Defence of Dr. George O'Neil for WA enquiry into Addiction Management

Dear Sir,

I gather that in Perth now you have an enquiry into addictive drugs. I have also been advised that certain self-nominated "experts" from Sydney have involved themselves in this Westralian discussion. I am led to understand also that some of the Sydney experts have been critical of the exemplary work of the world pioneer Dr. George O'Neil. The acknowledged leader of this coterie is Dr. Alex Wodak of St. Vincent's hospital Sydney.

Dr. Wodak is well known to be one of the world's most vociferous proponents of the legalization and decriminalization of all addictive drugs. Notwithstanding an increasing scientific literature on the well known toxicity of these agents involving diverse effects as signficant as causing foetal malformations, cancer, an acceleration of the ageing process, frequent psychological disorders, a veritable multitude of respiratory conditions and permanent gene damage, Dr. Wodak is well publicized to be of the view that because these agents are popular, there should in fact be no protection of the public from their multitude of severe effects. In other words the bar of protection for our vulnerable young people should be at ground zero or removed completely.

Dr. Wodak is also the doyen, architect and principal exponent of the harm minimization movement, as suggested by his paper in 1995 entitled *"Harm Reduction Means What I choose It to Mean."* [1]. He went on in another place to describe the vision of his nascent movement in somewhat more detail when he provided further details in the same year that harm minimization may in fact be defined as *"Policies and programs which are designed to reduce the adverse consequences of mood altering substances* ***without necessarily reducing their consumption****."*[2] The remainder of the article goes on to offer some excuses why this novel public health agenda did not need to concern itself with a quantitative increase in drug use itself; an increase which has now occurred twice under the watchful tutelage of Dr. Wodak, first in relation to our heroin plague, and only arrested by John Howard's much maligned "Tough on Drug Strategy", and more recently as admitted by Wodak's committee's own work, in relation to prescription opiates, which continues unabated and accelerating at the present time, as the WA committee will no doubt have heard in other evidence.

What is less widely known in the community, but quite well known in circles which are concerned about drug use and monitor its activities, is that Wodak has not infrequently characterized his harm minimization movement as merely the front runner of full drug decriminalization and legalization. One such statement was noted on the Australian Drug Reform website and down loaded some years ago (see attached), but people with an interest in this field are aware of many occasions where he has said just this. That such sentiments continue to be current with this so-called expert was amply demonstrated on a recent ABC Lateline interview with Leigh Sales recently when he was commenting on our increasing prescription opiate use. [3] In this sense Wodak's avowed motivations for his representations on behalf of his harm minimization conceptualization can only be viewed as disgenuous at best or frankly misleading at worst.

As stated methadone is widely regarded as the "gold standard" in addiction management, and the Sydney coterie frequently make such comments. It is important to recognize that methadone's now iconic status has bestowed on it profound idiomatic significance way beyond its role as a treatment for heroin addiction. Methadone is particularly important as it is the flagship treatment of the harm minimization lobby, and forms the classic paradigm as the pattern for new drug development in addiction medicine. The classic chestnut goes *"Since methadone is the most effective treatment we have ever had in addiction medicine, our only problem is that we do not have a methadone for all the other addictions."* One has heard this said by some of the most very senior people both in the USA and in Australia. The implications are positively scary - if a kid has a toke on a joint one of these doctors will place them on the "methadone for cannabis" where they will stay for life, and from where they can go on to graduate to other addictive drugs. So the true situation with methadone is very

important to discern, and critical for our whole understanding of the public health discussion which must now occur around it.

In reality the medical literature contains 23 major side effects of this drug which are not at all recognized by the industry. The list is currently un-referenced, but with over 10,000 papers listed at the National Library of Medicine Online [4] there are lots to choose from. Referencing this list is presently a work in progress, and these papers (over one hundred) are available to the interested reader upon request. Many of these side effects are very major and include:

1. Immune suppression and immune stimulation, which is believed to underlie, many common disorders such as heart attack and stroke, cancer, osteoporosis, diabetes, dementia and the ageing process itself;
2. Weight Gain, up to 8kg/year, and including high rates of obesity
3. Cancer risk
4. Blood Pressure / Hypertension
5. High Sugars / Diabetes, pre-diabetes,
6. High Cholesterol
7. Sedation / sleepiness, loss of energy and drive and life
8. Over 90% get a psychological / psychiatric disorder requiring treatment, leading to very high rates of benzo (often alprazolam / "Xanax" or olanzepine "Zyprexa" use which)
9. Exacerbate weight gain and immune dysfunction and sedation
10. Lack of activity
11. Very high rate of other substance use including toxic agents such as cannabis tobacco pills and speed
12. Addiction maintenance – it is a treatment aimed at deliberately perpetuating long term drug use almost indefinitely
13. Bone loss and disease, including osteoporosis and osteopaenia,
14. Dental disease – often devastating – related to immune suppression, bone loss, increased infection, altered appetite and taste attractiveness
15. Difficulty of Detox and getting off it,
16. Hormonal suppression which is associated with hardening of the arteries,
17. Hardening of arteries
18. Premature ageing
19. It increases the rate of QTc prolongation and Torsades de Pointes; slowing the heart rhythm, and making it more likely for the heart to stop suddenly causing death, especially in:
    i) Patients with liver disease – 70% have Hepatitis C;
    ii) Patients on other drugs – most are;
    iii) Patients on more than 60mg daily – the widely recommended dose range
20. Adverse effects on babies and baby development, especially brain development into childhood and adolescence and schooling years – learning difficulties
21. Effects on stem cell suppression – growth / tissue recovery inhibition
22. Significant death rate which is higher than that of control populations – the naltrexone implants reduce the death rate to that of the general population!!
23. Ongoing use of heroin is presumed normal - at least half their patients continue to use heroin in their own surveys. This is in contrast to naltrexone where drug use is much more exceptional and unusual.

It is hard to think of a more lethal or a more unsavoury cocktail. To admit that this "treatment' or "management" program is to be applied long term almost horrifies credulity. That an extensive program has been entrained for some decades now to "maintain" the status quo of opiate addiction, demands an explanation and a national account.

It should be noted that none of these issues are so problematic with naltrexone therapy. Indeed the research which has been done in this area, suggests that all these effects are reversed by naltrexone.

Some of the underlying processes involved here are believed to be that while methadone suppresses stem cell growth by about 30% naltrexone up-regulates it by about 30%. Therefore methadone patients (at 70% or normal) have about half the stem cell activity of naltrexone patients (130% of normal). Secondly methadone and long term opiates tend to primarily suppress and secondarily stimulate the immune system, both of which are very deleterious changes. Naltrexone reverses both of these impacts. Thirdly it turns out that the immune dysfunction powerfully stimulates the stem cell inhibition related to all addictive drugs, so that patients actually sustain powerful "triple whammy" mechanism underlying many of the above effects.

However when it comes to naltrexone Dr. Wodak's ultra-liberal values appear to strangely evaporate apparently instantaneously. Naltrexone was first synthesized by Matossian at Blumberg's suggestion at Endo laboratories in 1963 [5], and widely used in clinical trials reported in the early 1970's, so that now, 46 years later, the drug may be considered to be definitely middle aged. From a clinical point of view it has effectively negligible toxicity. Concerns were earlier expressed that naltrexone may have been assoicated with depression, suicidality or liver disease but these have all been dispelled by further reports and studies. The remaining concern relates to the death rate accompanying relapse to heroin use after naltrexone tablets are ceased. However on careful measuring, such concerns have not been found to relate to naltrexone delivered by the Perth implants, notwithstanding the concerns of the pro-drug cadres. Detailed investigations of this question in contemporary Australia have been published both from Perth [6] and from Brisbane [7,8], one comparing naltrexone implant patients with methadone and two with series of buprenorphine treated patients. Methadone is frequently referred to as the "gold standard" treatment in this area, and buprenorphine is widely acknowledged for its now well verified safety record, so these comparisons were both important studies in the real world against gold standard treatments and rigorous treatment conditions. The two Brisbane reports were very large series, as Dr. Reece has treated 75% of all the detoxification episodes in Queensland 2001-2007 according to official figures, and these two reports involved over 1300 naltrexone implant patient-years, and 8000 buprenorphine patient-years. Implant naltrexone was not only exonerated, but actually compared superiorly to buprenorphine in all treatment comparison groups, in a statistically highly significant manner. Similar remarks applied in Perth to the comparisons with methadone.

The other reservation which the Sydney cadre publicize in relation to the naltrexone implants is that the release rates of naltrexone from its depot matrix has changed. Indeed for it has improved. It is a matter of record that the active life of the O'Neil implants dropped from about 5.5 months to 4 months, and presently stands at about 12 months. Plans are afoot to extend this to the order of 21 months. O'Neil is conducting some of the most sophisticated tests internationally on the factors governing the release rates of the drugs from plastic depot matrices. These data may be placed into context by noting that the longest available therapeutic duration in the USA is active for only 1 month. Moreover no heroin override deaths have occurred in a patient with naltrexone implants in place, and the very rare cases of continued heroin use (less than 2%) readily yielded to the insertion of a further implants. Based upon my own clinical experience, in these respects the performance of the O'Neil implant far out-stripped the Chinese implant from Shang-hai which was apparently a direct copy of the O'Neil's device. It is more than a little paradoxical that the Chinese device appears to enjoy TGA approval at least to the level of having been granted an importation permit, than the O'Neil device does. Such entrenched administrative bias is at least consistent with the imposed views of the supervising Sydney cadre. In other words the supposed theoretical weakness of the Perth implants is more than made up for by their overwhelming efficacy in clinical practice. Once again the criticism of the Sydney coterie is exposed as another smokescreen for their underlying ignorance and lack of experience with the implants themselves, and their fixated ideological unpreparedness to squarely admit to their own short-comings.

Scientifically one of Wodak's greatest achievements was to have set up the "National Centre for Drug and Alcohol Research" (NDARC) at UNSW in Sydney. Whilst purporting to conduct genuine research into Australia's various addiction epidemics, this institute has faithfully supported and justified Wodak personal pro-drug agenda since its inception despite the massive and voluminous

evidence to the contrary ever since. This institute has been amply funded directly from Federal funds since its inception, and has used its prestige as the flagship of Australian addiction research to win many other grants, all dedicated to aspects of the pro-drug agenda, and apparently at the same time, obfuscating the real situation. Given the multiplied millions which have been invested by this nation in this group, it can only be regarded as perverse that they have only recently begun to recognize the obvious harms related to amphetamine and cannabis, now that the international literature has so overwhelmingly acknowledged these facts. It is also not widely recognized that there are no basic scientists at NDARC, as the place is staffed almost exclusively by psychology trained professionals with no background or formal education in prescribing any medications, basic neuroscience, genetics and DNA repair, and oxy-radical damage and immune mediated mechanisms, mitochondrial science, or stem cell pathologies, all of which are foundational to drug induced damage and processes impinging on the organism. Therefore addiction science in this nation continues to be uninformed on the basic underlying processes of cell biology and neuroscience as this area is specifically deliberately and methodically excluded from funding considerations on specious grounds in this country. The popular agenda on drugs can therefore be set unopposed by ideologically driven psychologists, completely unchallenged by scientifically informed hard biological facts, in virtual complete disregard of the findings of modern neuroscience, ageing science and stem cell advances.

Clearly this gaping research chasm in the basic sciences cries out for correction if Australia is ever to begin to confront our burgeoning addiction epidemics from a basis in scientific fact and reality.

In practice Dr. Wodak's group have enormous influence with the Therapeutic Goods Administration (TGA) of the Federal Health department in Canberra. Influence from his ideological circle was recently brought to bear to interfere with TGA administration in the matter the special access scheme administration to force the closure of Dr. O'Neil's clinic for one month. Category A Special Access patients include those with serious illnesses accompanied by elevated rates of death. Heroin addiction is widely recognized to have about a 13 fold elevation of the death rate, but for the Sydney coterie this somehow implied that heroic addicts in Western Australia were not thereby qualified. This reasoning was naturally quite obscure. Thankfully Dr. O'Neil's clinic has now re-opened, apparently resulting from the Prime Minister's direct and forthright intervention.

One notes with interest the profound attention and accolades heaped upon Professor Ian Webster of Sydney for his dedication to the care of homeless persons [9] (attached). Dr. O'Neil's "PHREE" program would be well known to you, wherein he personally attempts to house and care for the homeless drug addicted patients he meets. At one stage this numbered 40 houses for his patients. Probably no other doctor in this country has personally contributed as much to the problems of the homeless as Dr. O'Neil. If Professor Webster has had accolades heaped upon him for his *in principal* involvement with this issue, even more should Dr. O'Neil be so recognized for his *in fact* involvement and personal support on this very challenging issue.

In recognition of the 70% rate of hepatitis C and the obviously territorial behaviour of opiate addicted patients, Dr. O'Neil established probably the world's first integrated drug addiction and hepatitis C clinic where patients could have their dependency needs and addiction issues addressed under the one roof at the specialist level. I understand that this arrangement has since been replicated in other centres internationally.

In short it is impossible to avoid the conclusion that the objections of the well known drug legalizers such as Dr. Wodak should be overlooked given their well known and widely publicized drug legalization agenda and the obvious irreconcilable conflict of interest which clearly exists. A lobby group coming from the fixed perspective of such ideological proponents is unlikely ever to find a cornerstone treatment which has been shown to produce a reduction in the use of all addictive drugs either palatable or acceptable. That they should do so within a paradigm which simultaneously

accepts the increasingly well documented harmful effects of the addictive agents they promote is at once offensive to commonsense, and may only be seen as a particularly evil betrayal of the goodwill of the Australian people who, justifiably, look to their well funded experts for advice on such far reaching subjects.

When we travel overseas, Dr. O'Neil is acknowledged as a brave and innovative pioneer. It is time this pathfinder status was more widely recognized in this country. I find it impossible to avoid the view that to continue the present vilification of him, as has been promulgated thus far within Australia by the ideological pro-drug forces, is at once obscene and duplicitous. Far from being un-researched as the Sydney group repeatedly claim, the Perth group have released 46 publications in this field. About five similar publications has also come from Brisbane using the O'Neil implant. In the USA a mechanism exists known as the "Orphan Drug" mechanism, whereby commercial sponsors of pharmaceuticals which have only doubtful or at best borderline commercial viability, but who are faced with nevertheless enormous commercial barriers to registration of their product, are assisted by Federal funds to gain registration status. We obviously urgently require implementation of a similar system here which is proofed against interference by well known advocates and lobbyists who are unlikely ever to find attractive any alternative other than unbridled indulgence, at least in the foreseeable future, and in at least in this lifetime.

O'Neil has received high wards from the AMA and many other accolades. It is high time he was recognized as such and given appropriate resources and status to allow and indeed to facilitate his righteous mission of helping all of Australia's kids and young people to get and remain drug free. It is way overdue in this country that we called a spade a spade, and banished the dissemblers from the forum and any others who would allow personal motivations to interfere with the setting and achievement of major and urgent national priorities.

Yours sincerely,

(Dr.) Stuart Reece.

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Regular article

Comparative treatment and mortality correlates and adverse event profile of implant naltrexone and sublingual buprenorphine

Albert Stuart Reece, (M.B.B.S., F.R.A.C.G.P., F.R.C.S. (Ed.), F.R.C.S. (Glas.), M.D.)*

Southcity Family Medical Centre and University of Queensland Medical School, Queensland 4101, Australia

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Abstract

There is increasing interest in the use of implantable naltrexone as a new treatment for opiate dependence. This center has been one of the leaders in this form of treatment in Australia and has recently completed a registry-controlled review of our mortality data. As part of the study of the safety profile of this therapy, we were interested to review both the treatment correlates of previously presented mortality data and of adverse events. A total of 255 naltrexone implant therapy (NIT) and 2,518 buprenorphine (BUP) patients were followed for 1,322.22 and 8,030.02 patient-years, respectively. NIT patients had significantly longer days in treatment per episode (mean ± standard deviation, 238.32 ± 110.11 vs. 46.96 ± 109.79), total treatment duration (371.21 ± 284.64 vs. 162.50 ± 245.76), and mean treatment times but fewer treatment episodes than BUP (all $p < .0001$). Serious local tissue reaction or infection each occurred in 1% of 200 NIT episodes. These data show that NIT economizes treatment resources without compromising safety concerns.

Keywords: Naltrexone implants; Buprenorphine; Mortality; Serious adverse events; Treatments

1. Introduction

Several fascinating articles relating to naltrexone implant therapy (NIT) including at least one randomized controlled study have appeared in recent times describing important potential applications for an antagonist-based pharmacotherapy in special opiate-dependent populations including pregnant patients (Hulse & O'Neill, 2002; Hulse et al., 2004), addicted physicians (Hulse et al., 2003), high-risk patients treated for repeated overdoses (Hulse et al., 2003, 2005), and indeed for the generality of opiate-dependent persons (Comer et al., 2006; Sullivan et al., 2006). Although in the United Stated various depot preparations of naltrexone are now marketed widely for use in alcohol dependence (Kranzler et al., 2004; Johnson, 2006), most of these only act for about one month (Dunbar et al., 2006, 2007; Hulse, Arnold-Reed, Ngo, & Reece, 2007; Reece, 2007d). Much longer acting naltrexone depot preparations are available from Western Australia with clinical activities from 6 to 8 months (Hulse et al., 2004), and from China.

Long-term opiate agonist maintenance therapy has achieved widespread acceptance globally based particularly upon the substantial reduction both of mortality rates (Gunne & Gronbladh, 1981; Gronbladh et al., 1990; Caplehorn et al., 1996; Ward et al., 1998; Caplehorn & Drummer, 1999; Digiusto et al., 2004; Brugal et al., 2005; Clausen et al., 2008) and of HIV seroconversion rates (Woody et al., 1997; Ward et al., 1998; Sullivan et al., 2005; UNAIDS, 2007), which have been demonstrated and replicated in a great many studies. Although these signal accomplishments are valuable and widely acknowledged, long-term agonist-based treatments have also been shown to be associated with appreciable mortality rates in both the medium (Brugal et al., 2005) and longer term (Hser et al., 1993; Caplehorn et al., 1996; Caplehorn & Drummer, 1999; Hser et al., 2001; Gibson et al., 2008; Davstad et al., 2009) and to be associated with an immunosuppressive (Pillai et al., 1991; McCarthy et al., 2001; Li et al., 2002; Suzuki et al., 2002; Cabral, 2006) state

Work was conducted at Southcity Family Medical Centre. This work is the work of ASR in its entirety.

Conflicts of interest: Naltrexone implants were sold to some patients through this clinic for use in their treatment on campus.

* Southcity Family Medical Centre, 39 Gladstone Rd., Hillgate Hill, Queensland 4101, Australia. Tel.: +61 738444000; fax: +61 738444015.
E-mail address: sreece@bigpond.net.au.

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that includes a compensatory immunostimulation (Reece, 2007a, 2007b, 2007c, 2007d), which may mollify with time (Novick et al., 1989; Ochshorn et al., 1989) to suppress cell replication (Zagon et al., 2002) and likely stem cell division (Reece & Davidson, 2007) and particularly affects the brain (Eisch & Harburg, 2006; Canales, 2007; Drake et al., 2007; Kolodziej et al., 2008). Addiction to various drugs including opiates has also been shown to be associated with a number of other changes such as osteoporosis (Kim et al., 2006), hair graying (Reece, 2007b), neuropsychiatric deficits (Dyer & White, 1997; Galarneau et al., 2006; Reece, 2008a, 2008b, 2008c; Schreiber et al., 2008), and dental abnormalities (Carter, 1978; Fan et al., 2006; Reece, 2007a, 2007b, 2007c, 2007d), all of which are changes characteristic of the ageing process and are features particularly of individuals in whom the ageing process is following a prognostically adverse trajectory (Franceschi et al., 2000; Vasto et al., 2007).

There are however few reports comparing agonist and implant antagonist-based treatments directly. Some articles exist comparing methadone-treated patients with NIT patients (Hulse et al., 2004; Tait et al., 2007). To the best of this author's knowledge, none have compared NIT with buprenorphine treatment (BUP). There are few reports comparing the mortality outcomes of NIT with agonist treatments (Tait et al., 2007), and none which examine the role of various treatment parameters in determining mortality and patient outcomes. Clearly, the relevant treatment predictors of outcome success and of prevention of mortality must be central guides to quality of care with any treatment. Treatment retention, generally assumed to be a central determinant of success with pharmacotherpeutic approaches for addiction, has not been well examined in a NIT cohort. There are few reports of adverse events in NIT (Hamilton et al., 2002; Hulse et al., 2005; Hulse, Low, et al., 2007).

The implications of such safety studies goes beyond the usual technical and treatment issues such as those raised above. With many treatments now adopting the agonist or partial agonist approach to the pharmacotherapy of addiction, including methadone, levo-alpha-acetylmethadol, buprenorphine, varenicline, buprenorphine–naloxone combination (McCann, 2008), corticotrophin-releasing factor agonists (Farrokhi et al., 2007), D3 dopamine receptor partial agonists (Desai et al., 2007; Martelle et al., 2007), cannabinoid agonists (Rock et al., 2007), and others, the agonist/partial agonist approach to therapeutics in this field is becoming fundamentally paradigmatic to the conceptualization of medications development. Clearly for other treatments to assume a valid and significant role in such a treatment milieu requires that fundamental studies of both safety and efficacy must be carefully planned and executed. Because such formal studies begin to appear in the published literature, they therefore implicitly carry proof of principle significance beyond their particular indication and have implicit implications for medications development across the field in addiction medicine. That is to say that the well-recognized success of opiate agonism with methadone merits detailed consideration of its safety and mortality profiles in view of its role as the paradigmatic proof of principle agent for diverse agonist treatments.

The present report has been prepared as part of a series of reports of a clinical audit of the NIT experience of this clinic (Reece, 2007a, 2007b, 2007c, 2007d) and as a companion article to another from this clinic related to absolute and standardized relative mortality rates to address these gaps in the literature. The study is structured as a naturalistic clinical audit and so does not have the advantages conferred by randomization. This report has been prepared as a chronicle to address the above-mentioned issues and to prepare the way at the conceptual level for formal examination of these issues by multimodality randomized studies, which are clearly indicated using the various longer term devices that are becoming increasingly available.

2. Methods

2.1. Patient recruitment and identification

All patients treated with naltrexone implants or sublingual buprenorphine at this clinic 2001–2007 were included in this study. Buprenorphine patients were identified from records held at the Dangerous Drugs Unit (DDU) of Queensland Health by first name, family name, and date of birth. All NIT patients were identified from a register held at the clinic by first name, family name, and date of birth. The date of censoring was October 23, 2007.

2.2. Patient treatment

Patients presenting for pharmacotherapy of their opiate addiction were treated with either buprenorphine in the standard manner or naltrexone implants as has been described (O'Neil et al., 2002; Reece, 2007a, 2007b, 2007c, 2007d). The formulation of buprenorphine that was used was "Subutex" (Reckitt Benckiser) up until about 2004 and "Suboxone" buprenorphine/naloxone combination tablet thereafter when that formulation became available in this country. After 2004, Subutex was administered only to pregnant patients, and the very occasional patient with a naloxone allergy. Patients requesting NIT were prepared by conventional detoxification methods first, often including a brief period of BUP. In general, at least 1 or 2 days of complete abstinence from opiates is required prior to implant insertion, depending on the nature of the particular opiate to which patients have been primarily exposed. This period of careful pharmacological preparation and supervision is regarded as the most important part of the procedure. It is a regulatory requirement in Queensland that all patients who undergo BUP must have their admission and discharge dates notified to the Central register held at the DDU. All NIT patients were identified by a unique confidential patient identifier to the Therapeutic Goods Administration (TGA) of the Federal Department of Health and Ageing in Canberra.

All applicable State and Federal regulations were complied with by the clinic throughout the various phases of treatment. BUP is subsidized by the Australian Federal Government. Medical treatment was provided free to buprenorphine patients, but they did incur a small daily dispensing charge at community pharmacies. NIT patients were required to fund their own therapy and were charged at this clinic prior to treatment. This created a financial barrier to treatment. This financial differential between the patient groups is discussed further in the Discussion section.

2.3. Naltrexone implants

Naltrexone implants were derived either from the "Wedgewood Pharmacy" in Sewell, NJ, or "Go Medical" in Perth, 200 Churchill Ave., Subiaco, Western Australia 6008. This clinic is a standard primary care facility and treats ambulatory patients. After administering a naloxone challenge, a naltrexone implant was inserted usually in the subcutaneous tissue low down in the anterior abdominal wall. Through a 1.5-cm skin incision, two long pockets were fashioned in the subcutaneous tissue of the abdominal wall, and one implant was inserted into each of these. Patients were given supplementary sedation and medication to control agitation and gastrointestinal disturbances such as vomiting and diarrhea as the naltrexone became effective over the first four hours. A precipitated detoxification reaction can still occur in patients who pass a naloxone challenge test because the binding constant of naltrexone is twice that of naloxone (Wikler, 1977; Gonzalez & Brogden, 1988).

2.4. Psychosocial treatment

All patients were offered referral for counseling, an option that most did not pursue. Twelve-step programs appear to be much less popular in this country than in other places such as the United States. In general, patients were more open to referral after the initial treatment episode. Patients who did avail themselves of counseling opportunities had their counseling performed either at public addiction (Alcohol Tobacco and Other Drugs) clinics or at dedicated counseling and community outreach services such as Drug Awareness and Relief Movement. Although patients were also able to access General Practitioner counseling at their scheduled clinic appointments, in general, this did not occur among implant patients because they tended to only rarely return for clinical review, outside of relapse situations, despite repeated invitations to do so.

2.5. Registry identification and matching

Formal negotiations were conducted with the Registrar of Deaths in the Attorney General of Queensland's Office to allow a matching process to occur. All information transfer procedures were undertaken with the strictest confidentiality. Full patients privacy was strictly maintained throughout the analysis. Patient identification data were submitted to the Central Register of Deaths. Vital status was determined by whether patients were known to have deceased on the register. Patients details were matched. A confirmed match was said to have occurred if concordant details for first name, family name, and date of birth occurred and if patients had not been seen in the clinic since the supposed date of demise.

2.6. Interval definitions and crossovers

The time of patient registration on buprenorphine was taken as the time of active patient treatment. The total treatment time was the sum of all these treatments for each individual patient. The number of patient treatments was the number of times they had been treated with either BUP or NIT. The mean duration of patient treatments was the mean duration of all their admissions to BUP. For naltrexone implant treatment, the notional duration of the Wedgewood implant was taken as 30 days in accordance with previous studies (Hulse, Arnold-Reed, et al., 2007). For the Go Medical implant, the notional duration of treatment was 297 days because this has previously been shown to be the maximum period for which such implants are likely to be active and maintain a serum naltrexone level greater than 1 ng/ml (Hulse et al., 2004). The 1-ng/ml level was chosen because it is most relevant to considerations of mortality, which is the major concern of this article. Crossover patients had both treatments. Crossover patients were described as being BUP-NIT where buprenorphine preceded NIT, and NIT-BUP where NIT was antecedent to BUP. In each case, the interval prior to the initiation of the change to the other treatment was taken as the treatment follow-up period, and the period after the commencement of the alternative agent was assigned to the second agent.

2.7. Data analysis and statistics

Categorical data were analyzed by "EpiInfo" of Communicable Diseases Centre, Atlanta, GA. All continuous data were analyzed, and graphs were prepared in "Statistica" (Statsoft, Oklahoma, USA). Where Levene's test for inhomogeneous variances was significant, the Student's t test was applied with separate variances. Cells with small sample sizes were manipulated with the Yates corrected chi-squared test or Fisher exact test as appropriate. A Macro was written in Microsoft Visual Basic for Microsoft Excel to allow calculation of the number of BUPs and the mean and total BUP durations from individual buprenorphine admissions data. A p value less than .05 was considered to be significant.

2.8. Informed consent and ethical approval and legal framework

This study was performed in the form of a clinical audit. All studies and procedures were approved by the Human

Research Ethics Committee (HREC) of the Southcity Medical Centre, which is a National Health and Medical Research Council approved HREC. All patients underwent the treatment they elected to pursue based on clinical, financial, and other factors. Because our patients' treatment was not perturbed in any way by the conduct of this research, strict confidentiality was maintained throughout, no identifying data were to be released, and personal details were in any case held in the clinic, the clinic HREC considered that individual patient consent was not required for entry of their data into the study database. All patients consented freely to their opiate treatment. Buprenorphine patients consented verbally in the usual manner. All NIT patients consented formally and in writing to undergo treatment. The legal framework surrounding NIT treatment was the compassion-based Special Access Scheme administered by the TGA in Australia, by which a patient with a potentially life-threatening illness can elect, together with their physician, to undergo treatment with a wide variety of medications, some of which may not be registered in this country at that time. All NIT patients are notified automatically to TGA at the time of their treatment in accordance with the relevant regulations.

3. Results

A total of 2,634 patients were followed up until October 23, 2007. Of these, 2,518 were treated with BUP and 255 with NIT. Seventy-six patients were treated with BUP prior to NIT, and 83 were treated with BUP after NIT. Twenty patients changed treatments in both directions. The total period in follow-up was 1,332.22 patient-years (p-y) for NIT and 8,030.02 p-y for BUP.

The mean age of the BUP patients was 33.73 ± 7.83 years (mean ± standard deviation) and that of the NIT patients was 32.50 ± 7.42 years (t = 2.36, df = 2,829, p = .01808). The mean age for the decedents in the NIT and BUP groups was 28.58 ± 2.49 and 34.40 ± 8.18, respectively (t = 0.14, df = 45, p = .1675). There was no significant difference between the NIT treatment group and the ages of patients dying after NIT (t = 1.05, df = 249, p = .293) nor between the BUP treatment group and the ages of patients dying after BUP (t = −0.55, df = 2625, p = .579).

Of the NIT patients, 70.6% were male, as were 72.60% of the BUP patients (χ^2 = 0.47, p = .494). Among the NIT decedents, 100% were male, which was not different from

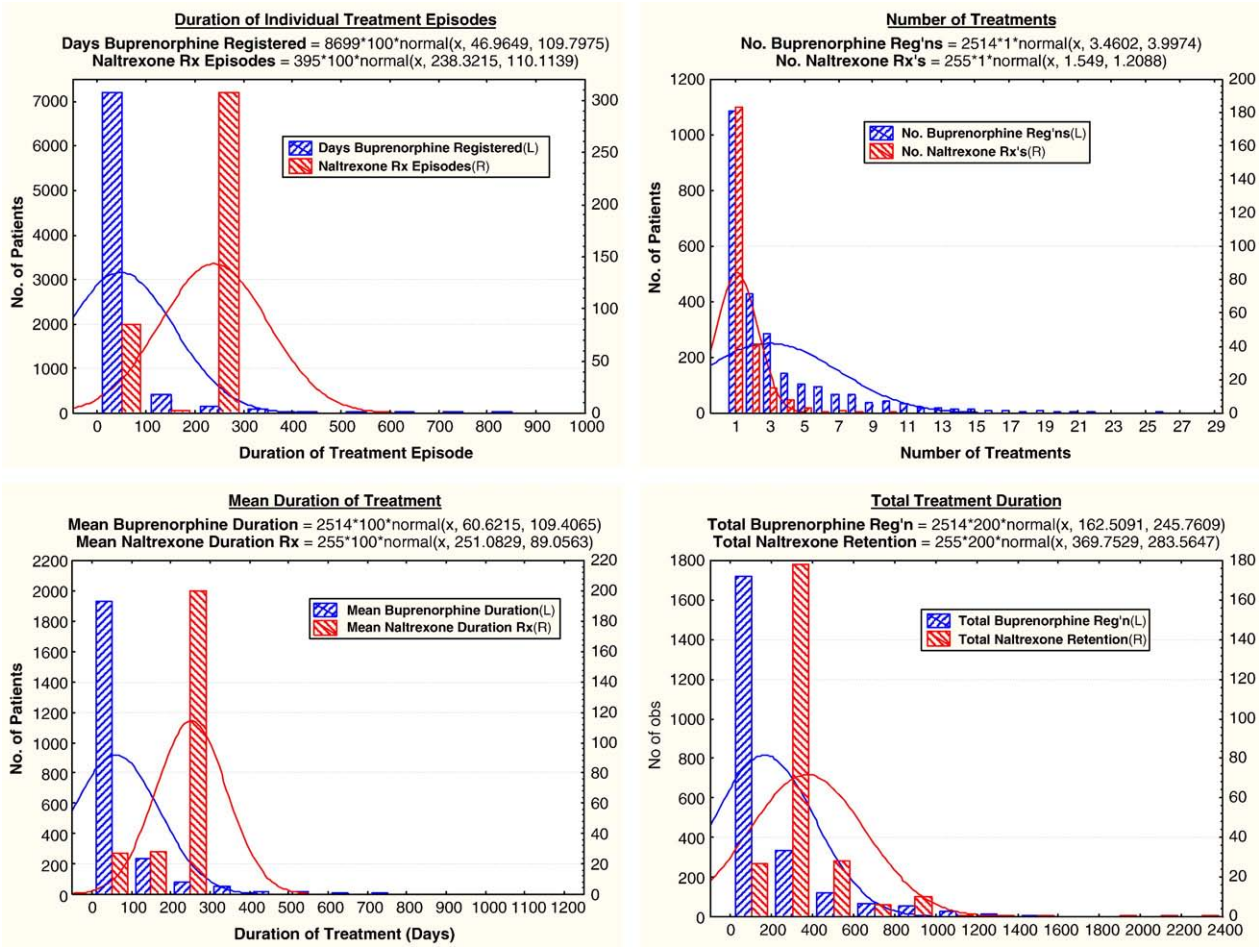

Fig. 1. Comparative treatment figures—frequency histograms. (A) Duration of individual treatment episodes. (B) Number of treatments. (C) Mean duration of treatment. (D) Total treatment duration.

Table 1
Summary treatment statistics

Naltrexone implant treatment statistics	Individual treatments	Patient treatment experience		
		No. treatments	Mean duration Rx	Total Rx duration
Count	395	255	255	255
Total treatment days (years)	94,584 (258.96)	395 (1.08)	64,070.64 (175.42)	94,584 (258.96)
Average (days or no.)	238.85	1.55	251.26	370.92
SD (days)	110.42	1.22	88.84	284.12
M (days)	297	1	297	297

BUP statistics	Individual treatments	Patient treatment experience		
		No. registrations	Mean duration Rx	Total registrations
Count	8,699	2,518	2,518	2,518
Total treatment days (years)	408,548 (1,118.54)	8,699 (23.82)	152,402.4 (417.26)	408,548 (1,118.54)
Average (days or no.)	48.31	3.46	60.62	162.51
SD (days)	144.45	3.99	109.41	245.76
M (days)	16	2	22.6	66

Rx indicates treatment.

the gender ratio among all treated NIT patients (Fisher exact test, $p = .327$). Among the BUP-treated patients, the gender ratio was 88.37% male, which was significantly higher than in the remainder of the BUP group (Yates corrected $\chi^2 = 4.55$, odds ratio = 2.87, 95% confidence interval [CI] 1.12–9.37, $p = .0329$).

Registry review revealed 5 "probable matches" in the NIT group and 74 in the BUP. Of these, 4 in the NIT group and 43 in the BUP group were confirmed patients. These death rates translate into crude mortality rates of 3.00 and 5.35/1,000 p-y in the NIT and BUP groups, respectively, and to standardized mortality rate ratios of NIT compared to BUP of 0.676 (95% CI 0.14–1.338).

Fig. 1A shows a frequency histogram for the duration of individual treatment episodes for NIT and BUP patients. The individual treatment episodes of the BUP patients clearly appear shorter than that of the NIT Cases. When the number of treatments for NIT and BUP patients are charted (Fig. 1B), the NIT patients appear to have had fewer treatments than the BUP patients. When the mean duration of treatment is charted, the NIT patients appear to have longer treatments than the BUP patients (Fig. 1C). Similarly, the total of all treatment durations shows that the NIT patients in general were maintained in treatment longer than BUP patients (Fig. 1D).

Quantification of these data is given in Table 1, which provides the summary statistics for the two treatment modalities both by individual treatment episode and for the whole of the patient treatment experience. The mean individual treatment episodes on NIT and BUP were 238.32 ± 110.11 versus 46.96 ± 109.79 days, respectively (t sep. var. = 33.78, $df = 430.34$, $p < .0001$). The numbers of treatments per patient were 1.55 ± 1.21 versus 3.46 ± 3.99 (t sep. var. = −17.30, $df = 996.38$, $p < .0001$). The averages of the mean durations of treatment were 251.08 ± 89.06 versus 60.62 ± 109.40 days ($t = 26.91$, $df = 2767$, $p < .0001$). The total treatment retention per patient was 371.21 ± 284.64 versus 162.50 ± 245.76 days ($t = 12.70$, $df = 2766$, $p < .0001$). The medians for these four parameters were individual treatment duration 297 versus 16 days; numbers of treatments per patient 1 versus 2; mean durations of treatment 297 versus 22.6; and total treatment retention 297

Table 2
Treatment comparisons by vital status

BUP	BUP treated	Deceased	*t* separate variance estimate	*df*	*p* 2-sided
All registrations duration (days)	47.31 (110.74)	26.83 (37.13)	6.05	176.72	$p < .0001$
No. registrations	3.46 (4.00)	3.19 (3.86)	0.46	43.56	.6464
Total registration duration (days)	163.72 (247.38)	85.26 (114.39)	4.33	48.98	$p < .0001$
Mean registration duration (days)	61.24 (110.42)	28.33 (37.27)	5.40	55.54	$p < .0001$

Naltrexone implant treatment	Alive	Deceased	*t*	*df*	*p*
All naltrexone implant Rx duration (days)	238.78 (109.78)	208.00 (137.87)	−0.68	393	.4973
Total naltrexone retention (days)	371.19 (286.24)	353.50 (78.28)	0.12	253	.9019
Total no. of implant	1.54 (1.22)	2.00 (1.15)	−0.74	253	.4594
Average Rx duration (days)	251.80 (88.84)	216.83 (93.68)	0.78	253	.4358

Table 3
Summary statistics—crossover patients' buprenorphine exposure

Group	No. registrations	Mean duration of registration	Total registration
BUP-NIT			
Minimum (days)	1	0	0
Maximum (days)	26	128.5	1,528
Median (days)	3	14.20	52.50
Average (days)	5.42	19.20	112.97
SD (days)	5.95	21.75	198.59
NIT-BUP			
Minimum (days)	1	1	3
Maximum (days)	26	930	1,780
Median (days)	2	35.65	123.50
Average (days)	3.91	85.01	212.74
SD (days)	4.96	131.69	297.32

versus 66 days. These data show that the NIT patients were treated a lesser number of occasions, but their total treatment retention, mean duration of treatment, and individual treatment duration were significantly longer, a trend emphasized by consideration of the median data.

Table 2 presents the mean and standard deviation of these four parameters by treatment type and vital status together with the applicable summary statistics. Although the number of treatments for the living and deceased buprenorphine patients was not significantly different, the individual registration duration, the total treatment duration, and the mean treatment duration were significantly greater in the total group than the deceased group (all three $p < .0001$). A similar comparison for the NIT group shows that none of these parameters was different between the two groups as defined by vital status.

Table 3 lists the buprenorphine exposure of patients crossing over between the two main treatment types, both from BUP to NIT and from NIT to BUP. It emphasizes again the fact of multiple buprenorphine registrations being usual with the average (±standard deviation) and median number of BUP treatments in the BUP-NIT group being 5.42 ± 5.95 and 3, and in NIT-BUP 3.91 ± 4.96 and 2. The average and median of the total treatment durations were 112.97 ± 198.59 and 52.50 in the BUP-NIT group and 212.74 ± 297.32 and 123.50 in the NIT-BUP group.

Table 4
Implant numbers used

No. implants	No. patients	% treated
1	255	65.05
2	76	19.39
3	29	7.40
4	15	3.83
5	7	1.79
6	5	1.28
7	4	1.02
8	2	0.51
9	1	0.26
10	1	0.26
Total	395	100.77

Table 5
Serious adverse events

Complication	*n*	%
Significant complications interrupting therapy		
Infection	2	1.0
Serious local tissue reaction	2	1.0
Subtotal	4	2.0
Minor complications		
Wound hematoma	2	1.0
Continued drug use	3	1.5
Local itch or swelling, Rx topical steroids	4	2.0
Several local lump, Rx oral steroids	3	1.5
Removed formally for psychiatric indications	2	1.0
Subtotal	14	7.0
Total	18	9.0

The number of naltrexone implants administered in the NIT group is shown in Table 4 as important background information. A total of 255 patients underwent 395 implant insertions. These were 77.72% from Go Medical implants and 21.52% from Wedgewood implants; in 0.76% of cases, both devices were used.

Some patients had both naltrexone implant and BUPs at different times. This was mainly related to the availability of financial or personal resources to the patients at different stages in their addiction careers, usually related to fluctuating levels of family attachment and associated personal support.

Of the four patients who died, three had Perth implants, and one had a New Jersey implant. The patients receiving the U.S. implant died from assault and murder 6 years after the implant was inserted, in a manner not thought to be drug related.

Table 5 lists the serious adverse events occurring in the first 200 implant episodes. In four cases, infection or a sterile local inflammatory reaction necessitated implant removal. Two cases had a significant wound hematoma, which settled with conservative measures. In four cases, topical steroid were used for local irritation, and in three cases, oral steroids were required. Three cases continued to use heroin and required further implants to be inserted. Two cases changed their minds about implant therapy and had the implants formally excised by a specialist surgeon. There were no verified cases where patients excised the implants themselves or had a friend do so.

No systematic database was collected of adverse events experienced by buprenorphine patients. A qualitative clinical impression was formed that relapse to dependent drug use was common in this group, together with injection site and serious dental infections.

4. Discussion

These data describe in some detail our morbidity- and mortality-related treatment experience with buprenorphine

and with NIT prior to its formal registration in this country. Although this work has not been conducted in the context of a formal clinical trial, the experience is nevertheless substantial in terms of numbers involved and length of patient follow-up and reflects real-world clinical outcomes in a high-risk patient group. Moreover, this study suggests a number of important practice points. Firstly, it is clear that although NIT insertion in our hands is a very treatment-intensive procedure, it results in significantly fewer treatment episodes and substantially longer treatment retention than the multiple episodes often of short duration encounters, which characterize BUP therapy in this group, as judged by individual treatment episode, mean, median, and total treatment duration statistics. Secondly, it was noteworthy that treatment retention was demonstrably better in the whole buprenorphine group than in the group of buprenorphine decedents, so that treatment retention is confirmed as a significant factor in conferring protection from mortality in this treatment modality. However, treatment retention was not shown to be a significant factor involved in the mortality of NIT patients. This may in part be related to the unusually long treatment retention achieved with NIT in its own right, although the small numbers of NIT decedents may also have impacted the statistical analysis. Finally, the adverse event profile descried in the first 200 NIT episodes was relatively benign with local complications necessitating the removal of only 2% of implants and 1% formally removed for psychiatric indications. Contrary to a common rumor, no implants were removed by patients themselves. Indeed, it is believed that our encounter with adverse events was improved after the initial experience reported in this article.

It should be noted that a companion article to the present report demonstrated that the mortality rates associated with NIT are remarkably low. They appear to be superior to rates reported in similar Australian methadone- (Tait et al., 2007; Degenhardt et al., 2008) and buprenorphine-treated patients and are not significantly different from the general Australian population. Further details in relation to the timing after NIT and BUP, standardized mortality rates are addressed therein.

It should also be noted that these statistics have been derived from a situation where naltrexone implants are not widely available either in Australia or in Queensland.

Overall, the picture that emerges is that although naltrexone implants require a brief period of intensive intervention with patients to safely and successfully induct them onto this treatment regimen, the general profile of treatment is not unduly adverse, the complication rate not unacceptable, and importantly patients are not exposed to any elevated mortality. Indeed, the several theoretical advantages of naltrexone exposure as opposed to the various opiate agonists and partial agonists, in relation to reversal of opiate-induced immunosuppression (Pillai et al., 1991; McCarthy et al., 2001; Cabral, 2006), cell replication (Zagon et al., 2002), and stem cell deficits (Reece & Davidson, 2007), and likely opiate-related neuropsychiatric (Dyer & White, 1997; Schreiber et al., 2008) and neurogenesis deficits (Canales, 2007; Drake et al., 2007), appear to be accessible to patients without necessarily exposing them to the elevated mortality risks, which may have characterized oral naltrexone therapy in opiate-dependent populations (Miotto et al., 1997, 2002; Digiusto et al., 2004). This may be particularly relevant to particularly vulnerable populations such as HIV-positive groups (Li et al., 2002; Suzuki et al., 2002). In this connection, it should be noted that in common with other Australian groups of intravenous drug users, the present cohort of patients has been shown several times to have a seroprevalence of hepatitis C of around 70% (Reece, 2007a, 2007b, 2007c, 2007d; Reece, 2008a, 2008b). The positive effects of naltrexone in hepatitis C virus-infected individuals have been previously documented (Jeffrey et al., 2007).

The separation of treatment retention from mortality prevention in the NIT group was of interest. It may however relate to the protracted period of therapy-associated NIT itself. Cases of early failure, usually in major users, requiring further NIT insertion, although of interest, parallel closely standard management techniques with other opiate pharmacotherapies such as buprenorphine and methadone, where the dose is quickly raised in relation to early patient response. The highest dose used in our experience was 10 Go Medical implants inserted in three treatments over 3.5 months. NIT retreatments are generally physiologically benign and uneventful and are therefore straightforward to manage pharmacologically.

The ability for wide dose variation in this group is a feature of this treatment, which is little remarked upon in the literature.

Similarly, most local complications related to surgery were relatively easily managed. Some patients required topical or oral steroids for a florid local reaction to NIT. Had this management of severe local wound swelling been better understood earlier in our series, it is likely that at least one of the severe local reactions necessitating implant removal may have been averted. Naltrexone has a mild documented local tissue irritant effect (Hulse et al., 2005; Hulse, Low, et al., 2007) to which some patients appear to have a particular aversion. The other patient with a severe local tissue reaction experienced this problem repeatedly with the implants from one source, but not at all with those from the other. It is therefore considered unlikely that it was the naltrexone itself that was providing the trigger to the local reaction, but perhaps some other component of the depot preparation. A few patients appeared to change their minds about a protracted commitment to the drug-free lifestyle inherent in the choice for NIT therapy. In some of these patients, reversal of their treatment decision could be revised by relevant manipulations in their social context applicable to workplace, home environment, or social relationships. This relatively benign morbidity profile is consistent with other reports (Hulse et al., 2005; Hulse, Low, et al., 2007; Comer et al., 2006).

It is important to note that there was no mortality in this series attributable either to the NIT insertion procedure or the detoxification process that generally accompanied it. Moreover, as previously mentioned, there were only two overnight hospital admissions in the present series of 1,803 naltrexone-based rapid opiate detoxification episodes. It should be underscored that positive mortality analyses such as are presently reported presume that safe and effective NIT induction treatments are available (Tait et al., 2008).

The Go Medical implants reported in this series have an active lifespan of several months and maintain drug levels greater than 2 ng/ml for 188 days and greater than 1 ng/ml for 297 days (Hulse et al., 2004). These periods represent 6.18 and 9.76 months, respectively (because an average month is 30.42 days). It is understood that naltrexone implants are now available, which maintain a therapeutic blood level greater than 2 ng/ml for almost 1 year. Furthermore, the therapeutic life of the Go Medical implants is also being extended toward this point. Thus, although this study may be open to criticism for using the same serum cutoff level for protection from mortality as for treatment efficacy, it is likely that both these time points will be significantly extended both at the present time and as the use of longer acting devices becomes more widely disseminated.

Factors such as the availability of such long-acting implants and ease of accessibility to BUP likely impact the generalizability of the present findings. The age and gender structure of our opiate-dependent population is similar to that reported from other centers both in this country (Darke, Dagenhardt, & Mattick, 2007) and abroad, so it is likely that most of the findings reported here are applicable to other treatment populations also. The ethnic and socioeconomic profile of our patient cohort has been described in earlier reports (Reece 2007a, 2007b, 2007c, 2007d). Although the factors described relating to treatment mortality and adverse events in the present report have not been broken down by sociodemographic subgroups, there is no a priori reason to suggest that the major findings from the whole group would not apply equally to special subpopulations. Nevertheless, detailed testing of this issue in various risk-stratified groups would require appropriately designed and powered clinical trials.

There are a number of limitations of the present research, one major one relates to the limited availability of NIT to this patient group. The financial barrier to its use has been mentioned several times. This study of the totality of our patient population did not provide an opportunity to interrogate this factor specifically. However, it was reviewed and discussed in an earlier report of a large segment of the present population and found to constitute a significant difference between the two groups (Reece, 2007a, 2007b, 2007c, 2007d). It is likely that its effect would only be controlled by randomization in a clinical trial context or after widespread subsidized marketing of one of the implant devices. There were several other limitations over the duration of this study. One of these related to the mandatory need for carers to look after patients during the critical preparation period prior to implant insertion and their unavailability in many cases. This appeared to be a feature of the poorly developed support services for NIT at this time, both on the East Coast of Australia and also in many other locations. For this reason, it is believed that results such as those that are presently reported and others that form part of this clinical audit (Reece, 2007a, 2007b, 2007c, 2007d) may represent the least advantageous analysis of experience with NIT. As a clinical audit from a medical clinic, this report was not randomized in design. As described herein, these various effects might be expected to have a confounding effect upon the results reported, but in different directions. Formal elucidation of the issues raised will likely require completion of randomized clinical trials, some of which are at present understood to be in progress.

In summary, this report completes a series of articles from the clinical audit from this unit and demonstrates that NIT can be used with low mortality rates, involves less patient treatment episodes than BUP, demonstrates superior patient retention, is flexible enough to accommodate dose variation for high-dose users or larger patients, and is accompanied by relatively minor morbidity. No implant or detoxification mortality was reported, and there were no cases where patients (or their friends) removed implants. These remarkably low rates of morbidity and mortality imply that there may be a role for very long-acting NIT in the pharmacotherapeutic armamentarium of the treatment of opiate addiction. It implies that the theoretical benefits of naltrexone can be gained without undue concern for exposure to excessive mortality rates. Combined with previous data demonstrating the long “tail” on the serum naltrexone curve with subcutaneous implants (Hulse, Arnold-Reed, et al., 2007), such data also suggest that the NIT-protected early experience of the drug-free lifestyle, which was previously marked by an elevated medium and long-term mortality, may potentially be safer than ever before.

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Mortality in heroin users 3 years after naltrexone implant or methadone maintenance treatment

Robert James Tait, (Ph.D., B.Sc. (Hons))*, Hanh Thi Thu Ngo, (B.Sc. (Hons)), Gary Kenneth Hulse, (Ph.D., B.B.Sc. (Hons))

School of Psychiatry and Clinical Neurosciences, University of Western Australia, QE II Medical Center, Nedlands, WA 6009, Australia

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Abstract

Concerns that treatment for heroin dependence using naltrexone may increase suicide rates during treatment and fatal overdoses posttreatment have been expressed. There is also disquiet about mortality during induction onto methadone. We assessed mortality during specific periods following treatment with naltrexone implants or methadone. Data were assembled using the Western Australian Data Linkage System. The methadone cohort comprised all those who started methadone in Western Australia during 2001–2002: The naltrexone cohort comprised all Western Australian heroin-dependent persons who received their first implant in 2001–2002. There were 15 (2.7%) deaths in the methadone cohort ($n = 553$) and 6 (1.8%) deaths in the naltrexone cohort ($n = 341$). Mortality rates for the "initial 14-day period," "stable treatment," and "overall" were 94.47, 0.0, and 5.83 deaths/1,000 person-years for the methadone group. In the naltrexone group, the rates "during first treatment (0–6 months)," "post first treatment," and overall were 0.0, 4.21, and 3.76 deaths/1,000 person-years. The age-standardized mortality rate ratio for naltrexone compared to methadone was 0.645 (95% confidence interval = 0.123–1.17). Increased mortality during induction onto methadone was confirmed. Evidence relating naltrexone to either increased suicide or overdose was not found. Overall mortality rates for naltrexone implant were similar to those for methadone, but increased mortality during methadone induction was avoided. © 2007 Published by Elsevier Inc.

Keywords: Methadone; Naltrexone; Record linkage; Mortality; Sustained release

1. Introduction

Worldwide, about 0.4% of the adult population abuses opioids, but this category of illicit drug use accounts for nearly 60% of treatment demand in Europe and Asia (United Nations Office of Drugs and Crime, 2006). Opioid use is also associated with a high level of mortality, with a meta-analysis reporting 8.6 deaths/1,000 person-years (p-y) (Hulse, English, Milne, & Holman, 1999). A European multicenter analysis reported standardized mortality rate (SMR) ratios ranging from 6.3 to 53.7 compared to the general population (Bargagli et al., 2006), with a meta-analysis giving a combined SMR ratio of 13.2 compared to the general population (Hulse et al., 1999).

Methadone maintenance treatment (MMT) is the oldest and best-established treatment for opioid dependence, with those on MMT displaying improvements across a range of health and social indicators (National Consensus Development Panel, 1998). MMT also results in a significantly lower mortality rate than opioid-dependent persons not on treatment (Caplehorn & Drummer, 1999) or those who have left treatment (Bartu, Freeman, Gawthorne, Codde, & Holman, 2004; Buster, van Brussel, & van den Brink, 2002). For example, a large (n = 5,200; 29,729 p-y) European study observed 68 illicit drug (illicit drug, methadone, or both) overdose deaths at a mortality rate of 2.2 deaths/1,000 p-y for

This work was conducted at the School of Psychiatry and Clinical Neurosciences.

* Corresponding author. University School of Psychiatry and Clinical Neurosciences, University of Western Australia, QE II Medical Center (MPC 521), Nedlands, WA 6009, Australia. Tel.: +61 8 9346 2281; fax: +61 8 9346 3828.

E-mail address: robert.tait@uwa.edu.au (R.J. Tait).

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those on treatment and 2.4 deaths/1,000 p-y for those who had left treatment (Buster et al., 2002).

Notwithstanding the established benefits of MMT, a number of studies have reported an elevated rate of fatal overdose in the initial weeks of MMT. For example, in the above study, a mortality rate of 6.0 deaths/1,000 p-y was observed for the first 2 weeks of MMT (Buster et al., 2002). This is consistent with the findings of a recent Australian study that estimated 3.4 deaths/1,000 p-y during stabilized MMT and 30 deaths/1,000 p-y during the initial "high-risk" period (Gibson & Degenhardt, 2005). Similarly, an earlier Australian study noted a greatly increased risk of overdose during the first 2 weeks of treatment (relative risk, 97.8) compared to those stabilized on MMT and to those continuing heroin use (relative risk, 6.7) (Caplehorn & Drummer, 1999).

One alternative to MMT that effectively blocks the effects of heroin use is the competitive opioid antagonist naltrexone, with a single orally administered 50-mg tablet providing protection against heroin overdose and blocking the euphoric effects of heroin for 24 hours (Kleber, 1985). In addition, tolerance to naltrexone does not appear to develop, even after extended periods of administration. However, the requirement for total abstinence from opioids can result in low levels of acceptance (Fram, Marmo, & Holden, 1989), and the requirement for daily compliance has markedly reduced the clinical utility of oral naltrexone. The development of sustained-release formulations of naltrexone that can maintain therapeutic blood levels for extended periods offers potentially safe, effective, and long-term protection against opioid overdoses while overcoming issues of poor medication compliance associated with oral naltrexone formulations (Comer et al., 2006).

However, although naltrexone delivered at an appropriate therapeutic level may have the ability to effectively negate opioid overdose (Hulse et al., 2005), concern that the purported depressogenic properties of naltrexone may increase suicide ideation and self-harm behavior has been raised (Miotto, McCann, Rawson, Frosch, & Ling, 1997; Ritter, 2002). Limited data from the United States also indicate that using some sustained-release naltrexone products maybe associated with serious and sometimes fatal complications, with 12 deaths related to early stages of treatment (Hamilton et al., 2002). Additionally, some authors have postulated an increased risk of both nonfatal and fatal opioid overdoses following cessation of naltrexone treatment or when changing treatment regimes (Digiusto et al., 2004; Oliver, Horspool, & Keen, 2005).

A number of potential mechanisms have been suggested to explain this possible increased risk of accidental opioid overdose following cessation of naltrexone therapy. Abstinence associated with naltrexone treatment may reduce tolerance to opioids, or chronic exposure to naltrexone may result in up-regulation of opioid receptors (White & Irvine, 1999; Digiusto et al., 2004). The former hypothesis is based on observations of an increased risk of overdose mortality due to reduced tolerance in humans following periods of abstinence, such as following incarceration (Darke, Ross, Zador, & Sunjic, 2000), with the implication being that the enforced abstinence created by naltrexone maintenance will have a similar effect. With respect to receptor up-regulation, this has been demonstrated with an increase in the number of opioid-receptor-binding sites in animal models (Tempel, Zukin, & Gardner, 1982; Yoburn & Inturrisi, 1988), but it is still unclear if it occurs in humans (Cornish et al., 1993). Additionally, naltrexone has also been shown to suppress the *subjective* effects of opioids more than *objective* physiological effects (Schuh, Walsh, & Stitzer, 1999; Verebey, Volavka, Mule, & Resnick, 1976), which may increase the chance of an overdose, as the user does not receive the expected level of feedback from a given level of opioid use but still experiences physiological effects such as respiratory depression (Digiusto et al., 2004). These effects could potentially be greater following prolonged abstinence from opioids and extended exposure to naltrexone after receiving implant treatment.

In a recent Australian study, a national assessment of morbidity related to oral naltrexone treatment for opioid dependence using the National Coronial Information System (NCIS) estimated 10 deaths/1,000 p-y during naltrexone treatment compared to 221 deaths/1,000 p-y in the 2 weeks posttreatment (Gibson & Degenhardt, 2005). The authors noted the difficulty of identifying naltrexone-related deaths via the NCIS because it is the absence of naltrexone (i.e., when treatment stops), rather than its presence, that is associated with overdose mortality, and they conclude that the true level of naltrexone-treatment-related overdose deaths may be greater than what these estimates suggest (Gibson & Degenhardt, 2005). Research involving systematic follow-up of a known cohort is required to overcome this methodological difficulty.

The objective of this study was to assess the mortality rate in two independent cohorts that received either sustained-release naltrexone implant treatment (NIT) or MMT in the same period. The MMT group, as the mainstream therapy, also acts as a control for historic changes in the study period, such as in the availability of heroin (Baker et al., 2004; Longo, Henry-Edwards, Humeniuk, Christine, & Ali, 2004). Also of interest were potential high-risk periods: Among people entering methadone treatment, the first 14 days are considered to be of elevated risk (Caplehorn & Drummer, 1999); for those receiving naltrexone, the end of treatment is likely to increase risk (Digiusto et al., 2004). Entry into naltrexone treatment may also be associated with depression and increased suicide risk (Miotto et al., 1997; Ritter, 2002) or complications associated with detoxification and withdrawal (Hamilton et al., 2002).

2. Method

Data on the two cohorts were assembled using the Western Australian Data Linkage System (WA DLS), which compiles

extensive administrative health information for individuals. The dataset analyzed in this study covered mortality in Western Australia. These data were collected prospectively (i.e., at the time of death) and were independent of the research team. Data were available up to mid 2006, giving a minimum of 42 months of posttreatment follow-up, as the latest treatment date was the end of December 2002.

2.1. Implant cohort

The NIT cohort consisted of all those who received their first naltrexone implant between January 2001 and December 2002. The cohort was identified from a private community treatment agency, which was the only facility in Western Australia offering this procedure. Participants were treated under the Australian Therapeutic Goods Administration Special Access Scheme. Each participant received a double (2.2 g) implant, which is reputed to maintain a therapeutic level of naltrexone (≥ 2 ng/ml blood) for nearly 6 months (Hulse, Arnold-Reed, O'Neil, Chan, Hansson, et al., 2004). Out of 437 participants who were treated, 384 lived in Western Australia and were thus available for follow-up via the WA DLS, but 5 did not provide consent for inclusion in the study. Three people had their implants removed on the first week after treatment and were also excluded, giving 76 (98%) of potential 384 cases.

The information provided by the manufacturer (GoMedical) and reported in previously published articles stated that the total amount of naltrexone per implant was 1.7 g (Hulse, Arnold-Reed, O'Neil, Chan, & Hansson, 2004; Hulse, Arnold-Reed, O'Neil, Chan, Hansson, et al., 2004). The manufacturer's analytical method used to determine this did not use pure reference standards and internal standards. Using these additional assurances, the manufacturer now more accurately calculates the amount of naltrexone per implant to be between 1.1 and 1.2 g. Although the naltrexone contents estimated by the two testing methods differ, the implants reported in all publications have been uniformly manufactured, producing an equivalent product (G. O'Neil, personal communication, September 2006).

2.2. MMT cohort

The cohort consisted of those who entered the MMT program for the first time between January 2001 and December 2002. The cohort was identified by the State Drugs, Poisons, and Therapeutic Goods Control Branch of the Department of Health of Western Australia ("MMT register").

2.3. Consent, patient confidentiality, and ethics

Those who received a naltrexone implant gave written informed consent for their records to be accessed for research purposes. Those in the MMT program did not give individual consent. Therefore, to protect patient confidentiality, the Department of Health of Western Australia released only nonidentifiable data to the researchers. The study received University of Western Australia human research ethics approval plus additional institutional (Department of Health of Western Australia, Confidentiality of Health Information Committee) approval to access the WA DLS.

2.4. Record linkage

Treatment crossover (i.e., a patient started on one pharmacotherapy and then moved to the alternative pharmacotherapy) could not be definitely evaluated as the team did not have access to named data on the MMT cohort. Therefore, data were inspected to identify any cases from the MMT group that had admission and other data identical to those in the implant group: 20 cases were identified as crossovers during the 2-year window (2001–2002). The number of days in Treatment 1 and the days in Treatment 2 until the censor date or death were calculated and allocated to the appropriate pharmacotherapy in the analyses involving crossover cases.

To assess the coverage of the WA DLS, the participant data were also linked to hospital morbidity, mental health morbidity databases, and electoral roll (which did not include demographic information). In the MMT cohort, of the 660 potential cases provided by the MMT register, there was 1 duplicate case, and 1 case was linked to a death before 2001: These two cases were removed. Of the remaining 658 cases, 575 (87%) were successfully linked in at least one database. From diagnostic codes, two cases were removed for receiving methadone for pain management, and 20 cases were removed for a separate analysis as people with treatment crossovers. This left 553 (84%) people who were eligible and identified for the main analysis. From the potential 376 people in the NIT cohort, 361 (96%) were identified through the WA DLS. After removing the 20 cases with crossover treatments for a separate analysis, the main analysis was based on the eligible and identified cohort of 341 (91%) people.

2.5. Analysis

Although not specifically designed as a comparative study, mortality outcomes for MMT and NIT were contrasted. To control for differences in the age structure of the cohorts and to allow comparisons unconfounded by differences in age, an indirect age-standardized mortality rate ratio was calculated using the MMT group as the reference population. The indirect method was used; it is more reliable where the sample is small (Breslow & Day, 1987). Standardization was stratified by 5-year age bands, except for those younger than 20 years or those older than 60 years at the time of first treatment. Before standardization, SAS PROC LOGISTIC was used to examine the potential confounding effects of patient's gender and age and their interaction with treatment group. Neither age nor gender was significantly related to risk of mortality. "Expected deaths" (Tables 1 and 2) are the product of the mortality rate in the

Table 1
Crude death rates, by time since treatment or crossover status

		Methadone maintenance cohort				Naltrexone implant cohort				
Status	Substrata	Deaths	Cohort size	Follow-up (p-y)	Crude rate	Deaths	Cohort size	Follow-up (p-y)	Crude rate	Expected deaths
Noncrossovers[a]	First 14 days	2	553	21.17	94.47	0	341	13.08	0.00	1.24
	First 6 months[b]	0	553	254.36	0.00	0	341	157.42	0.00	0.00
	Remaining period	13	553	2,296.45	5.66	6	341	1,424.39	4.21	8.06
	Total	15	553	2,571.98	5.83	6	341	1,594.89	3.76	9.30
Crossovers[a]	MMT–NIT	0	13	6.75	0.00	2	13	55.84	35.82	0.00
	NIT–MMT	0	7	28.56	0.00	0	7	5.52	0.00	0.00
	Total	0	20	35.31	0.00	2	20	61.36	32.59	0.00
Overall	Linked[a]	15	573	2,607.29	5.75	8	361	1,656.25	4.83	9.53
	Linked and nonlinked	15	656	2,994.53	5.01	8	376	1,727.94	4.63	8.66

Notes. (Crude) Death rates are calculated per 1,000 p-y.
See the Analysis section for the calculation of expected deaths and person-years.
[a] Applies to eligible participants who were identified via the WA DLS.
[b] The period excludes the first 14 days of treatment.

MMT cohort and the person-years of observation in the NIT cohort (i.e., the number of deaths that would be expected in the period of observation if the NIT cohort had the same mortality rate as the MMT cohort). This figure provides a comparison for the actual number of deaths in the NIT cohort for each age band. Person-years of observation for each case were calculated as the time between initial treatment and the censor date or death.

3. Results

3.1. Group characteristics

In the MMT cohort, there were 329 (59%) male participants and 199 (36%) female participants, and there were missing data on 25 (5%) people who were only identified in the electoral roll. The male participants were significantly older than the female participants, 32.0 years ($SD = 8.9$) versus 30.2 years ($SD = 9.0$): $t = 2.2$ ($df = 526$), $p = .029$. In the NIT group, there were 137 (40%) female participants and 204 (60%) male participants. The male participants were significantly older than the female participants, 28.8 years ($SD = 7.4$) versus 27.0 years ($SD = 7.9$): $t = 2.1$ ($df = 339$), $p = .037$. The crossover group comprised 20 people, of whom 13 moved from MMT to implant treatment (6.75 p-y of MMT and 55.84 p-y of NI) and 7 moved from implant to MMT (5.52 p-y NIT and 28.56 p-y MMT). There were equal numbers of male and female participants, but the male participants were significantly older, 25.4 years ($SD = 2.5$) vs. 22.2 years ($SD = 3.7$): $t = 2.3$ ($df = 18$), $p = .035$.

The MMT group participants were significantly older than the NIT group participants, 31.3 years ($SD = 9.0$) versus 28.1 years ($SD = 7.7$): $t = 5.69$ ($df = 803.0$, Levene's

Table 2
Deaths of participants as identified by the WA DLS, classified by gender or age, excluding treatment crossover cases

		MMT				NIT				
Strata	Substrata	Deaths	Cohort size	Follow-up (p-y)	Crude rate	Deaths	Cohort size	Follow-up (p-y)	Crude rate	Expected deaths
Gender	Male	9	329	1,529.81	5.88	5	204	944.09	5.30	5.55
	Female	6	199	920.15	6.52	1	137	650.79	1.54	4.24
	Missing	0	25	122.03	0.00	–	–	–	–	–
Age (years)	< 20	1	30	141.19	7.08	0	36	164.35	0.00	1.16
	20 to <25	1	107	504.15	1.98	1	100	466.17	2.15	0.93
	25 to < 30	4	134	604.47	6.62	2	88	422.33	4.74	2.79
	30 to < 35	3	86	402.37	7.46	1	57	262.70	3.81	1.96
	35 to < 40	3	85	388.75	7.72	0	28	130.15	0.00	1.00
	40 to < 45	2	44	203.91	9.81	1	20	95.01	10.53	0.93
	45 to < 50	1	30	147.07	6.80	0	10	47.31	0.00	0.32
	50 to < 55	0	5	24.64	0.00	1	2	6.89	145.14	0.00
	55 to < 60	0	3	13.55	0.00	0	0	0	N/A	0.00
	≥60	0	4	19.85	0.00	0	0	0	N/A	0.00
	Missing	0	25	122.03	0.00	–	–	–	–	–
Overall		15	553	2,571.98	5.83	6	341	1,594.88	3.76	9.30

Notes. Person-years—rounding to two decimal places account for differences in strata totals.

correction), $p < .001$, but gender distributions were similar. Table 1 shows the number of deaths in participants who received NIT or MMT, and the periods of observation stratified by crossover status or time since treatment. The crude rates for the noncrossover cases were 5.83 and 3.76 deaths/1,000 p-y for the MMT and NIT groups, respectively (nonsignificant difference, $p = .357$). In the treatment crossover group, there were two deaths in 96.67 p-y of observation (20.69 deaths/1,000 p-y). If these deaths (both male participants, aged 32 and 26 years) and the associated periods of observation are added to the denominators of the crude death rate, the rate for MMT falls to 5.75 deaths/1,000 p-y and the rate for NIT increases to 4.83 deaths/1,000 p-y.

3.2. Nonlinked participants

There were 83 people in the MMT cohort and 15 in the NIT group who could not be linked by the WA DLS. If they are assumed to be alive at the census point, they would contribute a further 387.24 and 71.69 p-y of observation to their respective denominators, in addition to the crossover cases. As shown in the last row of Table 1, the inclusion of these periods decreases the crude death rates to 5.01 and 4.63 deaths/1,000 p-y for MMT and NIT, respectively.

3.3. High-risk periods

There were two deaths during the first 14 days of MMT, there were zero deaths in the remainder of the first 6 months, and there were 13 deaths up to the censor date. The mortality rates for the "initial 14-day period," "stable treatment," and "overall" were thus 94.47, 0.0, and 5.83 deaths/1,000 p-y. In the NIT group, there were no deaths in either of the periods covering the first 6 months, and there were six deaths in the remaining time after the first treatment. From the 341 cases, there were 170.5 p-y in the initial period of treatment (based on the assumption that the implants provided 6 months of treatment) and 1,424.39 p-y "post first treatment." The mortality rates for the period "on first treatment," post first treatment, and overall were thus 0, 4.21, and 3.76 deaths/1,000 p-y of observation.

3.4. Standardized mortality ratios

Table 2 shows the gender- or age-specific rates for the two groups: The table excludes the 25 MMT recipients whose gender and age at treatment were unknown. Both male and female participants in the NIT group had lower crude death rates than their counterparts in the MMT group. Across the age strata, there was no consistent pattern favoring either the MMT group or the NIT group. The expected number of deaths in the NIT cohort was 9.30, with 6 deaths observed. Thus, the SMR, with the MMT cohort as the reference, is 0.645 (95% confidence interval [95% CI] = 0.123–1.17). When the periods of observation and deaths from the crossover cases are added, the SMR increases to 0.839 (95% CI = 0.257–1.42).

3.5. Cause of death

Table 3 shows key phrases from the summary text in the mortality database relating to each death. In the

Table 3
Summaries of causes of death and number of days since initial treatment

Group	Days posttreatment	Summary cause of death
MMT	1	"… respiratory impairment… associated with combined drug effect… suffered accidentally"
MMT	1	"… combined respiratory depressant drug effect (miritazapine and benzodiazepines, methadone and cannabis) suffered accidentally…"
MMT	335	"… epileptic seizure"
MMT	595	"Ligature compression… deliberately self-inflicted"
MMT	675	"Multiple injuries suffered accidentally… collided with a motor vehicle"
MMT	682	"Ligature compression… deliberately self-inflicted"
MMT	781	"… diabetic ketoacidosis… associated with chronic pancreatitis"
MMT	787	"Prosthetic aortic valve dehiscence…"
MMT	825	"Acute opiate toxicity suffered accidentally…"
MMT	900	"Acute opiate toxicity… suffered accidentally…"
MMT	960	"Diabetic ketoacidosis"
MMT	988	"Accidentally self-inflicted acute combined respiratory depressant drug effect…"
MMT	1,096	"Upper gastrointestinal bleed…cancer"
MMT	1,283	"Incomplete registration: cause of death subject to coronial investigation"
MMT	1,642	"Incomplete registration: cause of death subject to coronial investigation"
NIT	521	"Multiple injuries suffered accidentally… collided with a motor vehicle"
NIT	675	"Multiorgan failure following status epilepticus and aspiration pneumonitis"
NIT	1,026	"Acute combined respiratory depressant drug effect of methadone, temazepam, and alcohol accidentally self-inflicted"
NIT	1,056	"Incomplete registration: cause of death subject to coronial investigation"
NIT	1,095	"Multiple injuries suffered… deliberately moved in front of a moving motor vehicle"
NIT	1,495	"Incomplete registration: cause of death subject to coronial investigation"
MMT–NIT	331 + 1,300	"Incomplete registration: cause of death subject to coronial investigation"
MMT–NIT	227 + 899	"Aspiration of vomitus… combined drug effect suffered accidentally… died as a result of their combined effects"

MMT group, there were five cases that were drug related (Cases 1, 2, 9, 10, and 12), including two cases on Day 1, both of which specified respiratory depression due to the use of drugs. Two deaths were described as deliberately self-inflicted (Cases 4 and 6). In the NIT group, two deaths were drug related (Cases 18 and 23), and one death was deliberately self-inflicted (Case 20). We inspected clinical records to determine the period between the last naltrexone implant and these overdose deaths. One (Case 18) died 50 days after the last implant, and one (Case 23) died 899 days posttreatment. In five cases, the results of coronial investigations were still pending.

4. Discussion

The study used a statewide record linkage system to follow up a sequential cohort of 376 people treated with a 2.2-g naltrexone implant over a minimum of 42 months. Data on a sequential cohort of 658 persons who entered MMT for the first time in the same period were also assembled to provide a comparison group because of the possibility of changes in heroin-related mortality associated with the reduction in the availability of heroin in Australia during the period under investigation (Longo et al., 2004) and also because MMT was considered the oldest and best-established treatment.

Although concern with a possible increased risk of both fatal and nonfatal heroin overdoses following cessation of naltrexone treatment has been raised, to date, studies on naltrexone implants either have involved small samples (Gibson & Degenhardt, 2005; Oliver et al., 2005) or have been limited to short-term follow-up of <12 months (Foster, Brewer, & Steele, 2003; Hulse et al., 2005). We believe that this study provides the first reliable long-term mortality data on heroin-dependent persons following NIT. With respect to MMT, the outcomes of the study were consistent with previous data showing elevated mortality rates during induction to MMT.

The naltrexone implant under investigation is reputed to maintain a therapeutically effective level of naltrexone (≥ 2 ng/ml blood) for nearly 6 months (Hulse, Arnold-Reed, O'Neil, Chan, Hansson, et al., 2004). Based on this assumption, the mortality rates for the naltrexone implant group during the three periods—on first treatment (0–6 months), post first treatment (> 6 months), and overall—were 0.0, 4.21, and 3.76 deaths/1,000 p-y of observation. For the MMT group, during the initial 14-day period, stable treatment (excluding the first 14 days), and overall, the figures were 94.47, 0.0, and 5.83 deaths/1,000 p-y. If all people who could not be identified by the WA DLS were assumed to be alive at the end of the study, the overall crude mortality rates would be 4.63 deaths/1,000 p-y for the NIT group and 5.01 deaths/1,000 years for the MMT group.

4.1. Mortality associated with entry into heroin treatment

The current results showing an absence of mortality associated with entry into NIT do not support the proposition of an increased risk of mortality due to the depressogenic properties of naltrexone at the time of entry into treatment (Miotto et al., 1997; Ritter, 2002). This is consistent with a recent literature review, which concluded that although there were theoretical reasons for this proposition, there were limited empirical data to support it (Miotto, McCann, Basch, Rawson, & Ling, 2002).

These data also contrast with a report from the United States indicating that the use of some sustained-release naltrexone products may be associated with serious and sometimes fatal complications in the period immediately postimplant (Hamilton et al., 2002). One explanation for these seemingly disparate results may be that many of the U. S. deaths may not be related to NIT per se but rather to potentially suboptimal postdetoxification care in highly opioid-dependent patients (O'Neil, Hulse, Armstrong, Little, & Murray, 2002).

The study replicated earlier findings (Buster et al., 2002; Caplehorn & Drummer, 1999; Gibson & Degenhardt, 2005) in relation to methadone, with two deaths in the initial 14 days of treatment, both of which were drug related (one implicated multiple drugs plus methadone) and involved respiratory depression. This equated to 94.47 deaths/1,000 p-y. The initial increase in mortality associated with MMT compared to NIT is likely to result from a number of factors. First, although heroin use is greatly reduced during MMT, methadone does not prevent co-use of heroin or other opioids (Gossop, Marsden, Stewart, & Kidd, 2003). Many heroin users engage in polysubstance use, especially co-use of central nervous system (CNS) depressants such as benzodiazepines, which have been identified as a major risk factor in fatal overdoses for those on MMT (Ernst et al., 2002). This co-use of heroin and other CNS depressant drugs while attempting to stabilize on a prescribed dose of methadone creates a potential for respiratory depression and an increased risk for accidental overdose. These previously raised concerns find support in this study, where both observed MMT deaths during the high-risk period resulted from polydrug use. Study data on MMT are also consistent with the findings of an Australian study, which noted that 12 of 13 deaths observed following MMT during the first 2 weeks of treatment were due to methadone or other drug toxicity (Caplehorn & Drummer, 1999).

In contrast to MMT, NIT blocks the effects of heroin and some other opioids. No heroin-related or other-drug-related deaths were observed in the first 6 months of treatment; indeed, the first death in the NIT cohort did not occur until nearly 2.5 years after the first treatment. These preliminary findings showing the absence of increased risk of mortality among heroin-dependent persons entering NIT may promote this as a preferred option for the management of high-risk patients, rather than MMT. This statement is premised upon

the assumption that safe opioid withdrawal, which is a prerequisite to NIT, can be effectively provided together with continuing care (O'Neil et al., 2002).

4.2. Mortality associated with NIT and cessation of treatment

There were no deaths during the initial 6-month period on NIT. It has previously been reported that this cohort incurred no opioid overdoses requiring hospital treatment during the first 6 months after treatment (Hulse et al., 2005). These figures contrast markedly with the short-term follow-up of 101 recipients of Wedgewood implants in the UK, which reported two deaths (suicide and pulmonary embolus) in the 12-week follow-up (Foster et al., 2003)—a level that approximates to 85.8 deaths/1,000 p-y. This may reflect different levels of aftercare and reinforces that, although effective in delivering therapeutic levels of naltrexone, implant management does not constitute a treatment in itself and should only be provided as part of an overall service, including ongoing medical and psychosocial follow-up.

Previous reports of a possible increased level of mortality following the cessation of oral naltrexone maintenance in formally opioid-dependent persons is disquieting (Digiusto et al., 2004; Gibson & Degenhardt, 2005) and, if correct, may also have implications for implant treatment. After the initial 6-month treatment period, there were six deaths in the remaining 1,424 p-y, at 4.21 deaths/1,000 p-y. We inspected clinic records for the two drug-related deaths to determine the time of final implant treatment. Neither died in the immediate aftermath of treatment cessation, so the argument for a reduction in tolerance does not appear to be applicable in these cases. One explanation for this is that although the currently investigated NIT delivers blood naltrexone at therapeutic levels for about 6 months, it continues to deliver subclinical blood naltrexone levels beyond this time. Although this may be insufficient to completely block the effect of heroin and other opioids, it may provide a level of prophylaxis against accidental overdose and may discourage entry back into the narcotic network. It is, however, notable that in 1,595 p-y of follow-up of the NIT cohort, there was only one opioid-related death, and this involved methadone in combination with other CNS depressants. With respect to increased suicidality, one case was observed in the NIT cohort. Although not statistically evaluated, this does not appear to be dissimilar to the comparison group (two cases).

4.3. Mortality associated with methadone

Notwithstanding the established benefits of MMT, overdose deaths occur for those on treatment and for those who have left treatment (Buster et al., 2002). A 15-year follow-up of MMT patients in Australia found that those on treatment had one quarter the risk of dying compared with those out of treatment (Caplehorn, Dalton, Haldar, Petrenas, & Nisbet, 1996). A meta-analysis found that this effect was replicated in European data and studies based in the United States, although the analysis of "out-of-treatment" data included both patients in "pretreatment waiting lists" and those whose out-of-treatment data only included time following initial induction onto methadone (Caplehorn et al., 1996). The current study only had information on the date of initial treatment. Whether patients remained stabilized on MMT or whether there were any discontinuities in treatment was unknown. Therefore, our estimate of the mortality rate for stabilized MMT could have been inflated compared to estimates based on those known to be continuously on MMT although no deaths occurred in this period.

4.4. Treatment crossover cases

Twenty people were identified as switching between treatment regimens. Recent data show that only a small percentage (approximately 3%) of methadone clients switch to oral naltrexone within 12 months of starting MMT (Shanahan et al., 2006). A similar small proportion switched to NIT in this study. The total number of days (and being "on treatment") reduces the risk of nonfatal opioid overdoses, but multiple treatment episodes are predictive of increased risk (Darke, Williamson, Ross, & Teesson, 2005). This finding may reflect the fact that the least stable clients are unable to adhere to treatment or that variations in opioid tolerance occur with changes in therapy (Darke et al., 2005). The rate of mortality in the crossover cases in this study (20.69 deaths/1,000 p-y) reinforces the need to encourage clients to stay in one form of therapy or to provide addition support to those who switch between treatments.

4.5. Limitations

To protect the confidentiality of those in the MMT cohort, no identifying details on this group were provided, and it was not possible to access detailed clinical or drug-use histories. The study relied on the accuracy of the data supplied by the State Drugs, Poisons, and Therapeutic Goods Control Branch. A lower proportion of the MMT compared to the NIT cohort was identified by the WA DLS. There are a number of possible explanations. First, the named data on the cohort may have been less accurate than the data we assembled on the NIT cohort. Second, the MMT cohort may have had a lower level of morbidity and, hence, would have been less likely to incur hospital admissions. Third, the MMT cohort could have included some people temporarily residing in Western Australia who had transferred from an interstate MMT program. These people would appear as new cases on the state methadone register but would be unlikely to have had previous (or subsequently, if they later returned to their state of origin) hospital admissions in Western Australia.

The use of a nonrandomized design means that causality cannot be imputed: Posttreatment differences may be due to preexisting differences in the study cohorts; thus, caution

should be exercised in the interpretation of between-groups comparisons. The authors noted that the MMT cohort was older at the time of initial treatment, so age standardization was used to control for this difference. In addition, there was the potential for people to change to different treatment regimens. Although we were able to identify some who changed between MMT and implant treatment in the 2 years (2001–2002) of "recruitment," we had no means of identifying those who moved to buprenorphine or psychosocial interventions or those who moved between MMT and NIT outside the recruitment window.

In the original MMT group, the linkage to a death before 2001 was confirmed following a clerical review by personnel at the WA DLS. One potential explanation is that the identity of a deceased person had been assumed. Nevertheless, this serves as a reminder that matches are performed on a probabilistic basis and that although errors are rare (Brameld, Thomas, Holman, Bass, & Rouse, 1999; Rosman et al., 2002), they do occur. However, this case may also represent an error in the MMT register.

5. Conclusions

NIT was not associated with increased mortality due to either increased suicidality or loss of tolerance to opioids, as has previously been postulated. The lack of a randomized design prevents definite assertions, but this study suggests that those entering either methadone treatment or NIT for opioid dependence have a similar prognosis, with the SMR for NIT compared to MMT being 0.645 (95% CI = 0.123–1.17).

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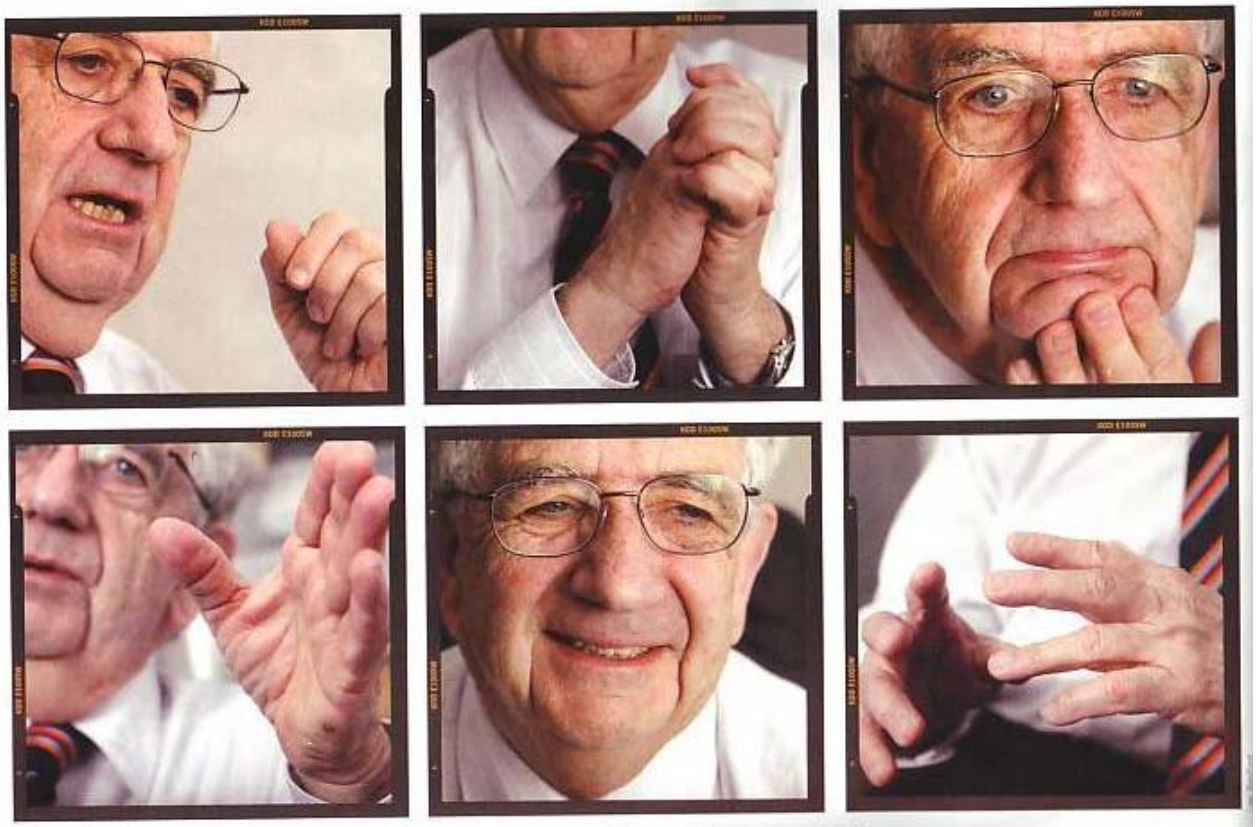

Champion of the forgotten

Emeritus Professor Ian Webster was recently awarded one of Australia's top honours – a Prime Minister's Award for Excellence. He explains the complexities of his specialty – addiction medicine – to *Shannon McKenzie*.

FOR the best part of his professional career, Emeritus Professor Ian Webster has championed the cause of those whom society – and to some extent, the health system – has forgotten.

A leading figure in the field of addiction medicine, Professor Webster has seen first hand the devastating effects of substance abuse and the frustrating struggle that many people must face to simply access the help they need.

His work in this field has spanned more than three decades, and in June he was formally recognised with a Prime Minister's Award for Excellence and Outstanding Contribution to Drug and Alcohol Endeavours.

He says he was both "surprised and pleased" at the honour, but even a cursory glance of his CV would make it clear why he received the accolade.

Currently a consulting physician at Liverpool Hospital in Sydney's west, he is also emeritus professor of public health and community medicine at the University of NSW. Until earlier this year, he was chair of the Alcohol Education and Rehabilitation Foundation for seven years, but has since taken up a position on its board of directors.

Professor Webster is also a patron of the Alcohol and other Drugs Council of Australia, chair of the NSW Expert Advisory Committee on Alcohol and Drugs, and president of the governing council of the Ted Noffs Foundation, an organisation providing essential services for young people with alcohol and drug problems.

While the focus of much of his work has been in alcohol and drugs, he is only too aware that substance abuse often goes hand-in-hand with mental illness. Yet, according to Professor Webster, the current health system is not able to cope with the complexities of dual diagnosis.

Nowhere is this more apparent than when examining the efforts to help homeless people, he says.

"Doctors are trained to make a specific diagnosis, but this can sometimes make only the smallest of differences. Their other problems are just so overwhelming," Professor Webster says, citing Dr Julian Tudor Hart's now famous inverse care law. "The more problems they have, the less likely they are to receive the help they need."

What is missing, he argues, are professionals who are able to assess such patients with such high levels of need, and then develop and coordinate a care plan based on their medical and social needs.

While such a role would be seen by many as falling into the realm of general practice, Professor Webster is unsure whether GPs have been afforded the necessary resources for this. He expresses great sympathy for GPs, snowed under with bureaucracy and bound by the MBS.

"Time is the most valuable thing we can offer patients [with complex needs]"

"GPs are becoming progressively overloaded; they do not have the time to sit and deal with patients with such complex needs," he says.

"With these patients, doctors must deal with complexities that take a hell of a lot of time – yet ironically time is the most valuable thing we can offer these patients."

He points to funding as another obvious problem, and one that is compounded by the fact that these patients are facing less socially acceptable problems.

"There is certainly a pecking order in the hospitals and health system as to which services get funded. High technical specialities are right at the top and the messy problems right at the bottom," he says.

"Diabetes, asthma, heart disease – these are all chronic conditions in which people will relapse. Yet, when we think about substance abuse, we tend to blame people for their relapses in a way we do not when it comes to something like heart disease."

Though he acknowledges these patients are "often difficult", Professor Webster remains passionate about them and his work.

"It is such an exciting field," he says, by way of explaining his passion for the past three decades.

"It involves every aspect of public health and law, and you can also do so much good by being involved.

"And the people you work with – they are often difficult – but at the same time they are warm and engaging. They are fascinating people who have often lived extraordinary lives."

Australian Drug Law Reform Foundation

What's New
The past, present and future of harm reduction: decades of misunderstanding.

The past, present and future of harm reduction: decades of misunderstanding.

A paper presented at the 15th International Conference on the Reduction of Drug Related Harm

Dr Alex Wodak,
St. Vincent's Hospital, Darlinghurst,
NSW 2010
Australia
T: (612) 9361 8012
F: (612) 9361 8011
awodak AT stvincents.com.au

Abstract:

Harm reduction enjoyed a long history well before AIDS but was rejuvenated in the 1980s when the enormity of AIDS, the centrality of HIV among injecting drug users and the imperative need for pragmatic and effective measures to control HIV among and from injecting drug users was recognised. The 'risk compensation hypothesis' in psychology and the notion of 'moral hazard' in economics and finance demonstrates the need in many disciplines for measurement of costs and benefits of policy options which directly reduce adverse consequences and thereby introduce the possibility of compensatory increased risk behaviour. The intellectual debate about harm reduction as the preferred drug policy option is now over as existing evidence is incontrovertible. The political debate will continue for some time. Opposition continues and will do so for the foreseeable future as most opponents are little influenced by data. Misunderstanding about harm reduction is widespread and largely willful. However, the definition of harm reduction has been poorly articulated and ambiguity about the role of prevention of drug use is still common. In many countries it is time to move from the first phase of harm reduction - focusing on reducing adverse consequences - to a second phase which concentrates on reforming an ineffective and harm generating system of global drug prohibition.

Introduction:

Harm reduction has been and continues to be widely misunderstood, often wilfully. If harm reduction is to continue to advance in the future, its supporters have to clarify these misunderstandings and also more clearly spell out their goals for the future. As Yogi Berra once said, "You've got to be very careful if you