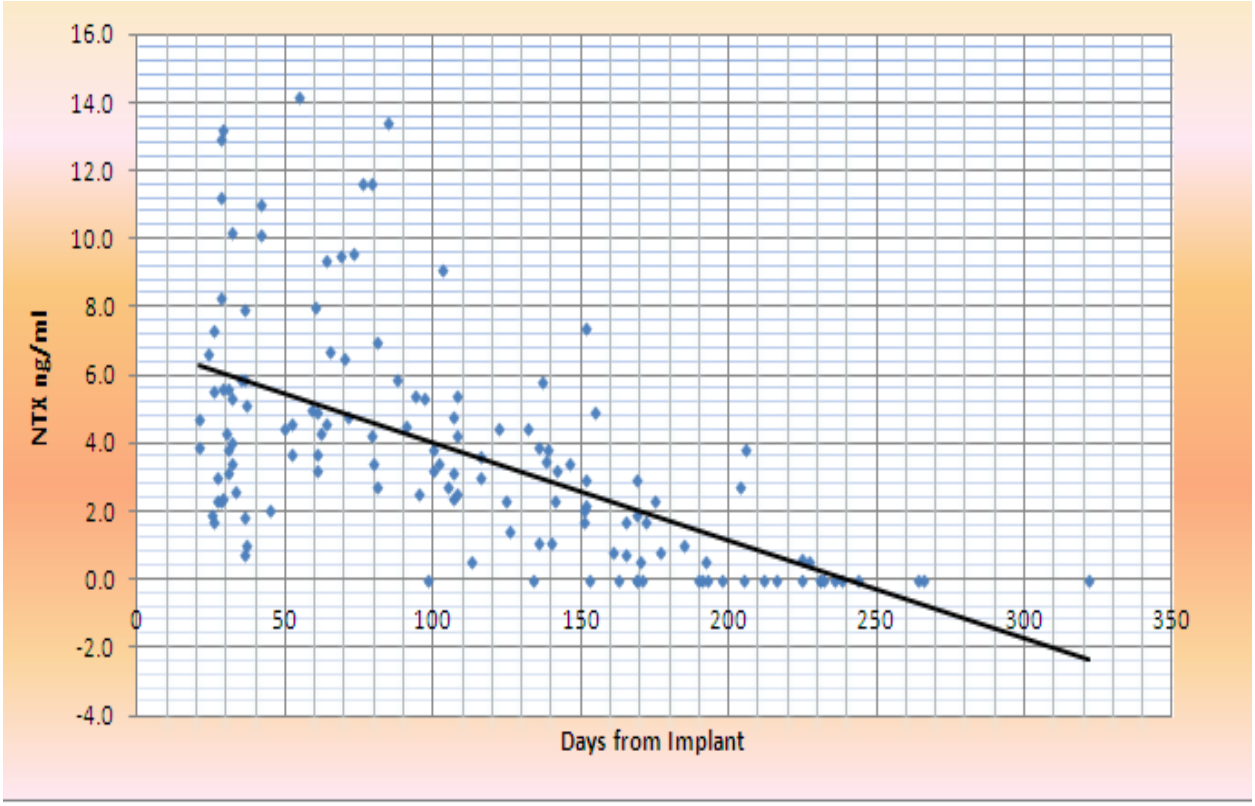

Chart 1. Levels of naltrexone as measured in blood serum at 6 months in ng/ml

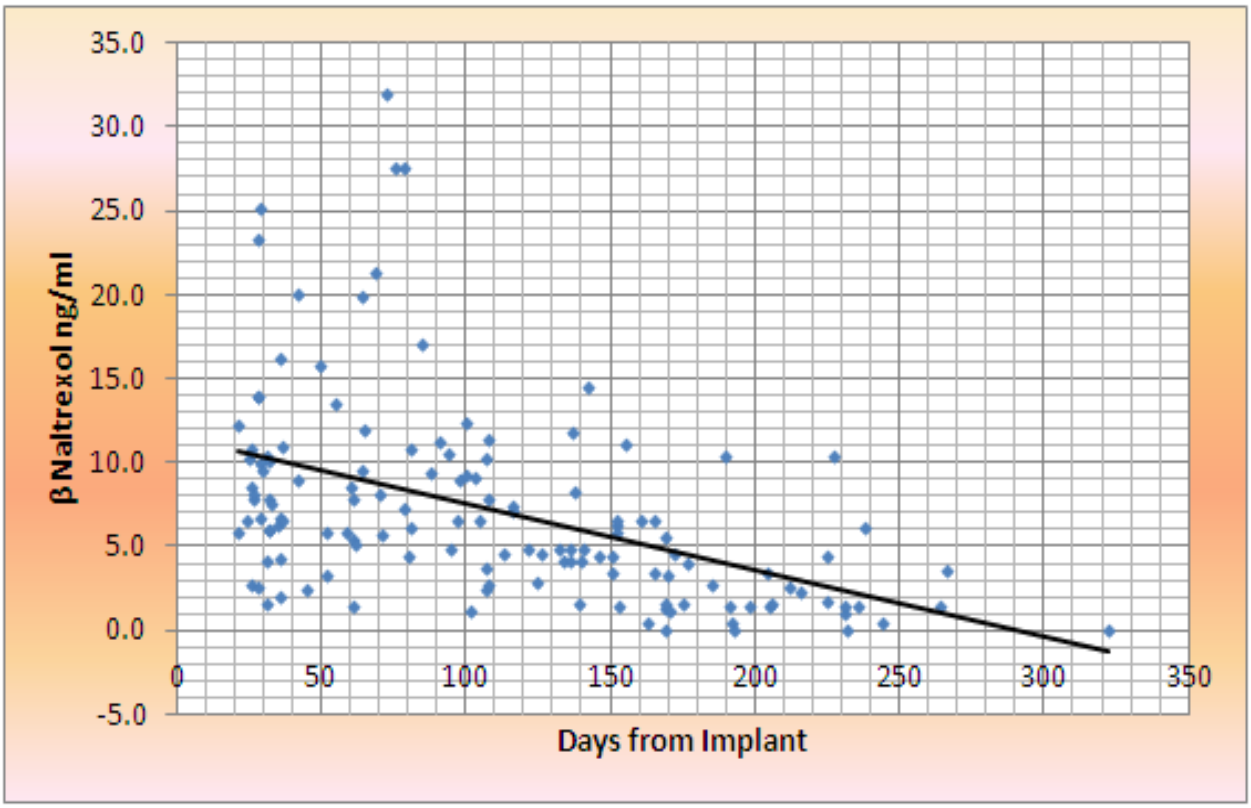

Chart 2. Levels of 6-beta-naltrexol as measured in blood serum at 6 months in ng/ml

Examination of the results of individuals showed that there were 9 subjects who recorded a level of naltrexone that was undetectable. The first occurred at 98 days, then at 134, 153, 165 (2), 170, 171 and 177. In all cases detectable levels of 6-beta naltrexol were recorded. There were no reported incidents of drug overdose during the trial period.

4. Discussion

The most important data to come from this study appears in Charts 1 and 2, showing the sustained release of naltrexone and its active metabolite for the claimed period of blockade. It effectively prevented heroin use for the vast majority over the time of the study.

It was hypothesised that blood serum levels of naltrexone would on average be above 1 ng/ml at 180 days, which is considered an effective blocking dose (Brewer and Streel, 2010). This was exceeded with the trend line crossing this point at approximately 200 days. There was a significant range of scores with one sample recording a non-detectable level of naltrexone at 98 days and 8 others at 134 to 177 days. A small number of the group starting using opiates late in the trial saying they could feel an effect that coincided with this early depletion of naltrexone after the analytic results were available some months later. There were no overdoses reported throughout the trial and it seems that the major active metabolite affords a degree of protection for some time after the naltrexone is not detectable, which accords with the observations of Brewer and Streel (2010). Subjective ratings of craving for opiates declined dramatically from the time before the implant was inserted compared to the period after insertion and were sustained for the 6 months. Nevertheless, ten reported that they had tried using heroin in the first month and all reported that there was no subjective effect and two started using heroin at 5 months, reporting little effect and some withdrawal. One has returned to being abstinent and continued counselling and the other continued to use on a

daily basis. There were no other adverse events reported apart from five tissue reactions and three implants extruded (7.8% and 4.6% resp), due to an inflammatory response. One subject relapsed to heavy cocaine use after one month, his implant extruded and he relapsed. Two others whose implant extruded after 3 months relapsed to heroin. Two others also showed early signs of rejection and were treated with a steroid anti-inflammatory medication and they did not proceed to extrusion, but settled without further problems.

In summary, of the 66 who enrolled in the study, 42 were opiate free after 6 months (63.6%) and this was confirmed by the results of the urine drug screens. All subjects showed a significant decrease in opiate use from daily use to no use or for some, infrequent use after 6 months. After 6 months only 6 subjects (9%) were confirmed as having relapsed to regular heroin use. Of these four returned for a 2nd implant. There were another 18 who were lost to follow up. It could not be confirmed if they were using regularly at 6 months.

Furthermore, the present study would seem to provide strong preliminary evidence that the use of implants is an effective solution to the problem of compliance and that the effect tends to last for some time after the antagonistic effects of the implant has worn off. It seems that the lack of positive reinforcement (no subjective effect), and the strong negative reinforcement (wasting money) associated with using opiates and lack of craving, whilst an implant is releasing naltrexone into the body, is sufficient to prevent use of the drug. This allows time for the development of more adaptive coping behaviours, and for the patient time to deal with the underlying psychological issues that so often compel people to use these drugs. It remains to be seen how many of these patients remain abstinent at longer follow-up intervals, although the trend seems to be that the longer time in treatment and the ability to effect change in lifestyle the more chance that long-term recovery will be sustained.

This benefit was evident by improved ratings on two measures of social functioning. Participants rated their self-esteem and general relationship quality comparably low before their detoxification from opiates and having the implant. As hypothesised, they showed increases in these ratings after their detoxification. It is expected that this would be indicative of improved mental health, greater social cohesion and an improvement in functioning that coincided with the blocking effect of the implant.

Overall the study demonstrates the potential for naltrexone implants to improve compliance rates, increase time in treatment and improve abstinence rates when compared to a comparable group taking oral naltrexone.

4.1 Limitations of Study

The major limitation of the study was the inconsistency in obtaining data including blood and urine samples from the participants. Appointments to come to the clinic were often not kept even though people were booked ahead of the scheduled collection dates and many were coming for follow up counselling. To overcome this problem we had to go to the homes of the participants to obtain the required information, particularly to collect date in the last phase of the study. This added considerably to the cost and time taken. Samples were collected over extended time periods that often did not coincide with the 1, 3 and 6 months scheduled timeframe. On the other hand this resulted in a broad spread of samples over the whole period of the study.

With regard to the other variables of interest, the study would have produced more robust results if subjects had been randomly allocated to different treatment conditions, whereas in this study patient groups were self-selected by personal choice to undergo home

detoxification and to have a naltrexone implant. In other words there was no control group, although the predominant aim was to examine naltrexone serum levels. Perhaps the patients who chose to use naltrexone might have been more motivated, selecting a treatment method that they had considered for some time and having found other alternatives not to be effective or to suit their goals or lifestyle choices. Alternatively this group may have felt they wanted to take responsibility for their own recovery and not proceed with the 'easy way'.

The study also comprised patients who were screened for serious psychiatric problems, levels of motivation and social support. Most patients were depressed when they entered the study and this was seen to be a product of the pharmacological effect of the drug and the negatives associated with the lifestyle of a drug user. It has always been our contention that the use of naltrexone should be limited to those who have a reasonable chance of long-term recovery. Notwithstanding, it can also be seen that the patient group presents with a range of psychological problems, which must be attended to, and with a history of multiple detoxification attempts, criminal activity and poly-drug use. None of these problems are considered to be a bar to inclusion in the program. As other researchers have pointed out, naltrexone should be targeted to those who can most benefit, and the benefits of research is to clarify the best way to utilise this medication. To get some indication of improvement in psychological well being we used subjective measures of self-esteem and quality of close relationships. Future studies might benefit from using standardised psychometric instruments to more accurately gauge change in this variable.

The other prominent feature was the large numbers of people who were non-contactable for one reason or another, especially in the latter period where this figure represented more than a quarter of the participants, many of whom may have been abstinent, although we could not confirm this. Despite considerable effort it was impossible to follow up some of the

participants, particularly those who went overseas or interstate and those who were incarcerated.

4.2 Future Research

Future research should include random allocation of subjects to different treatment conditions, although matching on significant confounding variables may be warranted before random allocation. It is also important to maintain other strategies, which have been shown to enhance outcomes and maintain the safety of the patients. Not only is this in keeping with the research, but there is also a strong ethical argument to proceed in this manner and to ensure equal access to supportive counselling. Even with the provision of counselling there appears to be a group of patients who are not likely to benefit from use of naltrexone and for whom methadone or buprenorphine is the preferred treatment.

While this was not the aim of the present study, in order to properly evaluate the usefulness of naltrexone it is important that future research examines longer term outcomes. The time-frame for collection of data should be extended to a point some years beyond the termination point of the implants. It is believed that the longer a person is in treatment the better the outcomes, and certainly the use of implants facilitates this. However, it has yet to be shown that the use of naltrexone implants translates directly into long-term improved outcomes.

The present study indicates the potential of the use of these devices in the treatment of opiate dependency and further research seems to be warranted. Clinical trials which are properly constituted with ethics approval and which extend well beyond the blocking effect of the implant, combined with biological testing of drug use, are necessary to confirm the results of this study.

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Statement From Author

The author of this research article, Ross Colquhoun, hereby states that:

(a) The material presented in this article has not been published in whole or part elsewhere

(b) This paper is not currently being considered for publication elsewhere

(c) The author has been personally and actively involved in the substantive work leading to the report, and will hold himself responsible for its content

(d) All relevant ethical safeguards have been met in relation to patient protection and research.

The implants were supplied by Civil Life Scientific Co., Shenzhen, China. Other costs associated with the study, including wages, telephone calls, consumables and overheads to collect, collate and analyse the data and write the paper was incurred by Addiction Treatment and Psychology Services and included some funding from the Addiction Treatment Foundation Inc. No-one involved in the study had or has any commercial or other relationship with Civil Life, the maker of the implant, or any of its subsidiaries or associated companies or personnel other than as a purchaser of the implants.

Signed: Ross M. Colquhoun

The Use of Methadone or Naltrexone for Treatment of Opiate Dependence: An Ethical Approach

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Abstract

The policy of Harm Reduction was adapted and implemented by the Australian health establishment in response to a rising epidemic of opiate use, dependency and death from overdose and fears of the spread of AIDs and Hepatitis C throughout the intravenous drug-using population in the 1980s. The Harm Reduction movement provided funding for the methadone treatment program, needle exchanges, education about safe use of drugs, a harm reduction approach by police, a safe injecting room in Sydney and the call for drug trials of heroin for maintenance purposes. This is despite the lack of evidence that these measures result in disease prevention, reductions in drug use and/or criminality, or that health is significantly improved. On the other hand, naltrexone has been shown to be non-toxic, safe with no significant side-effects, highly effective in providing high rates of detoxification, and helpful in improving long term drug free status. Being drug free significantly reduces all risks associated with drug addiction. In Australia, since the year 2000, recent major reductions in the numbers of individuals using opiates and dying of overdose indicate that the enforcement of legal penalties and reduction in supply, has resulted in a reduction in demand and a greatly reduced rate of mortality. It seems these policies need to be part of a broad-based and coherent policy on preventing harm from drug use. This also applies to abstinence-based treatment approaches. Opiate dependent people have a right to the best form of treatment available and the right to choose to be drug-free and that includes naltrexone treatment incorporating those components which maximise effectiveness and safety.

Introduction

In recent years, a philosophy and policy of Harm Reduction has been adopted and implemented by the Australian health establishment in response to a rising epidemic of opiate use, dependency, and death from overdose. This change follows the liberalisation of laws relating to contraception and abortion, and a shift in emphasis toward individual civil rights in opposition to concepts of for some people, social engineering and for others, community values and rights. In the early 1980's the spread of HIV/AIDS was primarily among the gay communities of inner city suburbs. In the face of a morally prejudicial call for homosexual men to forego sexual relationships to manage the spread of the disease, a program of harm minimisation was initiated, which recognised this group's right to freely express their sexuality. It was based on education and prevention measures and research into and implementation of treatment to minimise and prevent harm to this group. Overseas studies also indicated that the other major risk group for contracting the disease was that group of people who used drugs, particularly opiates and amphetamines intravenously, and who often shared needles (Drucker & Clear, 1999; Day, 2003). Harm minimisation was then applied to allay the fears of the spread of AIDs and Hepatitis C throughout the intravenous drug-using population and then among the general population they interacted with (Drucker & Clear, 1999).

History and Background

In the 1980s, the Labor Government in Australia at the time, adapted the Harm Reduction approach for this intravenous drug-using group and provided funding for the methadone treatment program, needle exchanges, education about safe use of drugs, and a harm reduction approach by police that minimised harassment of drug users on the streets and emphasised health interventions to save lives (Wodak & Lurie, 1996). More recently, the introduction of a safe injecting room in Sydney and the call for trials of heroin for addicts was initiated (Wodak & Lurie, 1996). The fundamental belief was that just as gay men had a right to form sexual relationships and to be free from harms associated with this activity, so

intravenous drug-users had a similar right to practice drug use free from harms, including criminal charges and police harassment, contraction of communicable diseases, through provision of clean needles and information on sterilisation of needles and safe injecting practices, and risk of overdose and death (Hathaway, 2002). The fact that there is a significant overlap between these groups has given added impetus to this push toward harm minimisation. This emphasis on human rights was made clearly by the Chief Minister in the ACT, Mr Jon Stanhope. In response to a request that the Government consider supporting trials of naltrexone implants in the ACT, his argument was that such a measure would infringe on the rights of drug-users and that it would entail some form of "enforced abstinence", which was unacceptable (Stanhope, 2002, personal correspondence). The fundamental right here was the prevention of harm, especially from HIV/AIDS and the obligation on society to protect people who chose to use drugs recreationally; the liberal provision of methadone was a major plank in this policy.

At the same time, traditional approaches to treatment, such as home or medicated detoxification, followed by rehabilitation programs such as therapeutic communities based on 12 step models, were falling out of favour among the advocates of harm minimisation (Drucker & Clear, 1999). These traditional treatment programs tended to see drug-use as problematic, often seemingly, from a moral perspective with condemnation of the drug user as a morally flawed person and with abstinence as the primary, or only, goal of treatment (Drucker & Clear, 1999). The new order saw this as an attack on the lifestyle choice of the drug user, an attack on their civil liberties and their right to be free of preventable harms associated with drug use. Instead of confronting the 'denial' or 'rationalisation' of the drug user for continuing the habit, some in the harm minimisation group adapted a counselling style, which sought to legitimise the drug users' choice and to empower them as an oppressed group, to defend their right to freely use whatever drugs they chose, licit or illicit (Goodfellow, 2004; Madden, 2004). A post-modern position underpinned this movement with the belief that no one has any objective knowledge of the rights and wrongs of these issues, and that the risk associated with drug use is socially constructed and not a matter of correct or rational knowledge and are culturally created and political in essence (Southgate, Day,

Kimber, Weatherall, MacDonald, Woolcock, Mc Guckin & Dolan, 2003). This was accompanied by the adaptation of Narrative Therapy to treat drug dependency (Campbell, 1999). In this paper, Campbell says: "Narrative Therapy is concerned with the repressive role of dominant discourses…. and potentially pathologising therapeutic discourses. In the drug and alcohol field, they may emerge as dependency stories or narratives" (p. 3). Moreover, this group advocated the idea that we were a 'drug using society' and that anything from coffee and aspros to heroin and ecstasy, were all drugs, the only difference being that some were arbitrarily declared to be legal and some were not, leading to a loss of free choice and the persecution of those who chose one drug as opposed to another. People who held this view often failed to differentiate between the relative harm of different drugs and the social factors affecting the way different drugs are used.

The same group also declared that the "War on Drugs' had failed and that we, as a society, should reduce our efforts to interdict supply; minimise our focus on the prosecution of drug suppliers and the deterrence and/or punishment of those who seek to use drugs; and divert the funds into treatment approaches, most notably the Methadone Maintenance Program (Wodak, 1997, Dillon, 1999; Goodfellow, 2004). The success of this program's major aim of preventing the spread of HIV/AIDS and Hepatitis C is not clear. While rates of HIV/AIDS transmission in the injecting drug user population is low in Australia, rates of Hep C infection among this group is very high, despite the harm minimisation policies of the last 25 years. It seems that harm minimization has a discordant effect on HIV and Hepatitis C, and therefore it is most likely that harm minimization strategies are not responsible for either effect: the effect on HIV seems to provide some evidence that harm minimization works well, whilst the effect on Hep C suggests that it is ineffectual. Hence, the most likely explanation is that it is not the prime mover of these disparate trends. (Caplehorn, McNeil & Kleinbaum, 1993; Southgate, Day, Kimber, Weatherall, MacDonald, Woolcock, Mc Guckin & Dolan, 2003; Wodak & Lurie, 1996).

Methadone v. Naltrexone

Despite the lack of evidence to indicate that disease prevention has been affected by the implementation of methadone maintenance, or that the perceived benefits in drug use, criminality and health are significantly improved (Caplehorn, McNeil & Kleinbaum, 1993; Reno & Aiken 1993; Mattick, Been, Kimber & Davoli, 2009), this same group tends to advocate strongly for the use of methadone as the preferred or Golden Standard treatment for opiate dependence (Wodak, 1997; Byrne, 1995; Byrne, 2004). This form of treatment was developed in New York in the 1960's as a substitute for more intensive and expensive interventions, especially among the city's African-American and Hispanic populations: to curtail crime, to reduce health costs, and to control the addict by requiring them to appear at a Government controlled dosing centre each day for treatment (Drucker & Clear, 1999). Despite this policy, the spread of HIV/AIDS among this injecting drug group in the United States is very high and the policy has failed to prevent the spread of this disease or Hepatitus C (Wodak & Lurie, 1996). The best evidence, following a Cochrane review of methadone compared to no treatment, shows that there is an increase in retention in treatment (which is not surprising given the addictive nature of methadone), but no significant improvement in criminality or mortality (Mattick, Been, Kimber & Davoli, 2009). Others would dispute this and claim that mortality is reduced significantly, by 20-40%, for those who cease injecting drug use, and remain in treatment on methadone (Drucker & Clear, 1999). They would claim that substitution treatment benefits users by reducing injection (Ward, Mattick & Hall, 1997). However, methadone is associated with continued injection of heroin and other drugs, as the overall median duration of injecting is longer for those who start methadone compared to those who don't. For those who do not start methadone treatment, the medium time of injecting is 5 years (with nearly 30% ceasing within a year) compared to a

prolongation of opiate use, and injecting for 20 years for those who do start substitution treatment (Kimber, Copeland, Hickman, Macleod, McKensie, De Angelis & Robertson, 2010). This means that if the risk that applies for injecting drugs is 4 times as long, then there is an overall increase in mortality for methadone when considered over the longer term. Many of the papers justifying methadone are done over only 6-12 months and up to 5 years, often with small samples (Drucker & Clear, 1999; Davoli, Bargagli, Perucci, Schifano, Belleudi, Hickman, et al, 2007; Hubbard, Craddock & Anderson, 2003; Gossop, Marsden, Stewart & Kidd, 2003; Darke, Ross, Teesson, Ali, Cooke, Ritter, et al, 2005). This is neither relevant nor informative, as many people stay on methadone for 20 to 40 years. This group's major criticism of antagonist treatment (naltrexone) for opiate dependency was the short retention times in treatment, and overdose due to reduced tolerance (Wodak, 1997; Bartu, Freeman, Gawthorne, Allsop and Quigley, 2002).

Therein lies an ethical dilemma as advocates of naltrexone treatment and abstinence face the problem of the practical application of treatment and whether those who attain abstinence can maintain it, given the high incidence of co-morbidity. Research and clinical knowledge indicates that there is a group who have been dependent on opiates, who tend to relapse at very high rates and that relapse for someone whose tolerance for the drug has been reduced, are prone to overdose and death (Fellowes-Smith, 2011). This was the case for oral naltrexone as people often ceased using it prematurely and succumbed to early relapse. However, this problem is common to anyone whose tolerance has been reduced. For example those leaving prison when tolerance is lowered, die at much higher rates from opiate overdose (2,6% within 28 days of leaving prison) than those are using heroin regularly (Larney, 2010). Treatment approaches that involved a support person to administer the medication each day minimised the problem, however, it placed an often unwanted burden on carers and left vulnerable those who did not have a reliable support person. Slow release naltrexone implants were seen as a vast improvement on compliance rates. An editorial in the Drug and Alcohol Review (2001), confidently predicted that: "Implants are a

logical method of attempting to ensure that the benefits of naltrexone are not undermined by poor compliance rates" (p. 349) and this has been borne out by recent research. Notwithstanding some risk remains even after a prolonged periods of abstinence.

One of the strongest arguments for methadone as a treatment is that the addict's tolerance is maintained at a high level by maintaining or increasing the daily dose to a level where the craving for other opiates is reduced or eliminated (Byrne, 1995; Byrne, 2004). Consequently use of heroin, even after a period of being 'clean', is not as likely to result in an overdose. Notwithstanding, there are a number of people who die each year with methadone being implicated in their death. Recent estimates put this at 0.7% per annum, (Fellows-Smith, 2011), and for those leaving prison rates of 1.6% have been found for those who are being dosed with methadone (Larney, 2010), often as a consequence of concurrent use of other CNS depressants and that those on methadone tend to stay on the drug for many years (Kimber et al. 2010; Caplehorn, Dalton, Haldar, Petranus and Nisbet, 1996).

However, naltrexone, a potent opiate antagonist, has been shown to have valuable properties for the treatment of addiction to opiates, such as heroin and methadone. The most important property is its ability to completely block the effects of heroin and methadone (Tennant, Rawson, Cohen, & Mann, 1984), making relapse to regular opiate use almost impossible while it is being taken or being released as an implant. Research has shown that a dose of 50-100mg of oral naltrexone provides effective protection against heroin for 2-3 days, and with chronic dosing, no accumulation of naltrexone or its metabolites have been observed (Meyer, Straugn, Lo, Schary, & Whitney, 1984). Naltrexone implants have been shown to effectively block the effects of opiates for between 180 and 240 days, thus allowing an extended drug free period to deal with social and psychological problems that would otherwise lead to early relapse and risk of overdose (Hulse, et la., 2009; Colquhoun, Tan & Hull, 2005). Moreover, naltrexone is non-toxic

(Volavka, Resnick, Kestenbaum, & Freedman, 1976; Meyer et al., 1984, Colquhoun, 2003a) and produces no clinically important side-effects (Volavka et al., 1976; Meyer et al., 1984; King, Volpicelli, Gunduz, O'Brien, & Kreek, 1997; Perez & Wall, 1980). Naltrexone use offers no (immediate) reinforcement and the discontinuation of naltrexone use produces no adverse effects or withdrawal symptoms. This contrasts with heroin and methadone use, which offers strong reinforcement immediately after use, and adverse effects, withdrawals, if use is discontinued (Comer, Collin, Kleber, Nuwayser, Kerrigan and Fischman, 2002). Naltrexone has been shown to be highly effective in providing high rates of detoxification (Colquhoun, 2010) and improving long term drug free status (Kunøe, et al., 2009, Hulse, et la., 2009; Colquhoun, Tan & Hull, 2005). Being drug free significantly reduces all risks associated with drug addiction (Kimber et al., 2010). In Australia, since around the year 2000, in the numbers of individuals using opiates indicate that the enforcement of legal penalties and reduction in supply has resulted in less demand and a substantial decrease in mortality due to overdose (O'Brien, et al., 2007).

The Argument for Harm Minimisation

With the coming to power of the Liberal Government, there was a shift in policy direction from Harm Reduction to Harm Minimisation. This policy placed less emphasis on harm reduction, ie., the rights of those who want to use illicit drugs, and more importance on minimising harm to those who are yet to experiment with drugs and the rights of the wider community who do not use illicit drugs. Hence greater emphasis has been given to supply reduction and interdiction, prevention, mainly through education and deterrence, diversion programs, and treatment, with abstinence as the ultimate goal (House of Representatives Inquiry, 2007; Road to Recovery, 2003).

Those who advocate for continuation of Harm Reduction policies fall into two broad and overlapping camps: those who argue for the rights of drug users to be able to choose to use illicit drugs because they enjoy it (Madden, 2004; Hathaway, 2002) and those who argue that those who use illicit drugs are often

the most marginalised groups who are alienated from the main stream and suffer mental health problems which they medicate using these drugs (Goodfellow, 2004). In both cases, they see the shift to Harm Minimisation, with an emphasis on deterrence and treatment, as persecution of these groups and as an infringement on their civil liberties. For Madden (2004) the recent report, "The Road to Recovery" (2003), spelt out the new, upcoming National Drug Strategy incorporating "harm prevention" to replace the harm minimisation approach. For her, Harm Prevention is seen as a two pronged approach including: prevention of all illicit drug use in the first place via supply and demand reduction strategies; and the promotion of drug treatment that sees abstinence from all drug use as the ultimate outcome.

Madden (2004) says that it carries the message that "people who use illicit drugs have "self-inflicted" problems and therefore do not deserve protection in terms of their health and human rights, do not deserve to be treated with dignity and respect, should at best be viewed as "sick" and as "victims" and should only be given two choices: don't use drugs in the first place or stop using; or, if you can't stop – "go into drug treatment but you must have life-long abstinence as your only goal." (p.2)

Alternatively, the views of Goodfellow and colleagues that present drug addicts as victims, and suggest that the reasons why some people use and ultimately become dependent upon certain drugs are largely social and environmental and that genetic factors often predispose some people to addiction (Goodfellow, 2004). Some of the risk factors impacting upon young people that are associated with drug dependence in later life include:

- depression, suicidal behaviour, exposure to crime, risk of homelessness;
- extreme economic deprivation, family conflict, low literacy/limited education, social isolation, and;
- a lack of appropriate community education about drug use and harm reduction (Hawkins, Catalano & Miller, 2000).

Opiate dependency is seen as a ‘chronic relapsing condition or disease’, which entails changes to the person’s nervous system, which may or may not be permanent. The harm minimisation position is that the addict is unable , for at least a short time (5 years) and sometimes never, to be cured, despite their best intentions and the help of well-intentioned help of others (Barnett, 1999. This mimics the Alcoholic Anonymous position of the chronic alcoholic who can never drink again, as it will inevitably lead to relapse to alcohol dependency. In this disease model of addiction, alcoholics are seen as different at a biological level compared to those who can drink socially and not become addicted. Or alcoholics had personality (or moral) flaws, which the rest of us were free of, which predisposed them to alcoholism and was incurable. In the present case though, advocates of harm minimisation suggest that the addict be maintained on their drug forever, either methadone, or preferably morphine or heroin (Barnett, 1999). Despite the arguments which stress the ‘lifestyle choice’ and human rights of the addict, this concept of difference, of being fatally flawed, persists. In this scenario, addicts are treated with disregard for their dignity, or their rights, often by health professionals, including those working in methadone clinics

Advocates of Harm Reduction suggest that a ‘zero tolerance’ policy, which the National Drug Strategy enshrines, tends to neglect the needs of those caught up in addiction, especially those with social or psychological problems, and deterrence can manifest as persecution of these vulnerable groups. This approach tends to neglect the need to protect young people from easy access to addictive drugs and the harms associated with them.

The cries that the “War on Drugs” is not winnable and we should abandon the fight (Wodak, 2002; Madden, 2004) is like suggesting that deterrence of drunk driving is not winnable and infringes on these people’s rights; so we should give up and allow them to create death and mayhem on our roads. Or that seatbelt use in Australia should not be enforced as ‘it harms no-one else’. Despite the suggestion that the ‘War on Drugs” is not reducing drug use, recent reductions since around the year 2000 in Australia in the numbers using opiates and dying of overdose, indicate that the enforcement of legal penalties and

reduction in supply has resulted in a reduction in demand. In the period from 1999 to 2003 it was estimated that A$5 billion in ham was avoided by Australia's adoption of a "'Tough on Drugs ' policy (House of Representatives Inquiry, 2007). Perhaps these policies need to be part of a broad-based and coherent policy on preventing harm from drug use. Just as a reduction in harm is associated with reduction in supply, there also seems to be benefits arising from abstinence-based treatments for those who want them. For this reason, methadone should be seen as a temporary harm minimisation approach for a small group of highly dependent and unmotivated addicts and not as a permanent or long-term treatment for the vast majority of this group. Methadone when used in this way is a form of social control that removes the person's opportunity to be drug-free and removes their dignity and capacity for choice.

The Right to Choose to be Drug Free

The overwhelming evidence is that most people who become addicted to a drug, including opiates, at some point become drug-free and go onto live 'normal' lives. Most people do this spontaneously without or with minimal intervention. (Kaufman, 1994; Robins, Helzer & Davis, 1975; Robins, Helzer, Hesselbrock & Wish, 1980; Donath, 2004). People who experience spontaneous remission from substance misuse often do so because of one or more of the following factors: increasingly negative outcomes such as health, accident or legal problems; the gradual worsening of important aspects of life such as personal relationships, financial problems; or positive life events such as marriage, work and children. These are all responses of individuals to the problems posed by addiction. Perhaps the overriding factor in the rate of dependency, and similarly, spontaneous recovery, is the access and availability of the substance to those who are addicted to it (Hall, Ross, Lynskey, Law & Degenhardt, 2000). Clearly, policies which emphasise the potential harm associated with drug use and the role of deterrents will have a major impact on rates of addiction and the time frame for remission (Kaufman, 1994). However, in an environment where there is a tendency to minimize harm or the consequences of drug use, an

acceptance of illicit drug use is viewed as a right, and where the drug is cheaply and readily available, then intervention is more likely to be needed to attain abstinence. While there still is a need to more fully explore the optimal techniques for the safe use of naltrexone, and how counselling can best help addicts and their families break free from heroin and methadone dependence, they have a right to choose to be drug-free. Naltrexone detoxification and the use of slow-release naltrexone implants provide this opportunity. (Colquhoun,2010; Hulse, Morris, Arnold-Reed, & Tait, 2009; Kunoe, et al., 2009; Colquhoun, Tan & Hull, 2005; Comer, Collins, Kleber, Nuwayser, Kerrigan, & Fischman, 2002).

Opiate dependent people have a right to the best form of treatment available and that includes naltrexone treatment incorporating those components which maximise effectiveness and safety. (Kimber et al. 2010). Naltrexone has now been shown to be highly effective in providing high rates of detoxification (Loimer, Lenz, Schmid & Presslich, 1991; Mattick, Diguisto, Doran, O'Brien, Shanahan, Kimber, J. et al., 2001; Colquhoun, 2010) and with the use of slow release implants retention in treatment is much higher and long-term abstinence is achievable. Moreover, there is a demonstrated reduction of mental health problems, overall improvements in physical health, dramatic reductions in crime, morbidity and mortality, and a chance to contribute to society in a meaningful way once more (Latt, Jurd, Houseman & Wutzke,2002; Comer, Collins, Kleber, Nuwayser, Kerrigan, & Fischman, 2002; Kunøe, et al., 2009, Hulse, et la., 2009, Colquhoun, Tan & Hull, 2005).

Therefore, the major argument in favour of naltrexone treatment is based on evidence of its safety and efficacy, but also on the ethical issue, and ultimately on the argument in favour of the human rights of the dependent person to be free from dependency.

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Dr Ross Colquhoun is a Clinical Health Psychologist working in private clinical practice since 1996. He specialises in the treatment of addictions and is a leader in the treatment of substance dependency, especially opioid dependency and in the neuroscience of addiction. He is principally responsible for the psychological assessment and treatment planning for substance dependent patients entering the program, which has a focus on concurrent treatment of co-morbid conditions. These include mental health problems, brain injury and chronic pain. He also has expertise in the prevention and treatment of psychological problems, especially burnout among health professionals, rehabilitation and couples and family counselling, and medico-legal reports. The practice employs two other psychologists/ psychotherapists and intern psychologists as well as nurses and doctors part-time. Information can be found at www.addictiontreatment.com.au

Dr. Colquhoun developed the concept of Mindcheck Wellness Centres to provide diagnosis and treatment planning for people with dementia and to support their families. As there is a three year delay between onset and diagnosis of dementia, he developed an on-line screening test for people who are concerned about their cognitive performance, as early intervention can significantly impact the progress of the disease, quality of life and functioning, and allows people a say in their care before it is too late. This can be found at www.mindcheck.com.au.

He has had two books published, “The Use of Naltrexone in the Treatment of Opiate Dependence”, (Lambert Academic, Germany), based on his doctoral thesis and “Is Dementia a Bigger Word than Cancer?” (Xlibris, USA). This book aims to encourage people to seek early assessment and to prepare people for dementia. It clearly explains what you might expect and what you can do in terms of prevention and treatment.