“Morbidity and mortality in patient with an opioid use disorder and their children following treatment with a sustained release naltrexone preparation”

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This thesis is presented for the degree of Doctor of Philosophy of The University of Western Australia

School of Psychiatry and Clinical Neurosciences

June 2017
Morbidity and mortality in patients with opioid use disorders and their children following treatment/exposure to implant naltrexone

Thesis declaration

I, Erin Kelty, certify that:

This thesis has been substantially accomplished during enrolment in the degree.

This thesis does not contain material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution.

No part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of The University of Western Australia.

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The research involving human data reported in this thesis was assessed and approved by The University of Western Australia Human Research Ethics Committee. Approval number: RA/4/1/4043 and RA/4/1/1864.

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This thesis contains published work and work prepared for publication, some of which has been co-authored.

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<tr>
<td>3-MAM</td>
<td>3-monoacetylmorphine</td>
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<tr>
<td>6-MAM</td>
<td>6-monoacetylmorphine</td>
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<tr>
<td>BUP</td>
<td>Buprenorphine</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
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<tr>
<td>DLB</td>
<td>Data Linkage Branch</td>
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<tr>
<td>CNS</td>
<td>Central Nervous System</td>
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<tr>
<td>DOH</td>
<td>Department of Health (Western Australia)</td>
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<td>DOR</td>
<td>Delta opioid receptor</td>
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<tr>
<td>EDDC</td>
<td>Emergency Department Data Collection</td>
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<tr>
<td>FSH</td>
<td>Follicle stimulating hormone</td>
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<tr>
<td>GP</td>
<td>General practitioner</td>
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<tr>
<td>HBV</td>
<td>Hepatitis B virus</td>
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<td>HCV</td>
<td>Hepatitis C virus</td>
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<tr>
<td>HMDS</td>
<td>Hospital Morbidity Data System</td>
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<tr>
<td>HPV</td>
<td>Human Papilloma Virus</td>
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<tr>
<td>HR</td>
<td>Hazard ratio</td>
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<td>HREC</td>
<td>Human Research Ethics Committee</td>
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<tr>
<td>ICD-10</td>
<td>10th revision of the International Statistical Classification of Diseases and Related Health Problems</td>
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<tr>
<td>IQR</td>
<td>Interquartile range</td>
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<tr>
<td>ISH</td>
<td>Intentional self-harm</td>
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<tr>
<td>KOR</td>
<td>Kappa opioid receptor</td>
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<tr>
<td>LH</td>
<td>Luteinising hormone</td>
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<td>MHIS</td>
<td>Mental Health Information Systems</td>
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<td>MMT</td>
<td>Methadone Maintenance Therapy</td>
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<td>MNS</td>
<td>Midwives Notification System</td>
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<td>MODDS</td>
<td>Monitoring of Drugs of Dependence System</td>
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<td>MOR</td>
<td>Mu opioid receptor</td>
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<td>Abbreviation</td>
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<tr>
<td>NAS</td>
<td>Neonatal Abstinence Syndrome</td>
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<td>NOP</td>
<td>Nociception receptor</td>
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<td>NHMRC</td>
<td>National Health and Medical Research Committee</td>
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<td>NSSI</td>
<td>Non-suicidal self-injury</td>
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<td>NTX</td>
<td>Naltrexone</td>
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<tr>
<td>OR</td>
<td>Odd ratio</td>
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<tr>
<td>OGF</td>
<td>Opioid growth factor</td>
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<tr>
<td>PTPY</td>
<td>Per thousand patient years</td>
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<tr>
<td>RCT</td>
<td>Randomized controlled trial</td>
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<td>RR</td>
<td>Rate ratio</td>
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<tr>
<td>SB</td>
<td>Suicidal behaviour</td>
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<tr>
<td>SIDS</td>
<td>Sudden infant death syndrome</td>
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<tr>
<td>SPCN</td>
<td>School of Psychiatry and Clinical Neurosciences</td>
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<tr>
<td>TGA</td>
<td>Therapeutic Goods Administration</td>
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<tr>
<td>UWA</td>
<td>University of Western Australia</td>
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<td>WA</td>
<td>Western Australia</td>
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<tr>
<td>WABR</td>
<td>Western Australian Birth Registry</td>
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<td>WADLS</td>
<td>Western Australian Data Linkage System</td>
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<td>WADR</td>
<td>Western Australian Death Registry</td>
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<td>WANIDD</td>
<td>Western Australian Notifiable Infectious Diseases</td>
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<td>WARDA</td>
<td>Western Australian Registry of Developmental Abnormalities</td>
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<tr>
<td>YLD</td>
<td>Years lived with disability</td>
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<tr>
<td>YLL</td>
<td>Years of life lost</td>
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And finally to my family: Mum, Dad and Tom

I would like to dedicate this thesis to Ian, and the many patients like him. Your experiences and lives have shaped this research and I hope that it can be used to improve treatment services in the future. Without you this research would not have been possible.
# Authorship declaration

This thesis contains work that has been published and prepared for publication.

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<thead>
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<td>“A retrospective cohort study of mortality rates in opioid dependent patients treated with implant naltrexone, oral methadone or sublingual buprenorphine.”</td>
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Location in thesis: Section 5.2

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Coordinating supervisor signature: [blank]
Date: 27/Nov/2016
Abstract

**Background:** The opioid antagonist naltrexone has been proposed as a treatment alternative to long acting opioid pharmacotherapies such as methadone and buprenorphine in the management of opioid use disorders. The use of oral naltrexone has struggled clinically due to patient non-compliance with the oral once daily medication. To combat compliance issues sustained release preparations have been developed. The safety of these preparations is still being assessed.

**Aims:** To examine and compare the health of patients with opioid use disorders treated with a sustained release naltrexone implant to those treated with methadone, buprenorphine or oral naltrexone, and to examine the health of children prenatally exposed to naltrexone and compare them to children exposed to methadone, buprenorphine and a cohort of controls.

**Methods:** Implant and oral naltrexone patient’s data (demographics and treatment data) was sourced from a drug and alcohol clinic, while methadone and buprenorphine data was identified from the Health Department records. Patient information was cross-matched against state and nation-wide routinely collected health data sets to determine rates of health events including mortality, hospitalisation, emergency department (ED) attendances, mental health events, and pregnancy. Pregnancies in which the neonate was exposed to naltrexone, methadone or buprenorphine and a cohort of non-dependent controls were also identified using the health data sets. Health outcomes (obstetric, neonatal and childhood) of the resulting mother-child dyad were examined and compared from conception, to birth and then through to the child’s 5th birthday.

**Results:** Crude mortality rates for patients treated with oral naltrexone were significantly higher than those treated with implant naltrexone. During the first 4 months following treatment, differences in the two groups were particularly apparent (26.3 per 1000 patient years (ptpy) for oral, 7.3 ptpy for implant patients). Differences in initial mortality rates following treatment were associated with high rates of opioid overdoses in oral naltrexone patients.
Crude mortality rates in patients treated with implant naltrexone were not significantly different to either methadone or buprenorphine. Rates of hospitalization were significantly higher in patients treated with implant naltrexone compared with both methadone and buprenorphine, as were rates of ED attendances in methadone treated patients, while rates of ED attendances in buprenorphine patients were comparable. The difference was most apparent during the first 28 days of treatment, where rates of hospital and ED attendances in naltrexone treated patients were almost double that of both methadone and buprenorphine. Additionally rates of mental health events (hospital admissions, psychiatric admissions, ED attendances) were significantly higher in patients treated with naltrexone, however this appeared primarily attributable to high pre-treatment mental health morbidity in female naltrexone patients.

The use of implant naltrexone was associated with high rates of birth. Rates of hospital and ED attendances during pregnancy, and complications during labour and delivery in the naltrexone-treated women were not statistically different to both methadone and buprenorphine. Health outcomes in naltrexone exposed neonates were superior to methadone in terms of increased birth size, reduced incidence of neonatal abstinence syndrome (NAS), and reduced hospital stay. Rates of NAS were also significantly elevated in buprenorphine exposed neonates compared with those exposed to naltrexone, however other outcomes were generally comparable. Compared with control neonates, naltrexone neonates spent more time in hospital following birth and had higher rates NAS. However they were not significantly different in terms of APGAR scores, overall rates of congenital anomalies, stillbirth or neonatal mortality. During childhood, rates of mortality in the naltrexone cohort remained comparable to the control group, however overall rates of hospital were elevated. Childhood incidence of mental health, cancer and reportable infectious diseases in the naltrexone cohort were not significantly different to control.

**Conclusions:** Compared with oral naltrexone, the use of implant naltrexone significantly reduced rates of crude mortality, however mortality rates were not significantly different to methadone or buprenorphine treated patients. Morbidity in the first 28 days of treatment appears to be elevated in naltrexone patients, but following this period they are comparable to both methadone and buprenorphine.
While rates of birth were significantly elevated in women treated with naltrexone, the health of both the mother and resulting neonate from conception to early childhood were comparable, if not better than outcomes in both methadone and buprenorphine.
1. Introduction

1.1. Opioids and the opioid system

The endogenous opioid system is a pivotal neurochemical system involved in sensory, motivational, emotional, and cognitive function. Endogenous opioids are comprised of 4 groups: endorphins, enkephalins, dynorphins and endomorphins. These endogenous opioids exhibit their effects by binding to the opioid receptors, which are located in the central and peripheral nervous system. The activation of the opioid receptor generally has an inhibitory effect, either on the postsynaptic release of neurotransmitters at the nerve terminal or the postsynaptic neuron. The opioid receptors are comprised of four main opioid receptor classes, the mu (MOR), kappa (KOR), delta (DOR) and nociceptin (NOP), with each receptor type responsible for slightly different opioid effects [1]. A wide range of exogenous opioids have also been found and synthesised, including morphine, codeine, diacetylmorphine (heroin), oxycodone, hydrocodone, methadone and buprenorphine. As per endogenous opioids, these drugs act on the opioid receptors, classically producing symptoms of euphoria, analgesia and sedation [2].

1.2. Opioid use disorders

The use of opioids has been recognised as an important part of medicine for many centuries. As early as the Neolithic period, records suggest that opium extracted from poppies was used as an anaesthetic, analgesic and method for euthanasia [3]. While opioids are still widely used today in modern medicine, their use has been somewhat tempered by their potential for abuse and dependence.

Opioid dependence is defined in the Tenth Revision of the International Classification of Diseases and Health Problems (ICD-10) as “a cluster of physiological, behavioural, and cognitive phenomena in which the use of opioids takes on a much higher priority for a given individual than other behaviours that once had greater value”. Although dependence on opioids is relatively rare in comparison to other substances such as alcohol and amphetamines,
with an estimated prevalence of 0.4% of the world’s adult population, opioids are thought to account for almost 60% of treatment demand in Europe and Asia [4].

One of the most commonly abused illicit opioids is heroin. Alarmingly, heroin rates as one of the most severe drugs in terms of physical and social harm, and dependence [5]. Heroin is highly addictive as a result of its high potency and rapid onset of action, with estimates suggesting that in developed countries one in four individuals who use heroin will become dependent [6]. When taken orally, heroin has a low oral bioavailability (<35%) and is subject to extensive first-pass metabolism and is thus not associated with the rush that accompanies other methods of administration. Accordingly to maximise effect, heroin is generally either injected or smoked. While heroin is a MOR agonist, due to its ultra-short half-life (1.3 - 7.8 minutes), the action of heroin is primarily attributable to the action of its metabolites, 6-monoacetylmorphine (6-MAM) and morphine on the MOR [7]. 6-MAM also has short half-life (5.4 – 52 minutes), however morphine remains present for much longer (half-life of 100 – 280 minutes) and additionally acts on both the DOR and KOR [7].

1.3. Factors leading to opioid use disorders

A number of individual and environmental factors have been identified as being associated with the initial use and experimentation with opioids. Males are more likely to use opioids compared with females, as are people with poor academic achievement/low academic aspirations, mental health disorders and antisocial behaviour [8, 9]. The prevalence of opioids and opioid use in the community and family/peer use of opioids has also been shown to be positively correlated with an individual’s use of opioids [10]. An individual’s perceived risk of opioids and their peer’s attitudes toward opioid use have also been found to be influential. Employment, religiosity, and optimism about the future have been shown to be protective [9].

Of those who do use opioids, only a fraction go on to become opioid dependent. A survey of first time heroin uses found that only 13.4% were dependent 12 months later [11]. The transition from opioid use to dependence is largely influenced by genetics, with opioid dependence having an estimated heritability of greater than 0.60 [12]. Genome-wide studies and a number of candidate gene studies in humans have identified a number of genes that
may contribute to genetic vulnerability to opioid dependence including genes encoding opioid receptors [13, 14], potassium signalling pathways [15] and dopamine receptors [16].

In addition to genetics, a variety of other factors have been identified as contributing to a person’s vulnerability to becoming opioid dependence. Persons who have a history of child and adult trauma, emotional, physical and sexual abuse are more likely to become opioid dependence, as are persons with a long history of drug use or start using opioids at a young age are more likely to become dependent [17]. Additionally social factors such as socio-economic status homelessness, unemployment, and poverty [17] and co-occurring mental health disorders [8, 12, 18, 19] have also been associated with an increased risk of opioid dependence.

1.4. Morbidity and mortality associated with opioid use

The use of illicit opioids has been linked with high rates of morbidity and mortality, either associated directly with the effect of the drug (i.e. dependence, opioid overdose, endocrine effects), or as a result of the associated lifestyle (i.e. suicide, injury, trauma, non-opioid drug overdoses)[20]. In 2010, the use of illicit opioids was associated with 7.2 million years of life lived with disability (YLD) and 2.0 million years of life lost (YLL), accounting for 43.7 and 55.3% of the YLD and YLL associated with illicit drug use [21].

Estimated rates of mortality in heroin using populations, range from 6.8 to 77.6 per 1000 patients years (ptpy) [20], a rate approximately 13 times greater than that among age and sex matched peers. Mortality rates vary distinctly between regions [22], with mortality rates in Australia amongst the lowest in the world, at between 8.9 and 18.0 ptpy [20].

Opioid overdoses are a major contributor to increased mortality rates in patients with opioid use disorders, and in many countries are the leading cause of death in such populations [20, 23, 24]. Opioid overdoses are typically the result of opioid induced respiratory depression, resulting in hypoxia and in severe cases death. Respiration is controlled principally through the medulla (ventral and dorsal respiratory group) and the pons (pneumotaxic and apneustic centre), with input from chemoreceptors, which respond to changes in blood gases (carbon
dioxide, oxygen) and pH. Rhythmic respiration requires the phasic activation and inhibition. In the ventral respiratory group, excitation is mediated by excitatory amino acids such as glutamate [25], while inhibition is mediated by GABA receptors [26]. A number of neurotransmitters have also been associated with changes in respiratory rhythm, including serotonin [27, 28], substance P [29, 30] and opioid peptides [31, 32]. Opioid peptides have largely been found to have an inhibitory effect on respiration, likely due to a reduction in glutamate induced excitation.

Counterintuitively, opioid overdoses are rarely associated with excessive consumption of opioids. In fact, analysis of blood morphine levels in fatal heroin overdoses have shown to significantly overlap with individuals who had died of other causes (for example homicide) who had consumed heroin in the 24 hours prior to their death [33-35]. Similarly, while rates of suicide and attempted suicide are generally very high in patients with opioid use disorders, opioids are rarely used as a primary means of suicide [36, 37]. For example, a study by Heale et al. (2003), interviewing 256 heroin overdose survivors found that only 9 survivors (3.5%) had intentionally overdosed [36]. Similarly, there is debate as to whether or not fluctuations in illicit opioid purity or the addition of contaminants are routinely responsible for opioid overdoses [38-41].

The occurrence of opioid overdoses has repeatedly been associated with a loss or reduction in tolerance. Tolerance to opioids develops quickly, with evidence of tolerance to morphine exhibited as early as eight hours during continuous intravenous infusions in rats [42, 43]. Following periods of abstinence, the tolerance built over periods of use is reversed and the opioid system up-regulates and re-sensitizes to an approximate pre-opioid use level. Such changes can occur within days and weeks, with an abstinence period of 5.4 days required to regenerate 50% of the intrinsic responsivity lost during the development of tolerance in fully tolerant morphine rats [44]. Upon return to use, patients often do not take into account changes in tolerance and use at pre-abstinence levels, resulting in excessive dosing or associated overdose. Such changes account for significant increases in opioid overdose mortality following release from prison and in-patient rehabilitation [45-47]. In addition, it appears that an individual’s tolerance to the respiratory depressant effects of opioids does not
necessarily develop at the same rate as tolerance to its euphoric and analgesic effects [48], making it harder for returning opioid users to calculate a safe dose [49].

Changes in tolerance can also occur situationally, based on Pavlovian conditioning theory. With repeat conditioning in which opioids are administered in a routine fashion for a prolonged period of time, it is believed that the individual begins to respond to the cues associated with opioid use prior to their administration. When these cues are absent (for example the individual uses in new location or routine), the pre-use response is not triggered and as such the body does not prepare, resulting in a greater response to the opioids (or reduced tolerance). One such example was described by Siegel and Ellsworth, in a case of a patient diagnosed with pancreatic cancer [50]. The patient was being treated with four morphine injections per day and was bedridden. After staying in his bedroom for approximately a month he was moved into the living room. While in the living room he received his next scheduled morphine dose, and quickly exhibited signs of opioid overdose (constricted pupils, shallow breathing). The patient died a few hours later. Similarly, a review of patients who had suffered an accidental overdose found that far fewer patients injected in their usual place of use or used an unusual injecting technique compared with those presenting for non-overdose related causes [50, 51].

While opioids alone cause sufficient respiratory depression as to cause hypoxia, the co-ingestion of other drugs has been found to play a significant role in a large percentage of opioid overdoses [39, 51]. Drugs that also depress respiration such as alcohol and benzodiazepines are also commonly associated with opioid overdoses. Alcohol both suppresses the release of glutamate and stimulates the GABA binding, while drugs such as benzodiazepines and barbiturates also facilitate GABA binding. In an examination of 953 heroin-related fatalities, 76% of cases involved heroin in combination with another drug, with 46% of cases involving alcohol and 27% involving benzodiazepines [34].

In addition to the use of illicit opioids, prescription opioids can also be significant contributors to opioid overdose and associated mortality, in fact in the USA, prescription opioids contribute to more deaths than illicit opioids [52]. As per illicit opioid use, the co-ingestion of alcohol and other drugs often plays a significant role in prescription opioid overdoses [53]. However unlike
illicit opioids, much higher rates of intentional overdose/suicide and distinctly high blood levels have been observed in the use of prescription opioids which are not used in the treatment of dependence such as codeine and tramadol [54].

For both pain management and the management of opioid use disorders, high rates of prescription opioid overdose mortality have been observed during induction onto treatment, particularly in patients with an opioid use disorder commencing a new opioid pharmacotherapy such as methadone. While careful dose titration is generally used during the induction period, selecting the correct dose for a patient moving from a short acting, intravenous administered opioids, with an unknown purity such as heroin, to an oral, long acting, pharmaceutical grade opioids such as methadone can be difficult. During the first week of methadone maintenance treatment, plasma blood levels gradually accumulate with a consistent daily dose because of the drugs long half-life (5 – 130 hours) [55]. During the first couple of days, this can result in insufficient dosing resulting in withdrawal symptoms and can result in patients supplementing their methadone with illicit opioids and other drugs with potentially deadly consequences. Towards the end of the induction period, methadone levels may begin to accumulate above the tolerance of the patients, also potentially resulting in overdose. Additionally the high levels of variability in the metabolism of methadone can make it difficult for prescribing physicians to predict what dose will be both efficacious and safe for the patient [55].

As per fatal opioid and non-opioid overdoses, non-fatal overdoses are a significant contributor to the morbidity associated with opioid use, with an estimated 20 – 25 non-fatal overdoses occurring for every fatal overdose [56]. While most non-fatal opioid overdoses have no complications or lasting effects, a range of sequelae have been observed following overdose, including pulmonary oedema, pneumonia, cardiac arrhythmia, acute cardiomyopathy, haemoglobinemia, and rhabdomyolysis [57-60].

In terms of morbidity, the most common consequences of opioid use disorders are tolerance and physical dependence with the appearance of withdrawal syndrome occurring with their discontinuation. Symptoms associated with opioid withdrawal include piloerection, lacrimation, diarrhoea, nausea, emesis, nervousness, irritability, restlessness and insomnia.
While the withdrawal syndrome may fall short of being life threatening, its presence often drives return to opioid use as a means of mitigating the withdrawal symptoms and drives other opioid related morbidity and mortality.

The route of administration of illicit opioids is a major contributor to the associated morbidity and mortality. While a number of routes exist including ingestion, inhalation and subcutaneous/intramuscular injection, intravenous administration has been the dominant route of the use of heroin in Australia, probably due to its price, purity and availability [61]. Intravenous administration is associated with increased exposure to the risk of transmitting blood borne viruses such as hepatitis B and C (HBV and HCV) and human immunodeficiency virus (HIV) as a result of sharing injecting equipment. Rates of HCV are particularly prevalent, with upward of 60% of intravenous drug users diagnosed with the disease [62-64]. While rates of HIV in Australia have remained very low, internationally intravenous use of heroin has significantly contributed to the spread of HIV [65, 66]. Additionally, samples of heroin have been shown to be frequently contaminated with a variety of bacterial and fungal pathogens associated with increased morbidity. For example in an Australian study, 5 of 12 heroin samples seized and analysed by police were found to contain bacterial DNA of a number of pathogens, including those from the Weissella, Bacillus and Streptocicous genera [67]. The presence of such pathogens, other contaminants and the use of poor aseptic techniques are associated with increased prevalence of a range of problems including abscess, cellulitis, infections, endocarditis, significant scarring/bruising, thrombosis, ulcers, and gangrene [68, 69].

The lifestyle associated with opioid use disorders is also a significant contributor to morbidity and mortality. In procuring drugs, individuals are not uncommonly involved in criminal activities including theft and drug distribution, and/or prostitution resulting in increased risk of homicide, injury and sexually transmitted diseases [70, 71]. Individuals with an opioid use disorder are also more likely to be homeless, suffer from malnutrition and have poor personal hygiene, all contributing to their overall health [72].

Compared to the general community, rates of mental health disorders are also elevated in patients with an opioid use disorder, contributing significantly to morbidity and mortality in
these patients. In a study of 222 injecting heroin users, 60% met the criteria for a lifetime anxiety disorder, while 51 had a current diagnosis. Additionally 41% of participants met the criteria for a lifetime depressive disorder, with 30% with a current diagnosis [73]. High rates of mental health disorders, translate directly to high rates of suicide, with suicide accounting for 3 – 35% of all mortality in heroin users or approximately 1.2 deaths ptpy and 14 times that of non-drug using peers [20, 74]. As per overdoses, the prevalence of attempted suicide is much higher with an estimated 10-20 attempts for every successful event [75]. The relationship between mental health disorders and substance use is complex. While the use of illicit substances appears to increase the prevalence of mental health disorders, the reverse also appears to happen, with individuals with mental health issues often being attracted to substance use [73, 76-78]. Similarly, the lifestyle associated with illicit opioid use can also be a significant trigger for mental health disorders.

While the short-term effects of opioids have been well quantified, the long-term effects of opioids are just starting to be understood. It has been hypothesized that long term exposure to opioids may result in increased rates of aging, as observed by an altered profile of common biomarkers associated with aging. This includes C-reactive protein, serum globulins and insulin-like growth factor, and increased prevalence of age related diseases such as cardiovascular disease, certain types of cancers, osteoporosis, diabetes, hepatic fibrosis and cirrhosis [79-81].

1.5. Treatment for opioid use disorders

While there are alternatives such as rehabilitation programs and counselling, the treatment of opioid use disorders has largely been based around a number of well-established pharmacotherapies including methadone, buprenorphine (with or without naloxone) and naltrexone. The three treatments largely work by acting on the different opioid receptors, with either agonist or antagonist activity (or a combination) (Table 1).
Table 1: Binding affinity and intrinsic activity of opioid pharmacotherapies naltrexone, naloxone, methadone and buprenorphine on the mu, kappa, delta and nociception receptor in humans [82].

<table>
<thead>
<tr>
<th>Binding Affinity (nM)</th>
<th>MOR</th>
<th>KOR</th>
<th>DOR</th>
<th>NOP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methadone</td>
<td>3.16 (0.72 – 5.6)</td>
<td>1000</td>
<td>1000</td>
<td>No binding</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>1.07 (0.21 – 1.5)</td>
<td>0.74 (0.62 – 0.8)</td>
<td>2.9 (1.3 – 4.5)</td>
<td>77.4 (^1)</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>0.36 (0.11 – 0.87)</td>
<td>1.47 (0.19 – 5.28)</td>
<td>23.4 (10.8 – 60.0)</td>
<td>No binding</td>
</tr>
<tr>
<td>Naloxone</td>
<td>3.63</td>
<td>30.25 (10.7 – 49.8)</td>
<td>152.0 (17 – 448)</td>
<td>No binding</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intrinsic Activity</th>
<th>MOR</th>
<th>KOR</th>
<th>DOR</th>
<th>NOP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methadone</td>
<td>Agonist</td>
<td>No Activity</td>
<td>No Activity</td>
<td>No Activity</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>Partial agonist</td>
<td>Antagonist</td>
<td>No Activity</td>
<td>Partial agonist</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>Antagonist</td>
<td>Weak antagonist</td>
<td>Antagonist</td>
<td>No Activity</td>
</tr>
<tr>
<td>Naloxone</td>
<td>Antagonist</td>
<td>Weak antagonist</td>
<td>Antagonist</td>
<td>No Activity</td>
</tr>
</tbody>
</table>

1. Study carried out in mice cells rather than human, results taken from Khroyan et al. (2015) [83]

MOR = mu opioid receptor; KOR = kappa opioid receptor; DOR = delta opioid receptor; ORL-1 = opioid receptor like 1; NOP = nociception receptor, nM = nanomolar

### 1.5.1. Methadone

Methadone is a long acting synthetic mu-opioid agonist. Methadone has an average half-life of 22 (range 5 to 130 hours), and bioavailability of 75% (36 – 100%), with less than 10% of the oral dose extracted by the liver during first pass metabolism [55], making it effective option for once daily oral administration. Methadone is primarily used as a maintenance or opioid replacement therapy, with milder but longer lasting effects than heroin. At present methadone maintenance treatment (MMT) is the most extensively established and researched treatment for opioid use disorder and has proven efficacy in terms of treatment retention, reduced heroin use and improved general health status [84-86]. In a Cochrane review of 11 randomised clinical trials, methadone was shown to significantly improve retention to treatment (RR: 4.44,
CI: 3.26 – 6.04) and reduce both self-reported and urine/hair measures of heroin use (RR: 0.66, CI: 0.56 – 0.78), compared with non-pharmacological approaches [86].

While the benefits of MMT are numerous, a number of concerns have arisen regarding its use. While MMT is successful at retaining patients in treatment, it is a highly potent and addictive opioid, making it difficult for patients to cease treatment, with the potential for elongated or indefinite dependence on methadone. In a study of 307 heroin addicts, those who were maintained on 80 mg of methadone per day, had an average length of treatment of 660 days, while those on 120 g remained on treatment for 1150 days [87].

Methadone is generally dispensed daily, commonly by a pharmacist or medical professional to reduce its diversion for illicit use. This requirement for daily supervised dosing can interfere with a patient’s employment and day-to-day activities. While supervision has limited the diversion of methadone for illicit use, diversion is not uncommon, with a lifetime prevalence of illicit methadone injecting of 52.6% amongst injecting drug users in New York City, USA [88], 51.9% of heroin users in Sydney, Australia [89], and 43.3% of patients in opioid dependence treatment in Zurich, Switzerland [90]. As such the use of illicit methadone is often a significant contributing factor in fatal and non-fatal methadone poisoning [91, 92].

Similarly, while methadone has been shown to significantly reduce illicit opioid use, the treatment offers no disincentive to completely cease illicit opioid use and many patients continue to use heroin and other opioids in addition to their daily prescribed methadone. In a sample of 652 patients currently in methadone maintenance treatment in the USA (and had been in the treatment program for at least three months), 28.5% had used heroin in the three months prior to the interview [93].

In addition, safety concerns have also arisen in regards to morbidity and mortality associated with MMT. High rates of opioid overdoses have been observed, particularly during induction and following cessation, as described in section 1.2 [94-96]. Between individuals, methadone varies significantly in terms of pharmacokinetic parameters including plasma half-life (15 to 55 hours), and bioavailability (36 – 100%), as well as volume of distribution (2 – 13L/kg) and total clearance (0.02 – 2.0 L/min) making induction of patients onto methadone a complicated [55].
For patients who rapidly metabolize methadone, standard dosage may be insufficient to inhibit withdrawal symptoms, encouraging patients to use illicit opioids in addition to methadone, while methadone doses in slow metabolisers can accumulate over the induction period to fatal levels.

The use of methadone has also been associated with cardiovascular anomalies [97, 98]. A study examining the electrocardiograms of 75 asymptomatic patients on methadone found cardiac abnormalities (most commonly QTc prolongation, prominent U waves, and Brady arrhythmias) in 61% of the methadone patients as compared with 0% in the control group [97]. Additionally, a post mortem examination of 168 hearts of opiate dependent patients (who had died of various causes) found only 4% to be classified as ‘normal’, with a range of cardiac abnormalities including infective endocarditis (active, healed or both, 46% of patients), cardiomegaly (66%), coronary artery disease (21%), acquired valvular heart disease (10%), and myocardial heart disease (8%) [99].

Other long term safety concerns associated with methadone include low bone density [100], and dental disease [101]. In the short and medium-term, common side effects of methadone include constipation [102], fatigue, sleep disturbances [103, 104], respiratory depression, sexual dysfunction [102] and amenorrhea and oligomenorrhea in women [105-108].

For some patients, the benefits associated with methadone far outweigh the potential negatives. However for other patient, particularly those who wish to become opioid free, alternative treatments may be a more suitable option.

1.5.2. Buprenorphine

Buprenorphine is a partial agonist of the mu opioid receptor and an antagonist of the kappa opioid receptor [109]. The partial activation of the mu opioid receptor produces much milder effects than full agonists such as heroin or methadone, while the drug’s high affinity for the mu receptor reduces the binding of other opioids [110] and the kappa antagonist component protects vital functions such as respiration [111]. These properties make buprenorphine arguably a better agonist treatment for opioid use disorders than methadone. Buprenorphine is subject to extensive first-pass metabolism resulting in very low oral bioavailability [112], with
sublingual administration being the preferred route of administration. The terminal
elimination half-life (mean range 3 – 44 hours) is sufficient to allow for daily, alternative day or
3 times a week dosing regimens [112].

The positive reinforcing and dependence producing opioid effects of buprenorphine make
compliance with the daily formulation superior to pure antagonists such as naltrexone [113].
Additionally, the protective features of buprenorphine (i.e. no respiratory depression) are
thought to contribute to a reduction in opioid overdoses as compared with pure agonists such
as methadone [114, 115]. However, while the risk of opioid overdose fatality is reduced, it is
not completely removed, especially when used in combination with other respiratory
depressants such as benzodiazepines, alcohol and other opioids [115-117].

While generally regarded as a relatively safe drug [114, 118], concerns have arisen regarding
the diversion and misuse of buprenorphine. In many countries, illicit buprenorphine is
considerably easier and cheaper to obtain than other opioids such as heroin and is associated
with fewer or less severe legal consequences [119], with buprenorphine use often seen as a
method of self-treatment or management of opioid withdrawal. The intravenous use of
sublingual buprenorphine has also been associated with numerous health problems, including
abscesses, cellulitis, thrombosis, phlebitis ulcers, gangrene, ischaemia and infections [120-
122]. Additionally if the diversion for intravenous use occurs after the sublingual wafer has
been placed in the mouth there is a risk of systemic fungal and bacterial infections from mouth
flora contamination [123].

To reduce the incentive for intravenous diversion, the initial sublingual formulation (Subutex ®)
was altered to include the opioid antagonist, naloxone (Suboxone ®), which if injected by an
opioid dependent person precipitates opioid withdrawal. However, the manufacturer argues
that when taken sublingually as prescribed, the low bioavailability, low dose and short half-life
of naloxone has little impact either itself or on the effect of the buprenorphine. Although the
addition of naloxone has been shown to reduce intravenous use and thus the relative street
worth of buprenorphine, parenteral use is still not uncommon [124]. Subutex and Suboxone
are currently the only buprenorphine preparations available in Australia for substance
dependence, however internationally other preparations and formulations are available including Zubsolv (suglingual tablet), Bunavail (buccal film), and Probuphin (implant).

A Cochrane review of buprenorphine showed that in comparison to methadone, at fixed high and medium doses, buprenorphine is equivalent to methadone in retaining patients to treatment and suppressing illicit opioid use, however when doses are flexibly delivered or low doses (2 – 6 mg per day) are used, patient retention is inferior to methadone treated patients [125].

### 1.5.3. Naltrexone

Naltrexone is a potent and long-acting opioid antagonist with a generally well tolerated safety profile [126]. Naltrexone is an unselective antagonist, binding to the mu, kappa and delta opioid receptors. When taken orally, naltrexone is highly absorbed (96%), however its bioavailability is much lower (5 to 40%) as a result of high rates of first past metabolism [127]. The plasma half-life of naltrexone is approximately 4 hours, however the receptor half-life of naltrexone on the mu opioid receptor is much longer, lasting 72 to 108 hours [128]. Naltrexone is primarily metabolised in the liver by dihydrodiol dehydrogenase, producing 6-beta-naltrexol, which is thought to contribute to the efficacy of naltrexone, with its own action on the opioid receptors. While the potency of 6-beta-naltrexol is only around 6% of naltrexone and it is less competitive at the mu receptor [129], the plasma and receptor half-life is substantially longer than naltrexone [129, 130]. To a much lesser tent naltrexone is also metabolised to 2-hydroxy-3-methoxy-6-beta-naltrexol and 2-hydroxy-3-methyl-naltrexone [131].

While pharmacologically naltrexone appeared to be the perfect pharmacotherapy to combat opioid addiction, clinical trials of oral naltrexone produced poor outcomes for a number of reasons. First, before being inducted onto oral naltrexone patients are required to be opioid free to prevent the naltrexone invoking severe withdrawal symptoms, however abstinence is often hard to achieve due to the effects of opioid withdrawal. Second, once participants are inducted onto naltrexone, ensuring patients take the once daily medication is difficult and patients often stop after days or weeks [132]. Thirdly, unlike methadone, which produces mild euphoria, pain relief, and sedation when taken, and withdrawal symptoms when not taken,
naltrexone is not associated with any positive or negative reinforcing effects which encourage compliance, making it easy for patients to drop out of treatment. In one study of 160 illicit heroin users inducted onto naltrexone, only 17% continued to be compliant at 6 months [133]. As such, the use of oral naltrexone was only shown to modestly reduce heroin use in initial studies.

A number of strategies have been trialled to address non-compliance issues, including the use of supervision by a salient other (generally family or friend), contingency management, and psychotherapies, with positive results [132, 134, 135]. However, such strategies limited the use of naltrexone to highly motivated patients and patients with strong support systems, excluding the ‘typical’ illicit opioid user. To combat problems with non-compliance, a number of companies set out to develop a sustained release naltrexone preparation, so that a single treatment would deliver the patient a therapeutic dose of naltrexone over a prolonged period of time, enforcing compliance. A number of such preparations have been developed including injectable technology such as Vivitrol® (USA)) [136], and implantable products such as the O’Neil Long Acting Naltrexone Implant (Australia)[137, 138], the Wedgewood Naltrexone Implant (USA)[139], the Civil Life Implant (China)[140], and Prodetexone (Russia)[141].

The first of such preparations to be registered by the Food and Drug Administration (FDA) in the USA was Vivitrol, a 30 day intramuscular sustained release injection. Despite having been registered since 2006 for the treatment of alcohol dependence, it did not receive approval for use in patient with an opioid use disorder until 2011 after opioid efficacy studies had been completed. Vivitrol was shown to be superior to a placebo in terms of self-reported median opioid-free days (99.2 v 60.4%), cravings (-10.1 v 0.7), and study retention (168 v 96 days) [142]. However this study received criticism for using a placebo control group rather than an alternative opioid pharmacotherapy such as oral naltrexone or methadone [143]. Additionally, while eliminating daily non-compliance issues, patients were required to return monthly for re-treatment.

The O’Neil Long Acting Naltrexone Implant was developed by Go Medical Industries P/L and has been used predominately in Australia under compassionate guidelines and clinical trials since 2001. The implant is comprised of 10 tablets made of compressed naltrexone poly-(DL-
lactide) microsphere coated in poly-(DL-lactide), with two implants commonly representing a single treatment. The implant is surgically placed into the subcutaneous tissue of the abdomen, under sedation and local anaesthetic. The procedure is usually an out-patient procedure, however the patient may remain in medical care if they undergo rapid opioid detoxification using clonidine/naloxone prior to treatment [144].

The naltrexone is gradually leached from the polymer, producing blood naltrexone levels above therapeutic levels of 2ng/ml for approximately 145 days, gradually decreasing to 1ng/ml by 214 days [145]. The polymer gradually biodegrades over approximately 3 years [138]. The implant, has demonstrated improved efficacy in comparison to oral naltrexone, reducing return to regular heroin use from 38% to 83% at 6 months post treatment [146] and compared to ‘usual treatment’ in Norway, reducing self-reported heroin use from an average of 17.9 days in naltrexone treated patients compared with 63.6 days in patients treated with ‘usual care’ [147].

While the sustained release naltrexone preparations appear to address the issue of non-compliance associated with the oral formation, a number of concerns have also arisen about the clinical safety of naltrexone both as a once daily formation and an extended release preparation. While the drug itself appears to be well tolerated, issues were raised about (i) use of non-opioid drugs as a substitute for opioids, (ii) risk of depression and/or suicide, (iii) difficulty in early termination of treatment (for example for pain management), and (iv) rates of opioid overdoses following cessation [148, 149].

While mortality rates in patients with an opioid use disorder treated with oral naltrexone remain comparable to other opioid pharmacotherapies whilst on treatment (approximately 10 ptpy), the risk of death following the cessation of treatment has been calculated to be as high as 221 ptpy [118, 150]. In comparison, in the heroin using population, mortality rates have been estimated at between 8.6 and 73.2 ptpy [151], while patients in substitution therapies such as methadone maintenance therapy (MMT) and buprenorphine have mortality rates of 5.6 to 15.2 ptpy [152-154].
The observed increase in opioid overdose mortality is thought to be associated with rapid loss of protection from naltrexone following the cessation of treatment [155], with similar rates of overdose mortality observed in opioid dependent patients in the weeks after leaving protected environments such as rehabilitation [45] or jail [46]. While taking the daily medication, patients are protected from large doses of opioids, however, due to naltrexone’s relatively short half-life, upon cessation the protection is lost, exposing the patient’s opioid naïve receptors (with tolerance dramatically reduced following opioid detoxification and induction onto treatment). Accordingly, if patients with limited opioid tolerance return to opioid use, even briefly, they may miscalculate their dose, often with fatal consequences. It has thus been hypothesised that the use of a sustained release naltrexone preparation, in which blood naltrexone levels decrease slowly, may reduce the incidence of opioid overdose. Additionally concerns have arisen that patients on naltrexone may consume excessive amount of opioids in an attempt to ‘override’ the antagonist effects [156].

A review of Australian coronial records between 2001 and 2004 identified 5 drug related fatalities in patients treated with implant naltrexone, with the authors arguing that patients treated with implant naltrexone were not protected from overdose. Notably however the study only identified one fatality involving opioids in a patient with an implant less than 6 months old (which is the outer duration of the longest implant available in Australia) and the type/manufacturer of the implants involved was not able to be identified [156]. Additionally, the study was unable to estimate the number of patients treated with implant naltrexone during this period.

Notwithstanding this, a study of 361 heroin dependent patients treated with the O’Neil implant found that in the 6 months prior to implantation the rate of non-fatal opioid overdose requiring hospital or emergency department attendance was 5.5%. While in the 6 months following treatment no overdoses were identified, with a reduction in overdose in the 7 to 12 months (post therapeutic) period compared to pre-treatment levels (0.8%) [157]. This data fit with the hypothesis that a slowly tapered release profile would be associated with fewer fatal opioid overdoses, compared with preparations such as oral naltrexone, where patients rapidly move from naltrexone protected to opioid naïve.
Comparisons of mortality rates in heroin dependent persons treated with the O’Neil Long Acting Naltrexone implant have found mortality rates to be comparable to both methadone (5.83 ptpy for methadone compared with 3.76 for implant naltrexone)[158] and buprenorphine (5.35 deaths ptpy for buprenorphine compared with 3.00 for implant naltrexone)[159]. The sample size used in the naltrexone cohort in each of these studies was not large enough to accurately assess change in mortality rates over time and examine cause specific mortality including fatal opioid overdoses (341 and 255 sequential patients respectively). As yet no direct large scale examination of mortality rates (including fatal opioid overdoses) in implant compared with oral naltrexone, methadone or buprenorphine has been published.

Another concern has been that during periods of naltrexone facilitated opioid abstinence, patients may opt to replace illicit opioid use with the use of other non-opioid drugs, as the result of a lack of the positive reinforcing effects of naltrexone and a desire to continue drug use or self-medicate. As such, it has been hypothesised that the experimental use of non-opioid drugs such as alcohol, benzodiazepines and amphetamines may increase while on naltrexone treatment and be associated with an increased risk of non-opioid overdose or other drug associated morbidity. Data to date however does not support this hypothesis, with comparisons of pre- to post-treatment non-opioid overdoses not increased [157]. Conversely, given naltrexone’s efficacy in the treatment of alcohol [160, 161] and amphetamine [162, 163] dependence the use of naltrexone may reduce the incidence of polydrug use. However, the large-scale examination of changes in non-opioid drug use/associated morbidity or a comparison to methadone or buprenorphine has yet to be reported.

The antidepressant and anxiolytic effects of opioids have been recognized for thousands of years [164]. More recently, the use of buprenorphine has been investigated as a treatment for depression in both opioid dependent and non-dependent patients with positive outcomes [165, 166]. Given the role of endogenous opioids in mood stabilisation, concerns have arisen regarding the potential for opioid antagonists to facilitate mental health disorders, particularly given the vulnerable nature of opioid dependent persons and high incidence of such disorders.
Ngo et al. (2007) examined rates of hospital admission with a mental health diagnosis before and after naltrexone implant treatment in a cohort of 359 heroin users and observed no increase in hospital admissions for mental health problems. In contrast, rates of all mental health problems, except mood disorders declined significantly post treatment [167]. In a randomised controlled trial of oral and implant (Prodetoxxon) naltrexone, despression, anxiety, and anhedonia were elevated at baseline, but reduced to normal within one to two months following treatment in patient who remained in treatment and did not relapse [168]. Similarly naltrexone has been shown to be effective in reducing self-injuring behaviour [169, 170]. As yet no direct comparison between mental health outcomes and self-harming/suicidal behaviour in implant naltrexone, methadone and buprenorphine has been published.

Additionally, the opioid system is complex and intricate with links to numerous other systems within the body. While low dose naltrexone has been used in the treatment of a wide range of diseases and disorders including Crohn’s disease [171], compulsive and self-injuring behaviours [170, 172], polycystic disease and infertility [173, 174], glycemic control in the metabolic syndrome [175], fibromyalgia [176] and cancer [177, 178], the effect of long term exposure to naltrexone is not well understood and warrants further investigation.

### 1.5. Pregnancy and opioid use disorders

While compared to males, females represent a smaller proportion of opioid users, accounting for approximately 32% of the opioid using population, there are an estimated 4.7 million opioid dependent women globally [179] and approximately 80 – 90% of these women are of a reproductive age. Opioids can be disruptive to menstruation, often resulting amenorrhea and oligomenorrhea, however pregnancy is not uncommon [111, 180-182]. Estimates in the US and Australia suggest that approximately 1 in 200 births is to a mother with an opioid diagnosis [183, 184]. Similarly, a survey of 204 non-pregnant opioid dependent women attending an outpatient opioid treatment program in Australia found that 28.9% of the women had previously had 6 or more pregnancies, with 6% having 10 or more [182]. Interestingly, it is estimated that 86% of pregnancies in opioid abusing women are unintended [185].
1.5.1. Pregnancy and neonatal outcomes

The use of illicit opioids during pregnancy has been associated with high rates of detrimental health outcomes in both the mother and the exposed neonate, including preeclampsia, pulmonary complications, third-trimester bleeding, gestational and neonatal loss, low birth weight, and prematurity [186-188] (Table 2). Opioids have the ability to cross the placenta to the fetus, with heroin reaching the fetus within one hour of maternal use [189]. As the half-life of heroin and its metabolites are so short, the fetus will often undergo daily cycles of intoxication and withdrawal which may result in fetal hypoxia, hyperactivity, and meconium aspiration [190].

Additionally, following birth, neonates also often undergo withdrawal as a result of the discontinuation of the maternal delivery of opioids and other drugs via the placenta. This withdrawal is typically termed neonatal abstinence syndrome (NAS) and is characterized by a cluster of symptoms commonly including irritability, hyperactivity, sleep disturbance, difficulty feeding, vomiting, and diarrhoea [191]. In infants chronically exposed to opioids in utero, high rates of NAS are generally observed (>50%), with a significant portion requiring treatment and hospitalization (Table 2).

The use of exogenous opioids during pregnancy may also interfere with the role that endogenous opioids play in pregnancy and partition. For example, endogenous opioids have been found to play a critical role in the regulation of both prolactin and oxytocin during pregnancy. Prolactin is involved in lactation, maternal behaviour, neurogenesis [192], while oxytocin stimulates contractions and dilation of the cervix during parturition [193]. Additionally blood levels of beta-endorphins increase to provide an anxiolytic and analgesic effect during child birth [194, 195]. As such the use of opioid agonist and antagonist may exhibit effects on numerous aspects of pregnancy, child birth and early childhood care.

However, the direct effect of exogenous opioids on health outcomes during pregnancy in clinical studies is largely confounded by a number of other risk factors commonly associated with illicit drug use. Such risk factors include high rates of blood borne viruses such as hepatitis
C and HIV, sexually transmissible diseases, cigarette smoking, alcohol and other drug use, mental health diagnoses and poor nutrition and self-care [187, 196, 197].

Although opioid use during pregnancy is associated with increased risk of poor maternal and neonatal outcomes, unlike alcohol and other non-opioid drugs, the abrupt cessation of opioids during pregnancy is not generally recommended for two reasons. Firstly, debate exists as to the safety of opioid withdrawal during pregnancy, with concerns that utero withdrawal (as a result of maternal withdrawal) may trigger spontaneous abortion or premature birth. While some studies recommend against opioid withdrawal [198, 199], others suggest it can be safely achieved during pregnancy [200, 201]. Secondly, apprehension has surrounded the potential for patients to return to opioid use following detoxification, possibly resulting in opioid overdose which may be fatal for both the pregnant opioid user and/or her neonate [198]. Accordingly, the management of pregnant opioid dependent women has generally centred on the use of long acting pharmaceutical grade opioids such as methadone and more recently buprenorphine, with the aims of both reducing the use of illicit opioids and facilitating a stable lifestyle which is more conducive to motherhood.

1.5.2. Methadone and pregnancy

As per illicit opioids, the use of methadone can be disruptive to menstruation [202], however the affects appear to be less, with improvements in menstrual cycle length following the commencement of methadone treatment [181]. However, patients often believe that methadone will impair their fertility sufficiently to not require the use of contraception, resulting in poor uptake of contraception and high rates of unplanned pregnancies [182, 185].

In many countries, including the USA, the UK and Australia, methadone has traditionally been the primary approach for the treatment of opioid dependent women. Methadone’s long half-life reduces fluctuations in opioid blood levels, eliminating the cycle of intoxication and withdrawal often observed in heroin dependent patients. Methadone is associated with high levels of compliance and the daily dispensing promotes contact with health professionals, resulting in increased pre-natal care. Compared with heroin, the maternal use of methadone is associated with increased prenatal care, reduced fetal mortality, and decreased growth
retardation [187, 188, 203]. Additionally, the use of methadone can minimize or eliminate the use of illicit drugs, reducing the associated risks such as infection.

However, while methadone has been associated with a number of benefits over the use of illicit opioids during pregnancy, methadone readily crosses the placenta to the fetus and thus many of the negative effect associated with illicit opioid use. Compared with drug-free controls, methadone is associated with poorer neonatal outcomes, including prematurity, the presence of NAS, growth retardation, respiratory difficulties and seizures [183, 204] (Table 2). Additionally, due to the methadone’s long half-life and purity, some neonatal outcomes, such as NAS, can be more frequent and severe compared with neonates exposed to illicit opioids [204](REF). Another concern has been that mothers can continue to use illicit opioids in addition to methadone.

1.5.3. Buprenorphine and pregnancy

Buprenorphine has recently been used increasingly in the treatment of pregnant opioid dependent women and has been shown to improve maternal and neonatal outcomes, reduce illicit drug use and increase pre-natal care. While the use of Suboxone (buprenorphine + naloxone) has generally been favoured over Subutex (buprenorphine alone) for the treatment of non-pregnant women, the reverse is true for pregnant opioid dependent women. The preference for buprenorphine alone is justified by desire to limit fetal exposure to a single exogenous compound (eliminating exposure to naloxone). This clinical decision is supported by animal studies where naloxone has been shown to produce maternal and fetal hormone changes, although the clinical significance of these effects are unclear. As yet only one clinical study has been published comparing the two buprenorphine preparations, with no significant adverse maternal neonatal outcomes related to the buprenorphine-naloxone combination observed [205]. Notably in this study, buprenorphine-naloxone data was compared with previously published data of buprenorphine use in pregnancy rather than a randomised to matched study control group. Prescribers of buprenorphine-naloxone also have concerns about its intravenous use, with the potential for naloxone to cause both maternal and fetal withdrawal symptoms [206].
Similarly to methadone, buprenorphine is transferred across the placenta to the fetus [207], however the transfer appears to be reduced, perhaps due to buprenorphine’s greater molecular weight [111]. In comparison to methadone, buprenorphine has been shown to be associated with reduced incidence and severity of NAS, shorter duration of hospital stay, increased birth size (length, weight, head circumference), longer periods of gestation, and reduced medical complications during labour and delivery [208-210], however methadone may be superior in terms of patients retention [208]. Additionally, patients may exhibit some withdrawal symptoms when moving from a full opioid to a partial agonist/antagonist such as buprenorphine.

**1.5.4. Naltrexone and pregnancy**

Naltrexone has been suggested as an alternative treatment for pregnant opioid dependent women. At present, only a small number of case studies have been conducted on pregnant patients treated with naltrexone. These case studies noted that all women remained heroin free throughout their pregnancies, with unremarkable neonatal and obstetric outcomes. This data provides preliminary evidence to support the use of sustained release naltrexone for the treatment of pregnant opioid dependent patients [211]. Notwithstanding, non-clinical animal research using a rat model has highlighted a number of areas of concern including changes in brain and cerebella weight, thicker somatosensory cortex, larger cerebellum, increased number of glial and granule neurons, and increased cell dendritic length and spine concentration in the hippocampus [111].

With sustained release naltrexone preparations becoming more readily available, concerns have arisen regarding the potential for women to become pregnant on treatment, particularly given the limited safety information available and the requirement for surgical intervention to cease treatment. Some clinical observations suggest that the incidence of pregnancy may increase following naltrexone treatment, potentially due to the cessation of opioids (and thus the restoration of normal menstruation), increased sex drive, re-establishment of relationships, and increased self-care (nutrition, hygiene etc.). Alternatively, the increased incidence may be directly attributable to naltrexone, with naltrexone shown to simulate luteinising hormone (LH) and follicle stimulating hormone (FSH) during the early follicular
phase of the menstrual cycle [212, 213]. As such, clinically naltrexone has been found to
induce ovulation and re-instate normal menstruation in non-opioid dependent women with
weight loss associated and hypothalamic, amenorrhea and polycystic ovarian disease [105, 174, 214].

Clinical research into the use of naltrexone and more specifically implant naltrexone during
pregnancy has been raised repeatedly as an integral part of the development of safe and
effective treatment for pregnant opioid dependent women [111, 215, 216], with patients
indicating an interest in naltrexone as an option for treatment during pregnancy [217].
Table 2: An overview of the effects of the use/exposure to opioids and opioid pharmacotherapies during pregnancy on maternal and neonatal outcomes

<table>
<thead>
<tr>
<th>Mother</th>
<th>Illicit opioids</th>
<th>Methadone</th>
<th>Buprenorphine</th>
<th>Naltrexone</th>
<th>Western Australia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth rates</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>-</td>
</tr>
<tr>
<td>Complications during labour/delivery (%)</td>
<td>?</td>
<td>51 [208]</td>
<td>31 [208]</td>
<td>?</td>
<td>63.9 [219]</td>
</tr>
<tr>
<td>Terminations (%)</td>
<td>?</td>
<td>4.4 [220]</td>
<td>3.3 – 12.8 [220, 221]</td>
<td>?</td>
<td>1.8 [222]</td>
</tr>
<tr>
<td>Twins (%)</td>
<td>1.16 - 2.9 [223-225]</td>
<td>0.4 - 2.8 [209, 226]</td>
<td>4.3 [209]</td>
<td>?</td>
<td>2.7 [219]</td>
</tr>
<tr>
<td>Birth Outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perinatal mortality (%)</td>
<td>3.0 - 10.7 [203, 227, 235]</td>
<td>2.4 – 3.4 [203, 238]</td>
<td>?</td>
<td>?</td>
<td>0.9 [234]</td>
</tr>
<tr>
<td>Infant mortality (%)</td>
<td>4.0 [225]</td>
<td>1.2 - 5.5 [209, 237]</td>
<td>1.0 [239]</td>
<td>?</td>
<td>0.1 [234]</td>
</tr>
<tr>
<td>Morbidity and mortality in patients with opioid use disorders and their children following treatment/exposure to implant naltrexone</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>---</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congenital anomalies (%)</td>
<td>2.9 - 26 [186, 223, 224]</td>
<td>0.4 – 15.4 [226, 232, 238, 244, 256, 260, 261]</td>
<td>0.3 – 9.8 [220, 232, 233, 239, 244, 247, 259]</td>
<td>?</td>
<td>5.8 [262]</td>
</tr>
<tr>
<td>Low birth weight (&lt;2500g) (%)</td>
<td>28.6 – 62.5 [223, 229, 231, 235, 241, 266]</td>
<td>7.7 - 37.5 [210, 216, 229, 231, 234, 261]</td>
<td>6.3 - 9 [210, 221, 244]</td>
<td>11.7% [216]</td>
<td>6.6 [219]</td>
</tr>
<tr>
<td>Special care (days)</td>
<td>33.2 [230]</td>
<td>5.9 – 35.5 [230, 255, 261]</td>
<td>19.4 [255]</td>
<td>?</td>
<td>-</td>
</tr>
<tr>
<td>Length at birth (cm)</td>
<td>46.1 - 47.3 [186, 223]</td>
<td>47.1 – 49.6 [208, 210, 220, 249, 261]</td>
<td>46.3 – 52.8 [208, 210, 220, 221, 261]</td>
<td>?</td>
<td>-</td>
</tr>
</tbody>
</table>
Morbidity and mortality in patients with opioid use disorders and their children following treatment/exposure to implant naltrexone

<table>
<thead>
<tr>
<th>Category</th>
<th>Measurement</th>
<th>Value</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Head circumference (cm)</strong></td>
<td>31.3 – 33.0</td>
<td>32.4 – 33.9</td>
<td>[210, 226, 232, 249, 250, 254, 255, 261, 263]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>32.8 – 34.7</td>
<td>[210, 221, 232, 246, 249, 250, 255, 258, 264]</td>
</tr>
<tr>
<td><strong>Preterm (&lt;37 weeks) (%)</strong></td>
<td>17.5 – 36.4</td>
<td>3.8 – 37.6</td>
<td>[203, 208, 210, 216, 220, 229, 232, 237, 238, 242-244, 249, 251, 252, 254-256, 260, 269]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.2 – 20</td>
<td>[208, 210, 220, 221, 232, 239, 244, 247, 249, 251, 252, 255, 258, 259]</td>
</tr>
<tr>
<td><strong>Apgar 1 min</strong></td>
<td>7.2 – 8.2</td>
<td>7.4 - 8.6</td>
<td>[216, 230, 231, 243, 249, 254, 255, 257]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8 – 9.4</td>
<td>[239, 246, 247, 249, 255, 257-259, 264]</td>
</tr>
<tr>
<td><strong>Apgar 5 mins</strong></td>
<td>8.4 – 9.0</td>
<td>8.0 – 9.9</td>
<td>[216, 230, 231, 242, 243, 249, 252, 254, 255, 257, 261]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8.6 – 9.9</td>
<td>[246, 247, 249, 252, 255, 257-259, 264]</td>
</tr>
</tbody>
</table>

* Category C: Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible.

** Category B3: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformations or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is uncertain in humans.

*** Median
1.5.5. Child outcomes

While the health of neonates exposed to opioids in utero as a result of maternal dependence has been the focus of numerous studies, research on these children extending beyond the first few weeks following birth is limited, and often only include small numbers. Research that has looked beyond the neonatal period generally focuses on child developmental, behaviour and mental capacity rather than morbidity and mortality. Within the few studies that have reported on morbidity and mortality, several health issues have been identified. In methadone exposed children increased incidents of microcephaly, visual abnormalities (including strabismus and nystagmus), elevated systolic blood pressure, and acute and chronic inner ear infection have been identified [271-273]. In buprenorphine exposed children, one study reported elevated rates of visual abnormalities (primarily strabismus) and infantile pyloric stenosis [239]. In another study, the oral health of buprenorphine exposed children was poorer compared to a control group, however this was primarily attributed to dental neglect [274].

The effects of naltrexone in utero exposure on the subsequent health of children is yet to be reported and remains a significant concern to mothers and health care providers when seeking a suitable treatment.
2. Aims and Objectives

The objective of this thesis is to examine and compare morbidity and mortality in patients with an opioid use disorder and children who have been treated with/exposed to a sustained release naltrexone preparation for an opioid use disorder. Specific primary objectives to be examined are:

1. Does the use of a sustained release naltrexone implants mitigate the high mortality rate associated with oral naltrexone?
2. Are mortality rates in patients treated with implant naltrexone comparable to mortality rates in patients treated with methadone, or buprenorphine?
3. How does morbidity compare in patients treated with sustained release naltrexone implant to those treated with methadone or buprenorphine?
4. Are birth rates in naltrexone treated women comparable to women treated with methadone or buprenorphine, and non-dependent controls?
5. What are the obstetric, neonatal and childhood risks associated with the use of sustained release naltrexone during pregnancy and how do they compare to methadone, buprenorphine and non-dependent controls?
3. Thesis Structure and Research Setting

3.1. Thesis structure

This thesis is comprised of three primary research topics. The first topic (chapter 4) is mortality in opioid dependent patients treated with oral and implant naltrexone. This chapter is comprised of a single paper and addresses the first aim of the thesis.

The second topic (chapter 5) is morbidity and mortality in opioid dependent patients treated with implant naltrexone, compared with opioid dependent patients treated with methadone and buprenorphine. In addition to all-cause morbidity and mortality, opioid overdoses and mental illness are examined in depth. This section covers aims 2 and 3 of the thesis and is comprised of 4 papers.

The final topic of this thesis (chapter 6) is the use of naltrexone in pregnant opioid dependent women, reporting on women and their children from conception through to 5 years of age. Outcomes in naltrexone exposed mother-child dyads are compared with methadone, buprenorphine and non-exposed mother-child controls. This section covers aim 4 and 5 of the thesis and is comprised of 3 papers.

3.2. Research setting

This thesis makes use of national mortality data via the National Death Index managed by the Australian Institute of Health and Welfare (AIHW) and state administrative data linked by the WA Data Linkage Branch (DLB).

The National Death Index is a Commonwealth database that contains records of all deaths registered in Australia since 1980 and the deaths of Australians overseas (on the provision that the deaths are reported to the Australian Embassy of the country in which they occurred). Probabilistic matching of the cohort data (oral and implant naltrexone treated opioid dependent patients), provided by Fresh Start Recovery Program, was performed by the AIHW Data Linkage Unit using the Integrity probabilistic matching software. For each potential match a weighting was assigned estimating likelihood of an accurate match, with the quality of matches revived by the research team. Matches with small discrepancies were re-checked against the patient’s file. The AIHW operates under a strict privacy regime based on section 29.
of The Australian Institute of Health and Welfare Act 1987. Ethics approval was required from both the AIHW and an independent NHMRC approved ethics committee (Bellberry Human Research Ethics Committee) to access the data.

The WA DLB was established in 1995 to create and maintain links within and between health and other datasets, to improve the usefulness, accessibility and efficiency of the use of routinely collected data in research [275]. Additionally the establishment of these links and linkage through a centralised agency also reduce the requirement for identifiable data, protecting the identity of participants. The quality of the links has been evaluated in audits and validity studies, with the proportions of invalid or missed links both estimated at 0.1% [275]. The WA DLB is a world leader in data linkage, terms of their capacity, scope and efficiency. The WA DLB utilises internationally accepted privacy preserving protocols, with the links created using probabilistic matching, clerical review and quality control mechanisms.

This study utilised core datasets regularly linked by the DLB including the Hospital Morbidity Data Collection, Mental Health Information System, Emergency Department Data Collection, The WA Cancer Registry, the Midwives Notification System, Births Registrations, Death Registrations, WA Electoral Roll. Additionally, the study used data from the WA Notifiable and Infectious Diseases System, the WA Register of Congenital Anomalies and the Monitoring of Drugs of Dependence System. This study was the first to utilise data from the Monitoring of Drugs of Dependence System. Approval to access this data was required from the DLB and the respective data custodians, the WA Department of Health Human Research Ethics Committee (HREC) and the University of Western Australia (UWA) HREC.

The use of these datasets allowed the examination of the health of all opioid dependent patients treated with naltrexone, methadone and buprenorphine within the study parameters. Encapsulating the whole cohort was an important aspect of this study, as it allowed for the examination of health of all patients entering treatment, and was not affected by patient loss to follow-up or selection bias created by study recruitment. Similarly is allowed sufficient patients numbers to examine rare events and sub-populations. Additionally the use of linked health data, allowed the examination of a wide range of health indicators, from mortality to cardiovascular health, reportable infectious diseases to pregnancy loss.
4. Mortality in Opioid Dependent Patients treated with Oral and Implant Naltrexone

4.1. Forward

The first research chapter examines mortality in opioid dependent patients treated with oral naltrexone compared to the O’Neil Long Acting Naltrexone implant, in order to answer the questions: “Does the use of a sustained release naltrexone preparation such as an implant mitigate the high mortality rate associated with oral naltrexone?”

This chapter is comprised of a single paper examining rates of mortality in all patients treated with oral or implant naltrexone in Western Australia between August 1997 and December 2009.
4.2. **Paper 1: Examination of mortality rates in a retrospective cohort of patients treated with oral or implant naltrexone for problematic opioid use**

Abstract

**Aims:** To examine and compare mortality rates in patients treated with oral and implant naltrexone.

**Methods:** Patients treated with oral naltrexone (n = 2155, 17,207 patient years) and implant naltrexone (n = 2389, 11,678 patient years) for problematic opioid use between August 1997 and December 2009 were identified from treatment records at a community not-for-profit drug treatment clinic. Fatalities were identified by matching treatment records with the National Death Index. Rates of crude, gender, age, treatment period and cause specific mortality rates were calculated for the two groups.

**Results:** Crude mortality rates for patients treated with oral naltrexone (8.78 deaths per 1,000 patient years (ptpy), 95% CI: 7.38 - 10.17) were significantly different to those treated with implant naltrexone (6.59 ptpy, 95% CI: 5.13 - 8.06) (p = 0.0339). In the first 4 months following treatment differences in the two groups were particularly apparent, with a mortality rate of 26.28 ptpy in patients treated with oral naltrexone compared to 7.34 ptpy in patients treated with implant naltrexone (p = 0.0003). Differences in initial mortality rates following treatment were predominately associated with high rate of opioid overdoses in oral naltrexone patients in the first 4 months following treatment (17.22 ptpy compared with 0.67 ptpy in implant naltrexone patients) (p < 0.0001).

**Conclusions:** The use of implant naltrexone was associated with a reduction in all-cause mortality and opioid overdose during the first four months following treatment as compared with patients treated with oral naltrexone.
Introduction

Since its initial US registration in 1984 for the treatment of opioid dependence, a number of safety concerns have been raised regarding the use of oral naltrexone [276]. These are: a) an observed increase in the number of opioid overdoses following cessation of oral naltrexone [150, 277], b) the potential for increased use of non-opioid drugs resulting in increases in fatal and non-fatal non-opioid drug overdoses [278, 279], and c) increases in depression and suicide possibly due to the inability of endogenous opioids to bind to the opioid receptor [276, 280].

Mortality rates for heroin using populations have been estimated between 6.8 and 77.6 per thousand patients years (ptpy), with clear geographic differences in mortality [20]. Mortality rates in Australia are among the lowest in the world, with crude mortality rates of between 8.9 and 18.0 [20]. Patients in methadone maintenance therapy (MMT) and buprenorphine maintenance have mortality rates generally between 4.5 to 15.2ptpy [94, 153, 154]. Mortality rates for oral naltrexone remain comparable to other drug treatments (approximately 10ptpy), however mortality rates have been calculated to be as high as 221ptpy in the 2 weeks following cessation of oral treatment [118, 150].

The observed increase in opioid related fatalities following the cessation of oral naltrexone is postulated to be associated with reduction in a patient’s opioid tolerance as patients transition from regular opioid use to naltrexone [150, 155, 281]. While taking daily naltrexone, patients are protected from opioid overdose, however, once the naltrexone is not present, low opioid tolerance can result in opioid dose miscalculation and accidental overdoses [150].

Recently a number of sustained release naltrexone products have been developed to overcome patient non-compliance with daily oral naltrexone use, and provide stable therapeutic blood naltrexone levels over an elongated time period [282]. The development of sustained release naltrexone preparations have also been associated safety concerns. As per oral naltrexone, issues have centred on the perceived potential for increases in fatal and non-fatal opioid and non-opioid drug overdoses following treatment, as well as potential increases in the prevalence of depression and suicide [143, 156]. These concerns recently received increased attention following the registration of the first sustained release naltrexone preparation for the treatment of opioid dependence by the Food and Drug Administration (FDA) in the United Stated of America [143, 283]. The preparation, known as Vivitrol ® is a 30 day sustained release injection, manufactured by Alkemes. Despite receiving FDA approval and
having been registered for alcohol dependence since 2006, criticism has been made on the lack of data available on the presence of fatal and non-fatal opioid overdoses [143, 283].

Similar concerns have surrounded the use of the O’Neil Long Acting Naltrexone Implant (OLANI) developed and produced in Australia by Go Medical Industries Pty Ltd [149, 156]. In contrast to the injectable formulation, this implantable treatment is surgically placed into the subcutaneous tissue, producing blood naltrexone levels above therapeutic levels of 2ng/ml for approximately 145 days, gradually decreasing to 1ng/ml by 214 days [145]. This preparation has also been shown to be superior to oral naltrexone in preventing return to regular heroin use in the 6 month following treatment [284].

A review of Australian coronial records between 2001 and 2004 identified five drug related fatalities in patients treated with implant naltrexone, suggesting the patients treated with implant naltrexone were not protected from overdose. Notably however the study only identified one fatality involving opioids in a patient with an implant less than 6 months old (which is the outer duration of the longest implant available in Australia) and the manufacturer of the implant was not identifiable [156].

Notwithstanding this, a study of 361 heroin dependent patients treated with the Go Medical implant observed a reduction in rates of non-fatal opioid overdoses requiring hospital admission from 5.5% in the 6 month prior to treatment to 0% in the first 6 months following treatment and 0.8% in the subsequent 6 months [157]. It was hypothesised that the implant’s slowly tapering release profile reduced fatal and non-fatal overdoses not only in the therapeutic period post treatment, but also post therapeutic period, where low levels of naltrexone have been demonstrated up to 12 plus months post treatment [145, 157].

Comparisons of mortality rates in heroin dependent persons treated with the Go Medical implant have found mortality rates to be comparable to both methadone (5.83 ptpy for methadone compared with 3.76 ptpy for implant naltrexone)[158] and buprenorphine (5.35 ptpy for buprenorphine compared with 3.00 ptpy for implant naltrexone) [159]. The sample size used in the naltrexone cohort in each of these studies was relatively small (341 and 255 patients respectively), limiting the ability to accurately assess change in mortality rates over time and the frequency of fatal opioid overdoses.

It may therefore be hypothesised that rate of opioid overdoses may be reduced in patients
treated with implant naltrexone as compared with patients treated with oral naltrexone.

The current study examined crude mortality rates in a large cohort of opioid dependent persons treated with oral or implant naltrexone. Additionally the study focused on deaths attributable to opioid and non-opioid drug mortality and suicide to determine whether there was evidence of an increase in all-cause and sub-group mortality in patients treated with implant compared with oral naltrexone.

**Methods**

**Subjects**

The study cohort consisted of 1467 patients treated with oral naltrexone, 1701 patients treated with implant naltrexone (OLANI) and 688 patients treated with both, at a community not-for-profit drug treatment clinic between August 1997 and December 2009. Patients included in the cohort were treated for problematic opioid use (most commonly heroin dependence) defined by self and clinically identified problems controlling the patient’s usage of opioids. Patients treated were predominantly male (61.25% oral and 62.87% implant), aged between 25 and 35 at the time of first treatment (27.24 ± 6.89 years for oral and 30.5 ± 7.71 years for implant) and between 30 to 40 years of age at the conclusion of the study (37.07 ± 6.99 years for oral and 35.41 ± 7.60 years for implant).

Patients were treated with oral naltrexone (prior to its registration in Australian in 2000) and implant naltrexone under the Therapeutic Goods Administration’s (TGA) Special Access Scheme which allows a physician to use a non-registered pharmaceutical product on a named patient basis to patients at an increased risk of morbidity or mortality. At present, implant naltrexone is only routinely used at a single clinic in Perth, Western Australia (WA) (the site examined in this study). While the site primarily treats WA patients, around 20% of all patients treated with implant come from interstate. Patients treated with oral naltrexone after 2000, following the registration of oral naltrexone in Australia, were prescribed oral naltrexone by a clinic physician.

In this study, an oral naltrexone treatment was defined as induction onto oral naltrexone. Patients were generally prescribed one 50mg tablet orally per day. In majority of cases, induction took place after rapid opioid detoxification (as described in [144]). An implant
naltrexone treatment was defined as the surgical insertion of a naltrexone implant/s (generally 1 to 3 implants). The implant composition and standard procedure used for the treatment of patients with this implant preparation have been described previously [285].

**Data Linkage**

Data from the two cohorts was submitted to the Australian Institute of Health and Welfare (AIHW), as a password protected document. The document contained the patient’s study ID, first given name, second given name, third given name, surname, gender, date of birth, date of last treatment, last known state of residence and the date of death (if known to be dead). Where patients were known by multiple names, multiple records were created for each known alias. Prior to submission, the two databases used to compile the data were cross-matched to detect abnormalities.

Once submitted to the AIHW, the patient database was cross referenced against the National Death Index (NDI), which lists all deaths occurring in Australia since 1980. Additionally, the database contains information on the death if Australians that occurred overseas, on the provision that the deaths are reported to the Australian Embassy of the country in which the death occurred. Data matching was undertaken by AIHW staff using the Integrity probabilistic matching software. For each potential match a weighting was assigned estimating likelihood of an accurate match. All potential matches were then manually checked. Matches with small discrepancies were re-checked against the patient’s file. Data provided by the AIHW included patient names, sex, date of birth, date of death, state registering the death, year of death registration, underlying cause of death and other causes of death. Cause of death (COD) was expressed as an ICD-10 code.

Subjects identified on the NDI registry that had died in Western Australia, but had not been assigned a COD were submitted to the Western Australia Registry of Births, Deaths and Marriages. COD was provided from the Registry as a single sentence summary. Clarification was sought for any ambiguous COD through the Coroner’s Court, for example to determine if an ‘acute combined respiratory drug effect’ involved the use of opioid or non-opioid drugs.
Data Analysis

Crude mortality rates were calculated using two approaches; initial treatment and all treatments, based on the separation of the patients into oral and implant naltrexone treatment groups. The initial treatment approach separated patients into oral and implant naltrexone treated patients based on their first naltrexone treatment. For patients who later moved on to the alternative treatment (i.e. changed from oral to implant), data collected after the new treatment was no longer included. In the all treatment approach, patients were separated into oral and implant naltrexone treatment group, with patients treated with both therapies were included in both treatment groups. In this method, the number of patient years attributed to each group was calculated from the commencement of a treatment to the commencement of the alternative treatment, with fatality assigned to the most recent treatment.

Additionally, age specific, age standardised, gender specific and cause specific mortality rates were calculated for patients in the oral and implant naltrexone treatment groups using the all treatment approach (with the exception of gender which was carried out using both methods). Age standardised mortality rates (ASM) were calculated using data obtained from the Australian Bureau of Statistics (ABS) on the age demographic of Australians aged between 18 and 75 in June of 2009 [286]. Cause specific mortality was examined for deaths associated with the three main causes of interest; opioid poisoning (T40.0–T40.4/T40.6/X42/X62/Y12), non-opioid poisoning (T40.5/T40.7-T40.9/T41.2/T42.3/T42.7/T43.0-T43.2/T43.6/T43.8/T51-T53/T59.0/T59.8/T59.9/T65.2/T65.3/T65.6/X41/X44/X45/X46/X49/X61/X65/X66/X69/Y11/Y14/Y15/Y16/Y19) and suicide/self-harm (X60 – X84/X87.0) using ICD-10 codes assigned to the fatalities.

Mortality rates were also calculated in terms of time following treatment. For the first 12 months following treatment, mortality rates were examined for 4 monthly periods. Following this, yearly periods were examined for 1 to 5 years and then for greater than 5 years for both treatment groups. The time following treatment was calculated as the period from the treatment date to the next treatment event or the end of the study if there was no subsequent event.

Confidence intervals (95%) were calculated for each of the mortality rates. A two-tailed Z test was used to compare mortality rates. A p-critical value of 0.05 was used.
the date of death was unascertainable the midpoint of the range given on the death certificate was used.

_Ethics_

This study protocol was reviewed and approved by Bellberry Human Research Ethics Committee (A148/08), and the AIHW Ethics Committee (EC 2010/1/7). Reciprocal approval was also ascertained from the University of Western Australia Human Research Ethics Committee (RA/4/1/4043).

**Results**

Oral patients were followed for a total of 17,207 patient years, in which 3,768 oral treatments were delivered, with an average of 1.75 ± 1.23 treatments per oral patient. The implant patients were followed for 11,678 patient years, and treated with 4,724 implant treatments, with an average of 1.97 ± 1.59 per implant patient. Oral patients were followed up for an average of 7.98 ± 3.94 years, while implant patients were followed up for an average of 4.88 ± 2.66.

_Crude Mortality_

For the 3,856 patients submitted to the AIHW, 228 fatalities were identified in the NDI following manual checking of the matches. 77 deaths attributed to the implant naltrexone group and 151 attributed to the oral naltrexone group. Mortality rates in patients whose first treatment was oral naltrexone were not significantly different to patients who were first treated with implant naltrexone (p = 0.1117), however using all treatments there was a significant difference (p = 0.0339) (Table 3).
Table 3: Crude and gender specific mortality rates for patients treated with oral or implant naltrexone (95% confidence intervals).

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral initial</td>
<td>8.92 (7.50 – 10.33)</td>
<td>9.84 (7.94 – 11.74)</td>
<td>7.46 (5.38 – 9.54)*</td>
</tr>
<tr>
<td>Implant initial</td>
<td>7.00 (5.10 – 8.89)</td>
<td>8.58 (5.93 – 11.23)*</td>
<td>4.32 (1.88 – 6.75)*</td>
</tr>
<tr>
<td>Oral all</td>
<td>8.78 (7.38 – 10.17)*</td>
<td>9.69 (7.82 – 11.56)</td>
<td>7.34 (5.29 – 9.38)*</td>
</tr>
<tr>
<td>Implant all</td>
<td>6.59 (5.13 – 8.06)*</td>
<td>8.40 (6.41 – 10.42)*</td>
<td>3.75 (1.97 – 5.53)*</td>
</tr>
</tbody>
</table>

* Significantly different (p < 0.05)

**Gender and Age Specific Mortality**

In patients treated with oral naltrexone, no significant difference was observed in gender specific mortality rates. However, females treated with implant naltrexone had a significantly lower mortality rate than males treated with the implant (p = 0.0010) (Table 4). A significant difference was observed in the youngest of the 5 age brackets (p = 0.0135), however there was no difference in the remainder. Age standardised mortality rates accentuated differences in crude mortality rates with 26.78 ptpy for oral patients (CI: 24.37 – 29.19) and 13.77 ptpy of implant patients (CI: 11.66 – 15.88).

Table 4: Age specific mortality rates in patients treated with oral or implant naltrexone, expressed ptpy.

<table>
<thead>
<tr>
<th></th>
<th>Oral</th>
<th>Implant</th>
</tr>
</thead>
<tbody>
<tr>
<td>18 ≥ age &gt; 25</td>
<td>10.27 (6.61 – 13.92)*</td>
<td>4.22 (1.10 – 7.33)*</td>
</tr>
<tr>
<td>25 ≥ age &gt; 35</td>
<td>7.74 (5.93 – 9.54)</td>
<td>6.92 (4.86 – 8.98)</td>
</tr>
<tr>
<td>35 ≥ age &gt; 45</td>
<td>9.08 (6.20 – 11.95)</td>
<td>5.79 (2.96 – 8.62)</td>
</tr>
<tr>
<td>45 ≥ age &gt; 55</td>
<td>9.01 (3.15 – 14.87)</td>
<td>8.40 (2.60 – 14.19)</td>
</tr>
<tr>
<td>≥ 56</td>
<td>77.68 (4.57 – 150.80)</td>
<td>34.60 (-3.87 – 73.07)</td>
</tr>
</tbody>
</table>

* Significantly different (p<0.05)
**Time Following Treatment**

In the first 4 months following treatment, mortality rates in oral naltrexone treated patients were significantly higher than patients treated with implant naltrexone (26.28 ptpy in oral compared with 7.34 ptpy in implant). In subsequent time periods there was only a significant difference between the treatments in 8 to 12 months (p=0.0010) (Figure 1).

![Mortality rates following treatment with oral (■) and implant (■) naltrexone.](image)

**Cause Morbidity**

Of the 228 fatalities recorded, 206 (90.4%) had a recorded cause of death, equating to 0.64 ptpys for the oral group and 1.03 ptpy for the implant group. Overdoses involving opioids, overdoses involving non-opioid drugs and suicide were the three most common causes of death (Table 5). No significant difference was noted between the two groups in the rate of each of the causes.
Table 5: Cause of death associated with patients treated with oral and implant naltrexone for drug dependence.

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Oral</th>
<th>Implant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overdose involving opioids</td>
<td>3.78</td>
<td>2.40</td>
</tr>
<tr>
<td>Overdose involving non opioid drugs</td>
<td>3.31</td>
<td>2.06</td>
</tr>
<tr>
<td>Drug overdose (opioids and/or non-opioid drugs)</td>
<td>5.00</td>
<td>3.25</td>
</tr>
<tr>
<td>Suicide</td>
<td>1.51</td>
<td>1.11</td>
</tr>
<tr>
<td>Unknown</td>
<td>0.64</td>
<td>1.03</td>
</tr>
</tbody>
</table>

The large increase in mortality observed in the first four months following treatment with oral naltrexone was primarily due to very high levels of opioid overdose fatalities, with rates of overdose death 25 times that observed in the implant treatment group for the same period (17.22 ptpy for oral compared with 0.67 ptpy for implant patients) (*p < 0.0001*). The statistical difference in opioid overdose mortality was apparent for the first 12 months following treatment, after which the difference was no longer apparent (Figure 2).
Morbidity and mortality in patients with opioid use disorders and their children following treatment/exposure to implant naltrexone

Figure 2: Opioid overdose (top), non-opioid drug overdose (middle) and suicide (bottom) mortality rates in patients treated with oral naltrexone (◻) and implant naltrexone (◼).
Notably in young patients (18 – 25 years), mortality associated with opioid overdose made up half of the total mortality rate in patients treated with oral naltrexone (5.13 ptpy), far greater than any of the other age brackets. In contrast there was no mortality associated with opioid overdose in young patients treated with implant naltrexone.

A single opioid fatality was detected within the first 4 months following treatment with implant naltrexone. The coroner’s report provided a primary diagnosis of acute opioid toxicity, with blood morphine levels of 16ng/ml (total) and 13ng/ml (free) (a ratio of 1.23 indicating a rapid overdose [287]), diazepam (0.7ng/ml), desmethyldiazepam (0.9 ng/ml), temazepam (0.03ng/ml), oxazepam (0.06ng/ml), tetrahydrocannabinol (0.9 ng/ml) and carboxytetrahydrocannabinol (95ug/L). Trace amounts of methamphetamines and amphetamines were also detected. Naltrexone was still present at levels of approximately 3ng/ml and 6-beta-naltrexol at approximately 23ng/ml.

Discussion

Crude Mortality

Mortality rates were found to be significantly higher in patients treated with oral naltrexone as compared to those treated with implant naltrexone. While crude mortality rates in patients treated with oral naltrexone were similar to previously published rates [118, 150], those for patients treated with implant naltrexone were higher than results published from two smaller studies assessing mortality outcomes associated with the same naltrexone implant preparation [158, 159]. Crude mortality rates for both oral or implant treatments were comparable to other pharmacotherapies for the treatment of opioid dependence including methadone and buprenorphine [152-154].

Gender and Age Specific Mortality

Rates of mortality were found to be significantly lower in females and young patients treated with implant naltrexone as compared with the oral alternatives. The low rate of mortality in young patients was treated with implant naltrexone was associated with a reduction in opioid overdose deaths. Rates of mortality in females treated with implant naltrexone also were significantly lower than males in the same treatment. Such figures match with the increased rate of risky behaviour, overdose, successful suicide and greater lack of concern regarding
health care associated with males and have been reported in other drug using populations [94, 154, 288].

Time Following Treatment

Comparison of the two treatments during the first four months following treatment, showed patients treated with implant naltrexone had significantly lower mortality rates (7.34ptpy) compared to those treated with the oral naltrexone (26.28ptpy). While patients treated with implant naltrexone would have maintained blood naltrexone levels at a therapeutic range for the first 4 months following treatment (unless the implant had been removed), the period in which oral patients remained compliant with medication is undeterminable. The length of time spent on oral naltrexone treatment is variable with patient compliance ranging from only a few days to 6 months or more [132, 289]. Hulse and Basso (2000) found that at 6 months following induction on to oral naltrexone, 51% of patients were still taking the medication daily. However of these patients 65% had stopped using naltrexone and used heroin before returning to the naltrexone program [132]. It is likely that the high rates of overdose were associated with the cessation of oral naltrexone treatment.

The notable early increased rate of mortality following induction onto oral naltrexone is similar to methadone, which has been observed to have an increased rate of mortality in the 2 weeks following induction onto the treatment (up to 94.47ptpy) [150, 158, 290] and following cessation (up to 48ptpy) [94, 154]. The initial increase in mortality associated with oral naltrexone is likely the result of treatment termination and return to opioid use, unlike methadone where increased early mortality generally attributed to difficulty in determining a safe and effective starting dose (i.e. patient variation in methadone tolerance, metabolism and excretion) and the concurrent use of other CNS depressant drugs such as benzodiazepines [115, 291]

Cause of Death

Opioid overdose was a major cause of death in the first year following treatment with oral naltrexone, while it contributed to only a small number of fatalities in patients treated with implant naltrexone. Such results concur with the previously published results indicating high rates of mortality following cessation of the oral treatment (high rates of opioid overdose death) [118, 150] and support the use of a gradually tapering sustained release naltrexone
preparation in preference to the oral formulation to reduce the occurrence of fatal opioid overdoses.

Although opioid overdose death was identified in a patient treated with implant naltrexone with therapeutic naltrexone blood levels (generally accepted as 1 to 2ng/ml) [292], blood morphine levels in this patient were more than 22 times the mean total morphine concentration observed in 10 fatalities involving intravenous use of morphine, with no other drugs present (mean 0.7ng/ml, range 0.2–2.3ng/ml) [293]. Furthermore, numerous other drugs were also present at therapeutic, sub-therapeutic levels or recreational levels. In conclusion, data suggests that while opioid overdoses can occur in patients treated with implantable naltrexone in the first four months following treatment, they are generally rare and require excessive levels of opioids with likely contribution from other drugs. This is consistent with previous research by Comer et al. (2002), demonstrating that very high doses of opioids can compete with naltrexone to produce opioid-effects [126].

Similarly, non-opioid drug mortality rates in patients treated with oral naltrexone in the first four months following induction were higher than patients treated with implant naltrexone. The high level of non-opioid overdose may correspond with the high rate of combination non-opioid and opioid overdose, with the two classifications not being mutually exclusive.

The data showed no evidence to support high rates of suicide in patients treated with either oral or implant naltrexone. While suicide rates were higher than reported for the general public, they were in line with previously published rates in opioid using populations or patients in opioid pharmacotherapies [74, 116, 152].

Limitations

Mortality rates obtained in this study should be considered the minimum with patients using a different name at the time of treatment, and fatalities occurring overseas possibly missed.

Additionally differences between the two treatment groups exist. Most notably, oral treatments were predominantly carried out between 1997 and 2001. For this reason, the length of follow up for patients treated with oral naltrexone was longer than those treated with implant naltrexone. Additionally, many oral patients were later treated with implant naltrexone, while very few implant patients reverted to oral naltrexone treatment.
While the data shows the implant preparation to be associated with significantly less patient mortality than patients treated with oral naltrexone, this may not be true for all sustained release naltrexone preparations. The ability of the Go Medical implant to reduce opioid overdose may be attributable to the slowly tapering pharmacokinetic profile, which provides a long-term prophylaxis against accidental opioid overdose. In contrast, shorter acting sustained release naltrexone preparations whose levels peak in the days following treatment and then drop below sub-therapeutic levels by 30 days may not offer the same level of protection.

**Conclusions**

The use of implant naltrexone appears to mitigate increases in mortality that are observed following cessation of oral naltrexone and reduce the risk of opioid overdose death in the first year following treatment. Given the reduction in mortality and previously demonstrated improved clinical efficacy of this implant naltrexone preparation compared to oral naltrexone [284], this implant has significant promise for advancing the “safe” management of opioid use disorders above that achieved by the use of oral naltrexone.
5. Morbidity and Mortality in Opioid Dependent Patients

Treated with Implant Naltrexone, Methadone and Buprenorphine

5.1. Forward

This chapter investigates morbidity and mortality in patients treated with implant naltrexone compared to the two most commonly used opioid pharmacotherapies: methadone and buprenorphine. Specifically it asks:

1. Are mortality rates in patients treated with implant naltrexone comparable to mortality rates in patients treated with methadone, or buprenorphine?
2. How does morbidity compare in patients treated with sustained release naltrexone implant to those treated with methadone or buprenorphine?

This chapter also looks more closely at two common causes of morbidity and mortality in opioid dependent patients: opioid overdose and mental illness, and how the three treatments compare. This chapter is comprised of four papers.
5.2. **Paper 2: A retrospective cohort study of mortality rates in opioid dependent patients treated with implant naltrexone, oral methadone or sublingual buprenorphine**

**Abstract**

**Aims:** To examine and compare mortality rates in opioid dependent patients treated with implant naltrexone, to those treated with methadone or buprenorphine.

**Methods:** Patients treated with implant naltrexone (n=1461), methadone (n=3515) or buprenorphine (n=3250) for the first time between 2001 and 2010 in Western Australia (WA) were cross‐matched against the WA Death Registry.

**Results:** Crude mortality rates in patients treated with implant naltrexone were not significantly different to either methadone (HR: 1.13, CI: 0.82 – 1.55, \(p = 0.447\)) or buprenorphine (HR: 1.01, CI: 0.72 – 1.42, \(p = 0.948\)). Similarly no difference observed between the three treatments in terms of cause specific or age specific mortality, however high rates of mortality were observed in methadone treated patients during the first 28 days of treatment (HR: 8.19, CI: 1.08 – 62.21, \(p = 0.042\), and in female patients treated with methadone (HR: 2.96, CI: 1.34 – 6.51, \(p = 0.007\)) compared with naltrexone treated patients.

**Conclusions:** Crude mortality in opioid dependent patients treated with implant naltrexone is comparable to both methadone and buprenorphine, however during the first 28 days and in females patients, naltrexone was associated with a lower mortality rates compared with methadone patients.

**Introduction**

Illicit opioid use is associated with high rates of mortality, as a result of the drug itself (and the co-ingestion of other substances) and the associated lifestyle. Estimates of mortality rates in heroin using populations, one of most commonly used illicit opioids, range from 6.8 to 77.6 per 1000 patients years (ptpy)[20]. While treating patients with an opioid use disorder generally reduces the risk of death in the long term, treatment can often be associated with short periods in which the risk is increased [94, 95]. These periods are usually associated with (i) changes in the use of opioid, i.e. moving from heroin to methadone [94], (ii) changes in
tolerance, i.e. detoxification/cessation of opioids [47], or (iii) removal of protective influences, i.e. release from prison, leaving residential rehabilitation [46, 96] or ceasing treatment [94, 150, 294].

The use of the long acting opioid agonist, methadone, has long been the best known medical treatment for opioid use disorders as part of a risk minimization strategy. While methadone has been shown to improve health and social outcomes [84], induction onto methadone and cessation of treatment has been associated with high rates of mortality [94, 291]. In an Australian study, rates of fatal accidental drug toxicity in the first two weeks following induction onto methadone was 70.4 ptpy, as compared with 0.72 deaths ptpy in the subsequent stable treatment period [291].

The use of buprenorphine, a partial agonist/antagonist of the opioid receptor, has arisen as an alternative to methadone. Buprenorphine has a higher affinity for the mu opioid than full agonist and can thus blocks or significantly reduce the effects of mu opioids. Additionally, the antagonist component creates a ‘ceiling’ on the maximum opioid activity so that vital functions such as respiration are protected [111]. As an additional safe guard, buprenorphine is available alone (Subutex ®) or in combination with the naloxone (Suboxone ®). The addition of naloxone, which works to block opioid receptors and precipitate withdrawal in dependent users when administered intravenously, reducing the incentive for intravenous diversion of the sublingual formulation [295]. These protective features are thought to contribute a reduction in opioid poisoning in buprenorphine patients as compared with those on methadone [114, 115]. However the risk of fatal opioid poisoning is not completely removed with the use of buprenorphine, especially in combination with other drugs such as benzodiazepines and alcohol which also depress respiratory function [115, 116].

Naltrexone is also registered for the treatment of opioid use disorders. In contrast to methadone and buprenorphine, naltrexone is a pure opioid antagonist, blocking the effects of opioids. The use of oral naltrexone has struggled clinically, with a lack of patient compliance with the once daily formulation reducing clinical efficacy. Additionally, immediately following cessation of oral naltrexone, increases in mortality, predominately as the result of fatal opioid poisoning, has been reported [150, 296]. To mitigate issues with compliance, several longer acting preparations have been developed. One such preparation, a subcutaneous implant, provides therapeutic naltrexone blood levels for up to 188 days following a single treatment
Morbidity and mortality in patients with opioid use disorders and their children following treatment/exposure to implant naltrexone [145, 216]. The use of this implant preparation does not appear to be associated with periods of increase mortality following this treatment period, presumably due to slowly tapering release profile [296]. While crude mortality rates in opioid dependent patients treated with this implant have been comparable to methadone and buprenorphine [158, 159, 296], criticism has arisen that a direct comparisons of mortality have not yet been carried out [297]. In this study, mortality in opioid dependent patients treated with implant naltrexone were compared to patients treated with methadone, or buprenorphine.

Materials and methods

Study Design
This study was a retrospective longitudinal follow up of opioid dependent patients treated with implant naltrexone (n = 1461), methadone (n = 3515), and/or buprenorphine (n = 3250) using state death records data to identify fatalities.

Subjects
Opioid dependent patients treated with methadone or buprenorphine (Subutex or Suboxone) for the first time in Western Australia (WA) between January 2001 and December 2010 were identified using the WA Department of Health’s Monitoring of Drugs of Dependence System (MODDS). Naltrexone implant patients were selected from records of opioid dependent patients treated at a drug and alcohol clinic in WA during the same period. Patient self-selected their treated. All eligible patients were above the age of 18 and residing in WA at the time of first treatment.

Data Collection
Data from the MODDS provided monthly records indicating a patient had received treatment within that month. Consecutive months were joined to form treatment periods. The data was then matched against the Authorization Database, which provided the date in which the patient was authorised to receive treatment and the date treatment was terminated. For period without an authorisation date, the commencement date was assigned the 15th of the month unless that fatality occurred before this date and then the 1st of the month was used. The termination date was assigned the last day of the month.

Linked data from WA Mortality Register was sourced via the WA Data Linkage System from January 2001 to December 2012 [275]. This included date and cause(s) of death (ICD-10-AM codes). Additionally, toxicology data from the WA Coroner’s Court was sourced for patients
who had died of alcohol or other drug poisoning. Toxicology reports were used to more accurately identify the drugs involved in each fatality.

Data Analysis
Crude mortality rates in patients treated with implant naltrexone were compared to patients treated with methadone or buprenorphine using Cox proportional hazard regression. Patients may have been treated with more than one treatment, and changing treatments was accounted for in the analysis, however treatments were excluded if the patient was on more than one treatment at that time. In addition to analysis of crude mortality rates, gender specific, age specific (age at the commencement) and cause specific mortality rates were compared.

Cause-specific mortality rates were examined based on the ICD codes assigned to each fatality (both primary and secondary causes were utilised, with up to nine ICD-codes available for each death) or the description of the cause of death if ICD-10 codes were unavailable. These causes included: opioid poisoning (T40.0–T40.4), non-opioid drug and alcohol poisoning (T36-39.9, T40.5-51), suicide (X60–X84, Y87.0), respiratory disease (J00 – J99), cardiovascular disease (I00 – I99), traffic/transport related (V00 – V99), and cancer (C00 – C99).

Mortality rates were also calculated based on the treatment phase: Induction period, on treatment, and off treatment. The induction period included the first 28 days of treatment, as this is considered a high-risk period particularly for patients on methadone. The on treatment period commenced at day 29 and for methadone and buprenorphine ceased at the termination date. For naltrexone the end of the on treatment period was 182 days post implantation, based on the pharmacokinetic profile of the implant and efficacy data [145, 146, 298]. However, due to patient variation in metabolism of naltrexone, if a patient transitioned onto methadone or buprenorphine between 121 and 181 days, this was used as the treatment period, as it was assumed that to transition onto either treatment naltrexone levels would need to be negligible. In two fatalities, methadone was present at therapeutic doses within a week of the patients having ceased methadone. However, the treatment data suggested they only received one day of treatment. It was deemed most likely that these patients were still on treatment at the time of death. The off treatment period commenced following the cessation of the treatment and continued until the patient received a new treatment, died or 31st of December 2012.
**Ethics**

This study protocol was reviewed and approved by the Department of Health Human Research Ethics Committee (2012/63) and the University of Western Australia Human Research Ethics Committee (RA/4/1/1864).

**Results**

The three cohorts had greater number of male to female, with first treatment generally commencing in their late 20’s and early 30’s (Table 6). Of the patients treated with an opioid pharmacotherapy, 29.7% of patients had been on two pharmacotherapies, while 8.3% had been on all three pharmacotherapies.

Table 6: Demographics of opioid dependent patients treated with implant naltrexone, methadone, and buprenorphine.

<table>
<thead>
<tr>
<th></th>
<th>Naltrexone</th>
<th>Methadone</th>
<th>Buprenorphine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>1461</td>
<td>3515</td>
<td>3250</td>
</tr>
<tr>
<td>% Male</td>
<td>64.4</td>
<td>66.7</td>
<td>65.5</td>
</tr>
<tr>
<td>Age ± st dev.</td>
<td>30.3 ± 7.9</td>
<td>31.9 ± 8.4</td>
<td>31.5 ± 8.3</td>
</tr>
<tr>
<td>Period of exposure (yrs)¹</td>
<td>1.0 ± 0.8</td>
<td>2.5 ± 2.6</td>
<td>1.9 ± 2.4</td>
</tr>
<tr>
<td>Period of follow up (yrs)</td>
<td>4.9 ± 3.3</td>
<td>5.5 ± 3.3</td>
<td>4.5 ± 3.4</td>
</tr>
</tbody>
</table>

St dev. = standard deviation, yrs = years

1. Including transition period

Crude mortality rates in patients treated with implant naltrexone were not significantly different to methadone (HR: 1.13, CI: 0.82 – 1.55, p = 0.447) or buprenorphine (HR: 1.01, CI: 0.72 – 1.42, p = 0.948) (Figure 3). There was also no significant difference between naltrexone and buprenorphine during the induction period, while on treatment or off treatment. However during the induction period, rates of mortality in methadone treated patients were significantly higher than naltrexone (HR 8.19, CI: 1.08 – 62.21, p = 0.042). During on-treatment and off treatment there was no significant difference between naltrexone and methadone mortality rates. While mortality rates increased with increasing age, there was no significant difference between naltrexone and methadone or buprenorphine in any of the age groups (Table 7).
There was no difference in risk of mortality in males treated with naltrexone compared with those treated with methadone (HR: 0.83, CI: 0.58 – 1.18, p = 0.300) or buprenorphine (HR: 0.83, CI: 0.57 – 1.20, p = 0.323). However, female patients treated with naltrexone had a significantly lower mortality rates compared with methadone (HR: 2.96, CI: 1.34 – 6.51, p = 0.007), but were not significantly different to buprenorphine (HR: 2.03, CI: 0.88 – 4.64, p = 0.095). The difference in mortality rates in females treated with methadone and naltrexone were not associated with difference in mortality as a result of opioid poisoning, non-opioid drug poisoning or suicide.

Rates of opioid poisoning in naltrexone treated patients were not significantly different to patients treated with methadone (HR: 0.67, CI: 0.42 – 1.08) or buprenorphine (HR: 0.77, CI: 0.47 – 1.26). Similarly, there was no significant difference between naltrexone and methadone or buprenorphine in terms of any of the causes of death examined (Table 7).
Table 7: Mortality rates in opioid dependent patients treated with implant naltrexone compared with patients treated with methadone or buprenorphine (per 1000 patient years).

<table>
<thead>
<tr>
<th></th>
<th>Naltrexone</th>
<th>Methadone</th>
<th>Buprenorphine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crude mortality</td>
<td>7.1 (5.3 – 9.4)</td>
<td>8.1 (6.9 – 9.5)</td>
<td>7.2 (5.9 – 8.7)</td>
</tr>
<tr>
<td>Treatment periods</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Induction</td>
<td>4.3 (0.1 – 24.1)</td>
<td>32.3 (18.5 – 52.5)</td>
<td>4.1 (0.5 – 14.9)</td>
</tr>
<tr>
<td>On treatment</td>
<td>6.5 (2.8 – 12.9)</td>
<td>5.1 (3.7 – 6.9)</td>
<td>4.6 (3.0 – 6.7)</td>
</tr>
<tr>
<td>Off treatment</td>
<td>7.4 (5.3 – 10.0)</td>
<td>9.4 (7.6 – 11.4)</td>
<td>9.1 (7.2 – 11.3)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>2.7 (1.1 – 5.6)</td>
<td>8.1 (6.1 – 10.6)</td>
<td>5.6 (3.7 – 8.1)</td>
</tr>
<tr>
<td>Male</td>
<td>9.7 (7.0 – 13.0)</td>
<td>8.1 (6.6 – 9.8)</td>
<td>8.0 (6.3 – 10.0)</td>
</tr>
<tr>
<td>Age of treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 – 25</td>
<td>3.6 (1.3 – 7.8)</td>
<td>6.1 (3.9 – 9.0)</td>
<td>5.2 (3.0 – 8.4)</td>
</tr>
<tr>
<td>26 – 35</td>
<td>7.9 (5.2 – 11.4)</td>
<td>7.5 (5.8 – 9.5)</td>
<td>5.9 (4.2 – 8.0)</td>
</tr>
<tr>
<td>36 – 45</td>
<td>8.2 (4.1 – 14.7)</td>
<td>9.2 (6.6 – 12.5)</td>
<td>9.6 (6.7 – 13.4)</td>
</tr>
<tr>
<td>46+</td>
<td>10.8 (4.0 – 23.5)</td>
<td>13.2 (8.5 – 19.7)</td>
<td>12.6 (7.0 – 20.8)</td>
</tr>
<tr>
<td>Cause</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opioids</td>
<td>3.9 (2.5 – 5.6)</td>
<td>2.9 (2.2 – 3.8)</td>
<td>3.3 (2.4 – 4.3)</td>
</tr>
<tr>
<td>Non-opioid drugs</td>
<td>2.7 (1.6 – 4.2)</td>
<td>2.9 (2.2 – 3.7)</td>
<td>2.5 (1.8 – 3.5)</td>
</tr>
<tr>
<td>Suicide</td>
<td>1.3 (0.6 – 2.4)</td>
<td>1.2 (0.7 – 1.8)</td>
<td>0.9 (0.5 – 1.5)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>1.3 (0.6 – 2.4)</td>
<td>1.0 (0.6 – 1.5)</td>
<td>0.7 (0.4 – 1.3)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>0.6 (0.2 – 1.5)</td>
<td>0.9 (0.5 – 1.4)</td>
<td>0.8 (0.4 – 1.4)</td>
</tr>
<tr>
<td>Traffic</td>
<td>0.6 (0.2 – 1.5)</td>
<td>0.3 (0.1 – 0.7)</td>
<td>0.3 (0.1 – 0.7)</td>
</tr>
<tr>
<td>Cancer</td>
<td>0.4 (0.1 – 1.3)</td>
<td>0.4 (0.1 – 0.7)</td>
<td>0.4 (0.1 – 0.9)</td>
</tr>
<tr>
<td>Unknown</td>
<td>0.9 (0.3 – 1.9)</td>
<td>1.6 (1.1 – 2.30)</td>
<td>0.6 (0.3 – 1.2)</td>
</tr>
</tbody>
</table>

* p < 0.05, ** p < 0.01 (compared with naltrexone treated patients, no adjustment has been made for multiple comparisons)

Discussion

In terms of mortality, implant naltrexone appeared to be a safe alternative to methadone and buprenorphine in the treatment of opioid dependent patients. Crude mortality rates in patients treated with implant naltrexone were not significantly different to patients treated with either methadone or buprenorphine. Similarly, while stable on treatment and off
treatment naltrexone was not shown to be different to either of the two comparison pharmacotherapies. Rates of mortality in methadone and buprenorphine treated patients were consistent with previously published rates [299].

Naltrexone was not associated with elevated rates of mortality observed in methadone treated patients in the first 28 days of treatment. As per this study, high rates of mortality was observed in patients during induction onto methadone. High rates of mortality in the weeks following induction onto methadone has been documented in a number of studies and are generally the result of increase rates of opioid poisoning [158, 291, 300]. High rates of fatal opioid poisoning during induction onto methadone may be reduced with patient training and dispensing of emergency naloxone to patients and/or close family and friends.

The risk of mortality in women treated with methadone was almost 3 times that of women treated with implant naltrexone. Surprisingly, the reduction in mortality was not associated with a reduction in any of the three main causes of dead: opioid poisoning, non-opioid drug poisoning and suicide. In general mortality rates in females are considered to be less than for males, with a systematic review of patients dependent on opioids (including methadone) finding mortality rates in males to be 1.3 times that of females, with the difference primarily attributed males having 1.7 times more opioid deaths than females [20]. While this held true for both naltrexone and buprenorphine patients, with lower rates of female mortality, rates in methadone were very similar in the two sexes (8.1 ptpy in females compared with 8.0 ptpy in males).

**Strength and limitations of the study**

This is the first direct comparison between mortality rates in opioid dependent patients treated with implant naltrexone, methadone and buprenorphine, and was able to incorporate all opioid dependent patients entering treatment for the first time between 2001 and 2010. However by utilising state health mortality data fatalities that occurred outside of WA may not have been included. Rates of cause specific mortality should also be taken as a minimum due to the high rate of death without a given cause of death.

Treatment was self-selected by the patients, thus significant and confounding difference between the three opioid pharmacotherapies may be present. For example, patients treated with implant naltrexone may have been more motivated to become opioid abstinent as they selected an opioid abstinence therapy rather than a maintenance therapy. Similarly implant
naltrexone patients may represent patients more willing to take risks, as demonstrated by a desire to try a new and currently unregistered treatment. Where possible, factors such as age and gender difference were controlled for. This selection bias may limit how these results can be generalised to other populations.

Conclusions
Implant naltrexone appears to be a safe alternative to methadone and buprenorphine in terms of mortality in the treatment of opioid dependence. Naltrexone was superior to methadone during the first 28 days and in the treatment of females patients compared with methadone.
5.3. Paper 3: Rates of hospital and emergency department attendances in opioid dependent patients treated with implant naltrexone, methadone or buprenorphine

Abstract

Aims: To compare rates of morbidity in opioid dependent patients treated implant naltrexone, methadone, and buprenorphine.

Methods: Treatment records for opioid dependent patients treated with implant naltrexone, methadone or buprenorphine were linked with routine, prospectively collected health data sets. Rates of hospital and ED attendances were calculated for each cohort and compared using Generalized Estimating Equations.

Results: Compared with rates of pre-treatment, following the commencement of treatment there was no significant decrease in rates of hospital admissions in patients treated methadone or naltrexone, however rates increased in patients treated with buprenorphine. ED attendances for both methadone and buprenorphine showed a significant reduction following the commencement of treatment, while ED attendance in naltrexone was not significantly different to pre-treatment rates.

Following the commencement of treatment, rates of hospitalizations was significantly higher in patients treated with implant naltrexone compared with both methadone (RR: 0.83, CI: 0.77 – 0.89) and buprenorphine (RR: 0.92, CI: 0.85 – 0.99), as were rates of ED attendances in methadone treated patients (RR: 0.85, CI: 0.78 – 0.92), while rates of ED attendances in buprenorphine patients were comparable (RR: 0.92, CI: 0.85 – 1.01). The difference was largely attributable to the induction period (0 – 28 days), where rates of hospital and ED attendances in naltrexone treated patients were almost double that of both methadone and buprenorphine. However after the initial period and following the cessation of treatment, rates of hospital and ED attendances in naltrexone treated patients were less than or equivalent to methadone or buprenorphine patients.
Conclusions: Rates of morbidity in opioid dependent patients treated with implant naltrexone were significantly elevated compared with methadone and buprenorphine in the first 28 days of treatment, however are comparable after this initial period.

Introduction

The use of illicit opioid is associated with high levels of morbidity and mortality, both as a result of drug use and the accompanying lifestyle. In 2010, opioid dependence was estimated to result in 7.2 million years of life lived with a disability, and 2.0 million years of life lost globally [21].

While alternatives exist such as rehabilitation programs and counselling, the treatment of opioid use disorders has largely been based around a number of well-established pharmacotherapies including methadone, buprenorphine and more recently, in some jurisdictions, sustained release naltrexone. The three treatments largely work by acting on the opioid receptors, with either agonist or antagonist activity or both.

Methadone, a pure opioid agonist delivered orally, has historically been considered the first line treatment for opioid use disorders, with well documented safety and efficacy. In a Cochrane review of 11 randomised clinical trials, methadone maintenance treatment (MMT) was shown to significantly improve retention to treatment (RR: 4.44, CI: 3.26 – 6.04) and reduce both self-reported and urine/hair measure of heroin use (RR: 0.66, CI: 0.56 – 0.78) compared with a non-pharmacological approach [86]. While the benefits of MMT are numerous, safety concerns have also arisen in regards to treatment associated morbidity and mortality, including high rates of fatal and non-fatal opioid overdoses during induction and cessation, increased risk of cardiovascular disorders [97, 98], low bone density [100], dental disease [101], and amenorrhea and oligomenorrhea [105-108].

Buprenorphine is a partial agonist/antagonist administered sublingually. The antagonist features provide some protection against opioid overdoses, while the agonist properties provide positive reinforcing effects that assists with daily compliance [113-115]. However, while the risk of fatal opioid overdose is reduced, it is not completely removed, especially when buprenorphine is used in combination with other respiratory depressants such as benzodiazepines, alcohol and other opioids [115-117]. A Cochrane review of buprenorphine showed that at fixed high and medium doses buprenorphine is equivalent to methadone in retaining patients in treatment and suppressing illicit opioid use, however when flexible or low
doses (2 – 6 mg per day) are used, patient retention is superior in methadone treated patients [125]. While generally regarded as a relatively safe drug [114, 118], concerns have arisen regarding the intravenous diversion of the sublingual preparation, resulting in abscesses, cellulitis, thrombosis, phlebitis ulcers, gangrene, ischaemia and infections [120-122]. Additionally if the diversion occurs after the sublingual tablet has been placed in the mouth there is a risk of systemic fungal and bacterial infections from contamination with mouth flora [123].

Naltrexone is a pure opioid antagonist. Naltrexone has a well characterised safety profile and is generally associated with minimal side effects, however the absence of a positive reinforcing effect has made patient compliance with once daily oral medication difficult, resulting in safety and efficacy issues [133, 301]. A number of sustained release naltrexone preparations have been developed to overcome non-compliance issues and research thus far has shown improved efficacy outcomes compared with oral naltrexone, and generally positive outcomes in terms of safety [146, 147, 296, 302]. Notwithstanding, a number of concerns still exist regarding the safety of sustained release naltrexone preparations including (i) use of non-opioid drugs as a substitute for opioids during treatment, (ii) risk of depression and/or suicide as a result of the blockade of endogenous opioids, and (iii) safety of the method of delivery (i.e. subcutaneous or intramuscular), and (iv) risk of opioid overdoses following treatment cessation when patient tolerance has been diminished [143, 149, 303]. While a number of small studies have been carried out examining the health of patients following treatment [302], a direct large scale comparison between implant naltrexone and methadone or buprenorphine has not yet been reported. Additionally, a comparison between patients treated with implant naltrexone and the general population has not been reported.

The study examined the rates of health events in opioid dependent treated with implant naltrexone and compared them with health events in opioid dependent patients treated with methadone or buprenorphine.

Materials and Methods

Subjects

Opioid dependent patients treated with methadone, buprenorphine or implant naltrexone for the first time between January 2001 and December 2010 in Western Australia (WA) were obtained from treatment records. Methadone and buprenorphine prescriptions were
extracted from the Monitoring of Drugs of Dependence System (MODDS), a state wide record of all individuals prescribed schedule 8 medications. Data on persons treated with implant naltrexone (O’Neil Long Acting Naltrexone Implant, Go Medical Industries Pty. Ltd) were taken from treatment records from the sole provider of implant naltrexone in WA for the duration of the study. The implant preparation was predominantly administered under the Special Access Scheme. This implant preparation was first used in WA in mid-2000, while buprenorphine (Subutex ®) and buprenorphine in combination with naloxone (Suboxone ®) was introduced in 2001 and 2006 respectively. Methadone has been used in WA since the 1970’s.

Data Linkage
Participant information (name, gender, date of birth, date of death, address, and treatment details) was provided to the DLB, where it was linked with the Hospital Morbidity Data Collection (HMDC), the Emergency Department Data Collection (EDDC), the Mental Health Information System (MHIS), the WA Notifiable and Infectious Diseases dataset (WANIDD) and the WA Death Registry (WADR). From these data sets, completed hospital admissions, emergency department (ED) attendances, mental health out-patient presentations, infectious diseases and deaths were extracted from January 1999 to December 2012, with the exception of ED attendances that were only available from 2002 onwards.

Treatment data for methadone and buprenorphine prescriptions from the MODDS provided monthly records indicating a patient had received treatment within that month. Consecutive months were joined to form treatment periods. The data was then matched against the Authorization Database, which provided the date in which the patient was authorised to receive treatment and the date treatment was terminated. For periods without an authorisation date, the commencement date was assigned the 15th of the month unless that fatality occurred before this date and then the 1st of the month was used. The termination date was assigned to the last day of the month.

Analysis
Crude rates of hospital admissions and ED attendances were calculated for patients treated with implant naltrexone, methadone and buprenorphine and expressed per 1000 patient years (ptpy). Additionally, rates of gender and age (age at commencement) rates of hospital and ED attendances were calculated, as well as rates of cause-specific hospital admissions and rates of priority/severity of ED attendances. Rates of cause specific hospital admissions were identified
using primary, co-diagnoses and additional diagnoses (up to 20 additional diagnoses) assigned
to each admission coded using ICD-10-AM codes. Types of hospital admissions examined
included opioid poisoning (ICD-10-AM T40.0 – 40.4), non-opioid drug poisoning (T36 - 39.9,
T40.5 - 51), mental health (F00 – 09; F20 - 99), intentional self-harm (X60–84, Y87.0), blood
(D50 - 89), cardiovascular (I00 – 99), digestive (K00 – 93), endocrine/nutritional/metabolic (E00
‐ 90), genitourinary (N00 – 99), infection (A00 – 99; B00 - 99), musculoskeletal (M00 – 99),
nerve (G00 - 99), respiratory (J00 – 99), and traffic/transport (V00 – 99). Priority/severity of ED
attendances were categories using the Australasian Triage Scale (1 – 5) assigned to each
attendances [304].

Rates of health events in naltrexone patients were compared to methadone and
buprenorphine patients using Generalized Estimating Equations with a negative binomial
distribution and a log link, taking into account rates of pre-treatment admissions (12 months
prior to any treatment) and gender.

Rates of hospital and ED events were also calculated based on the treatment phase: Induction
period, on treatment, and off treatment. The induction period included the first 28 days of
treatment, as this is considered a high risk period particularly for patients on methadone. The
on treatment period commenced at day 29 and for methadone and buprenorphine ceased at
the termination date. For naltrexone the end of the on treatment period was 182 days post
implantation, based on the pharmacokinetic profile of the implant and efficacy data [145, 146,
298]. However, due to patient variation in metabolism of naltrexone, if a patient transitioned
onto methadone or buprenorphine between 121 and 181 days, this was used as the treatment
period, as it was assumed that to transition onto either treatment naltrexone levels would
need to be negligible. The off treatment period commenced at following the cessation of the
treatment and continued until the patient received a new treatment, died or the 31st of
December 2012. Periods in which patients were exposed to more than one treatment were
excluded from analysis.

**Results**

**Demographics**

The study was comprised of 5646 opioid dependent patients treated with methadone (n =
3515), buprenorphine (n = 3250), and/or implant naltrexone (n = 1461). Of the 5646 opioid
dependent patients, a total of 17 308 separate opioid pharmacotherapy treatment episodes
were recorded between January 2001 and December 2012: methadone (n = 6887), implant naltrexone (n = 3259), and buprenorphine (n = 7162) (Table 8). Of the patients treated with an opioid pharmacotherapy, 29.7% of patients had been on two pharmacotherapies, while 8.3% had been on all three pharmacotherapies. There was 436 occasions when a patient was on more than one treatment at the same time i.e. receiving both methadone and buprenorphine on the same day (2.5% of all episodes); these periods were excluded from analysis.

Table 8: Opioid dependent patients treated with implant naltrexone, methadone or buprenorphine for the first time between January 2001 and December 2010 in WA.

<table>
<thead>
<tr>
<th></th>
<th>Naltrexone</th>
<th>Methadone</th>
<th>Buprenorphine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>1461</td>
<td>3515</td>
<td>3250</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>64.4</td>
<td>66.7</td>
<td>65.5</td>
</tr>
<tr>
<td>Age ± st dev.</td>
<td>30.3 ± 7.9</td>
<td>31.9 ± 8.4</td>
<td>31.5 ± 8.3</td>
</tr>
<tr>
<td>Period of exposure (yrs)</td>
<td>1.0 ± 0.8</td>
<td>2.5 ± 2.6</td>
<td>1.9 ± 2.4</td>
</tr>
<tr>
<td>Period of follow up (yrs)</td>
<td>4.9 ± 3.3</td>
<td>5.5 ± 3.3</td>
<td>4.5 ± 3.4</td>
</tr>
<tr>
<td>Median dose per treatment (mg) (IQR)</td>
<td>NA</td>
<td>47.0 (34.6 – 65.0)</td>
<td>13.0 (8.0 – 20.0)</td>
</tr>
<tr>
<td>Median treatment length per episode (years) (IQR)</td>
<td>0.50 (0.46 – 0.50)</td>
<td>0.63 (0.18 – 1.72)</td>
<td>0.30 (0.10 – 0.99)</td>
</tr>
<tr>
<td>Average number of treatments (range)</td>
<td>2.2 (1 - 27)</td>
<td>2.0 (1 - 12)</td>
<td>2.2 (1 - 14)</td>
</tr>
</tbody>
</table>

St dev = standard deviation, IQR = interquartile range

Hospital admissions

Compared with pre-treatment rates, there was no significant difference in rates of hospital admissions in patients treated with implant naltrexone (RR: 1.04, CI: 0.95 – 1.15) or methadone (RR: 1.02, CI: 0.96 – 1.09) following treatment commencement. Although not evident in terms of crude rates of hospitalization (532.3 pre and 500.4 post), following entry into treatment with buprenorphine, rates of hospital admission significantly increased (RR: 1.12, CI: 1.04 – 1.20).

Comparing across pharmacotherapies post treatment, rates of hospitalizations was significantly higher in patients treated with implant naltrexone compared with both
mortality in patients with opioid use disorders and their children following treatment/exposure to implant naltrexone

methadone (RR: 0.83, CI: 0.77 – 0.89) and buprenorphine (RR: 0.92, CI: 0.85 – 0.99). The difference was largely attributable to the induction period onto treatment (0 – 28 days), where rates of hospital admissions in naltrexone treated patients was almost double that of both methadone (RR: 0.55, CI: 0.47 – 0.66) and buprenorphine (RR: 0.62, CI: 0.52 – 0.73) (Table 9). Notwithstanding, following the first 28 days on implant naltrexone, rates of on treatment hospitalization were similar to those of methadone (RR: 1.10, CI: 0.98 – 1.23), and significantly lower compared to those treated with buprenorphine (RR: 1.20, CI: 1.06 – 1.35). Similarly following the cessation of treatment, there was no difference between naltrexone and methadone (RR: 0.93, CI: 0.85 – 1.01) or buprenorphine RR: 0.99, CI: 0.90 – 1.07).

Following entry onto pharmacotherapy treatment, male (RR: 0.80, CI: 0.73 – 0.87) and female patients (RR: 0.88, CI: 0.79 – 1.00) treated with methadone and males treated with buprenorphine (RR: 0.86, CI: 0.78 – 0.94) had significantly lower rates of hospitalisation in comparison to their female counterparts treated with naltrexone. Female patients treated with buprenorphine however were not significantly different to naltrexone (RR: 1.02, CI: 0.90 – 1.15).

Table 9: Rates of hospital admissions per thousand patient years in opioid dependent patients treated with implant naltrexone, methadone and buprenorphine.

<table>
<thead>
<tr>
<th></th>
<th>Naltrexone</th>
<th>Methadone</th>
<th>Buprenorphine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre / post treatment commencement</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Pre-commencement†</td>
<td>597.5</td>
<td>484.5</td>
<td>532.3</td>
</tr>
<tr>
<td>- Post-commencement</td>
<td>558.1</td>
<td>451.7***</td>
<td>500.4*</td>
</tr>
<tr>
<td><strong>Treatment periods</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Induction (0 – 28 days)</td>
<td>1248.7</td>
<td>652.2***</td>
<td>740.7***</td>
</tr>
<tr>
<td>- On treatment (29+ days)</td>
<td>503.9</td>
<td>429.2</td>
<td>661.9**</td>
</tr>
<tr>
<td>- Off treatment</td>
<td>541.4</td>
<td>460.1</td>
<td>497.7</td>
</tr>
</tbody>
</table>

* p < 0.05, ** p < 0.01, *** p < 0.001 (compared with naltrexone-treated patients, no adjustment has been made for multiple comparisons)

† Hospital admissions in the 12 months prior to any opioid pharmacotherapy

In patients who commenced treatment between the age of 26 and 36, rates of hospitalisation were significantly higher in patients treated with implant naltrexone compared with both methadone (RR: 0.62, CI: 0.57 – 0.68) and buprenorphine (RR: 0.67, CI: 0.62 – 0.74), while in
participants under 26 rates of hospitalisation in naltrexone treated patients was significantly lower compared with patients treated with buprenorphine (RR: 1.21, CI: 1.04 – 1.41) but were not significantly different to methadone (RR: 1.02, CI: 0.88 – 1.18). In the two older age brackets (36 – 45 and ≥46), there was no significant difference between the three groups in terms of rates hospitalisations (Table 10).

For the total period post treatment entry rates of mental health events were significantly lower in methadone treated patients compared to naltrexone (RR: 0.69, CI: 0.62 – 0.77), while rates of mental health events in buprenorphine patients were not significantly different to naltrexone, however they did increase rather than decrease like the other two treatments.

Rates of admissions for traffic accidents were significantly higher for methadone patients compared to naltrexone (RR: 1.54, CI: 1.31 – 1.80). Rates of cardiovascular hospital admissions were significantly reduce in naltrexone treated patients compared with both methadone (RR: 1.51, CI: 1.23 – 1.86) and buprenorphine (RR: 1.38, CI; 1.11 – 1.71).

Table 10: Pre- and post-commencement of treatment type specific rates of hospital admissions in opioid dependent patients treated with naltrexone, methadone or buprenorphine.

<table>
<thead>
<tr>
<th>Gender</th>
<th>Naltrexone</th>
<th>Methadone</th>
<th>Buprenorphine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male: pre</td>
<td>441.0</td>
<td>411.8</td>
<td>415.7</td>
</tr>
<tr>
<td>Male: post</td>
<td>458.3</td>
<td>393.3***</td>
<td>423.0**</td>
</tr>
<tr>
<td>Female: pre</td>
<td>880.8</td>
<td>630.5</td>
<td>761.8</td>
</tr>
<tr>
<td>Female: post</td>
<td>730.8</td>
<td>567.2*</td>
<td>651.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age at first treatment</th>
<th>Naltrexone</th>
<th>Methadone</th>
<th>Buprenorphine</th>
</tr>
</thead>
<tbody>
<tr>
<td>- 18 – 25: pre</td>
<td>613.3</td>
<td>539.1</td>
<td>551.3</td>
</tr>
<tr>
<td>- 18 – 25: post</td>
<td>476.5</td>
<td>466.0</td>
<td>513.5*</td>
</tr>
<tr>
<td>- 26 – 35: pre</td>
<td>596.5</td>
<td>466.4</td>
<td>456.4</td>
</tr>
<tr>
<td>- 26 – 35: post</td>
<td>605.4</td>
<td>435.4***</td>
<td>519.0***</td>
</tr>
<tr>
<td>- 36 – 45: pre</td>
<td>586.2</td>
<td>492.8</td>
<td>672.6</td>
</tr>
<tr>
<td>- 36 – 45: post</td>
<td>489.9</td>
<td>410.5</td>
<td>388.0</td>
</tr>
<tr>
<td>- 46 +: pre</td>
<td>781.5</td>
<td>604.9</td>
<td>654.5</td>
</tr>
<tr>
<td>- 46 +: post</td>
<td>586.2</td>
<td>492.8</td>
<td>672.6</td>
</tr>
</tbody>
</table>

Cause specific
Morbidity and mortality in patients with opioid use disorders and their children following treatment/exposure to implant naltrexone

<table>
<thead>
<tr>
<th>Category</th>
<th>Pre</th>
<th>Post</th>
<th>Pre</th>
<th>Post</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioids</td>
<td>20.5</td>
<td>18.5</td>
<td>24.0</td>
<td></td>
</tr>
<tr>
<td>Opioids</td>
<td>14.8</td>
<td>17.3</td>
<td>14.8</td>
<td></td>
</tr>
<tr>
<td>Non-opioid drugs: Pre</td>
<td>65.0</td>
<td>46.9</td>
<td>52.6</td>
<td></td>
</tr>
<tr>
<td>Non-opioid drugs: Post</td>
<td>38.1</td>
<td>37.3</td>
<td>31.9</td>
<td></td>
</tr>
<tr>
<td>Mental health: Pre</td>
<td>183.4</td>
<td>129.7</td>
<td>135.4</td>
<td></td>
</tr>
<tr>
<td>Mental health: Post</td>
<td>169.3</td>
<td>112.3***</td>
<td>156.2</td>
<td></td>
</tr>
<tr>
<td>ISH: Pre</td>
<td>63.0</td>
<td>47.5</td>
<td>49.8</td>
<td></td>
</tr>
<tr>
<td>ISH: Post</td>
<td>40.9</td>
<td>35.1</td>
<td>29.3</td>
<td></td>
</tr>
<tr>
<td>Respiratory: Pre</td>
<td>23.3</td>
<td>25.6</td>
<td>28.3</td>
<td></td>
</tr>
<tr>
<td>Respiratory: Post</td>
<td>24.2</td>
<td>23.9</td>
<td>22.6</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular: Pre</td>
<td>10.3</td>
<td>18.8</td>
<td>23.1</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular: Post</td>
<td>17.7</td>
<td>27.2***</td>
<td>25.6**</td>
<td></td>
</tr>
<tr>
<td>Traffic1: Pre</td>
<td>41.8</td>
<td>36.4</td>
<td>43.4</td>
<td></td>
</tr>
<tr>
<td>Traffic: Post</td>
<td>34.9</td>
<td>54.2***</td>
<td>30.2</td>
<td></td>
</tr>
</tbody>
</table>

* p < 0.05, ** p < 0.01, *** p<0.001 (compared with naltrexone-treated patients, no adjustment has been made for multiple comparisons)

ISH = intentional self-harm

1. Included pedestrians injured in transport accidents.

**ED attendances**

Compared with pre-treatment, rates of ED attendances for both methadone (RR: 0.88, CI: 0.83 – 0.93) and buprenorphine (RR: 0.89, CI: 0.87 – 0.92) showed a significant reduction following the commencement of treatment, while post treatment rates of ED attendance in naltrexone (RR: 0.95, CI: 0.88 – 1.04) were not significantly different to pre-treatment rates (Table 11).

Overall in the total period following the commencement of treatment compared across the pharmacotherapies, rates of ED attendances in patients treated with implant naltrexone were comparable to buprenorphine patients (RR: 0.92, CI: 0.85 – 1.01), while rates in methadone patients were significantly lower (RR: 0.85, CI: 0.78 – 0.92). In contrast, during the induction period, rates of ED attendances were very high, approximately double that of both methadone (RR: 0.53, CI: 0.46 – 0.62) and buprenorphine (RR: 0.50, CI: 0.43 - 0.59). However following the first 28 days on treatment and following cessation of treatment, there was no significant difference between the three groups.
Morbidity and mortality in patients with opioid use disorders and their children following treatment/exposure to implant naltrexone

Table 11: Rates of ED attendances per 1000 patient years in opioid dependent patients treated with implant naltrexone, methadone or buprenorphine.

<table>
<thead>
<tr>
<th></th>
<th>Naltrexone</th>
<th>Methadone</th>
<th>Buprenorphine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre / post treatment commencement</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-treatment</td>
<td>1467.8</td>
<td>1390.3</td>
<td>1476.9</td>
</tr>
<tr>
<td>Post-treatment</td>
<td>1265.7</td>
<td>1166.0***</td>
<td>979.5</td>
</tr>
<tr>
<td><strong>Treatment periods</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Induction</td>
<td>3593.8</td>
<td>1961.8***</td>
<td>1776.4***</td>
</tr>
<tr>
<td>- On treatment</td>
<td>1303.3</td>
<td>1312.5</td>
<td>907.6</td>
</tr>
<tr>
<td>- Off treatment</td>
<td>1154.0</td>
<td>1012.4</td>
<td>981.1</td>
</tr>
</tbody>
</table>

* p < 0.05, ** p < 0.01, *** p < 0.001 (compared with naltrexone-treated patients, no adjustment has been made for multiple comparisons)

Female patients treated with methadone and both male and female patients treated with buprenorphine have significantly lower rates of ED attendances compared with naltrexone patients of the same genders (Table 12). Rates of age specific ED attendances were not significantly different between the three treatments, with the exception of the 36 – 45 year age bracket in which lower rates of ED attendances were observed in patients treated with methadone compared with naltrexone (RR: 0.80, CI: 0.69 – 0.93).

Mid-urgency triage codes (2 – 4) were significantly elevated in patients treated with naltrexone compared to both methadone and buprenorphine, while there was no significance difference in rates of high urgency ED attendances (triage 1). Rates of low urgency triage scores were significantly elevated in methadone patients compared with naltrexone patients.
Table 12: Pre- and post-rates of type specific ED attendances in opioid dependent patients treated with implant naltrexone, methadone and buprenorphine.

<table>
<thead>
<tr>
<th>Gender</th>
<th>Naltrexone</th>
<th>Methadone</th>
<th>Buprenorphine</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Male: Pre</td>
<td>1267.5</td>
<td>1310.5</td>
<td>1252.2</td>
</tr>
<tr>
<td>- Male: Post</td>
<td>1075.9</td>
<td>1105.8</td>
<td>911.6*</td>
</tr>
<tr>
<td>- Female</td>
<td>1844.3</td>
<td>1900.2</td>
<td>1552.4</td>
</tr>
<tr>
<td>- Female</td>
<td>1600.8</td>
<td>1287.1***</td>
<td>1118.4**</td>
</tr>
</tbody>
</table>

**Start age**

| - 18 to 25: Pre | 1260.9     | 1285.7    | 1278.6        |
| - 18 to 25: Post | 1241.1     | 1093.7    | 974.0         |
| - 26 to 35: Pre | 1630.2     | 1482.6    | 1317.1        |
| - 26 to 35: Post | 1275.6     | 1337.1    | 991.5         |
| - 36 to 45: Pre | 626.2      | 516.7     | 733.7         |
| - 36 to 45 | 555.4      | 395.5**   | 446.4         |
| - 46 +: Pre | 603.8      | 397.1     | 517.0         |
| - 46 +: Post | 912.8      | 460.5     | 670.9         |

**Triage codes**

| - 1: Pre | 26.0       | 13.3      | 12.1          |
| - 1: Post | 24.0       | 16.1      | 15.8          |
| - 2: Pre | 148.6      | 124.5     | 118.0         |
| - 2: Post | 152.5      | 109.7***  | 104.8***      |
| - 3: Pre | 462.6      | 401.6     | 381.8         |
| - 3: Post | 413.0      | 318.3***  | 294.2*        |
| - 4: Pre | 584.2      | 573.6     | 570.7         |
| - 4: Post | 507.7      | 398.7***  | 379.1***      |
| - 5: Pre | 244.3      | 274.4     | 390.4         |
| - 5: Post | 164.9      | 320.8***  | 182.3         |

* p < 0.05, ** p < 0.01, *** p < 0.001 (compared with naltrexone-treated patients, no adjustment has been made for multiple comparisons)

1. Only includes patients treated after January 2003 (naltrexone = 962; methadone = 2 547; buprenorphine = 2 313)
2. ED admissions in the 12 months prior to any opioid pharmacotherapy
Discussion

Methadone was associated with the longest median treatment period, with patients staying on treatment for approximately 7.5 months. In contrast, buprenorphine patients only remained on treatment for around 3.5 months, while naltrexone patients had a pre-defined treatment period of 6 months. This is congruent with a meta-analysis, which found a significant difference in methadone and buprenorphine retention to treatment (RR: 0.83, 95% CI: 0.73 – 0.95). Patients were transient. Within treatments, patients frequently moved on and off treatment with an average of 2 episodes per treatment, although some patients had more than 10 treatments per pharmacotherapy. Similarly, 38% of patients entered more than one treatment and with patients on average having 3 treatment episodes (17 308 treatment episodes in 5646 patients). However, alarmingly in 2.5% of treatments, patients were on more than one treatment at the same time. While in some cases this may be due to errors in the recording of treatment timing, it is suggested that better communication is required to ensure that patients are not allowed access to more than one opioid pharmacotherapy at any one time, to ensure the maximum efficacy of the treatment.

Naltrexone was associated with elevated rates of morbidity following the commencement of treatment, compared with both methadone and buprenorphine. The induction period (0 – 28 days) was a particularly vulnerable period for patients treated with implant naltrexone with high rates of both hospital and ED attendances. For naltrexone patients, who had been on opioids prior to treatment this four week period also corresponded with opioid detoxification, which may have at least partially attributed to the very high rates during this period. After this period, morbidity was largely comparable between the three treatments.

Following the commencement of treatment, naltrexone was associated with higher rates of hospital admission with a mental health diagnosis compared with methadone patients. Concerns have arisen regarding the effect of naltrexone on mental illness, given the likely roll endogenous opioids play in mood stabilization, and the potential for drug substitution in naltrexone patients who are no longer able to use opioids. However crude rates of mental health hospital admissions were lower following naltrexone treatment, while in comparison rates increased in patients treated with buprenorphine. Additionally, rates of pre-treatment mental health hospitalization in patients treated with implant naltrexone appeared substantially higher than pre-treatment rates in patients treated with methadone and
buprenorphine. Further research is required to examine when these events are occurring (induction, on treatment, off treatment), in which patients (gender, age, drug history) and the type of events (type of mental illness/non-opioid drug).

Naltrexone was associated with lower rates of cardiovascular hospital admissions compared with both methadone and buprenorphine. Opioid dependence has been associated with high rates of cardiovascular disease and cardiovascular abnormalities in both illicit opioid user and those on opioid pharmacotherapies such as methadone [97, 99]. Interestingly, measures of arterial stiffness (a cardiovascular risk factor) and vascular age have been observed to be at least partially reverse in opioid dependent patients following treatment with a sustained release preparation of the opioid antagonist, naltrexone [305]. However, it is unclear if the alteration in cardiovascular risk is the result of naltrexone or its facilitated abstinence from opioids.

Elevated rates of hospital admission for traffic accidents in participant treated with methadone are of concern. Such has been observed previously in methadone patients [306], as has impairment in psychomotor skill which may be the cause of increased rates of traffic accidents [307-309].

Clinical implications

Programs using implant naltrexone need to ensure high levels of support during the first 4 weeks following implantation, as this can be a high risk period. To tailor support for this period, further information is required as to the type of events causing this spike in hospital and ED attendances.

Strengths and limitations

This is the first large longitudinal study directly comparing implant naltrexone to methadone and buprenorphine, however the study is naturalistic and thus pre-treatment differences between patients entering the three treatments may exist. Such differences appear apparent in terms of the rates of pre-treatment morbidity.

Although WA is generally considered very isolated, over the follow up period it is likely there was a degree of migration out of the state. Health events occurring outside of WA would not have been captured in the study. Similarly, the study only had access to reported cases of
blood and sexually transmissible diseases, thus any undiagnosed or unreported cases would not have been included.

Conclusions
The use of implant naltrexone was associated with high rates of morbidity in the first 28 days of treatment compared with methadone and buprenorphine, however following this initial period on treatment and following the cessation of treatment morbidity in naltrexone patients was similar to methadone and buprenorphine.
5.4. **Paper 4: Fatal and non-fatal opioid overdose in opioid dependent patients treated with methadone, buprenorphine or implant naltrexone**

**Abstract**

**Aims:** To compare rates of fatal and serious but non-fatal opioid overdose in opioid dependent patients treated with methadone, buprenorphine or implant naltrexone, and to identify risk factors for fatal opioid overdose.

**Methods:** Opioid dependent patients treated with methadone (n=3515), buprenorphine (n=3250) or implant naltrexone (n=1461) in Western Australia for the first time between 2001 and 2010 inclusive, were matched against state mortality and hospital data. Rates of fatal and non-fatal serious opioid overdoses were calculated and compared for the three treatments. Risk factors associated with fatal opioid overdose were examined using multivariate cox proportional hazard models.

**Results:** No significant difference was observed between the three groups in terms of crude rates of fatal or non-fatal opioid overdoses. During the first 28 days on treatment, rates of non-fatal opioid overdose were high in all three groups, as were fatal opioid overdoses in patients treated with methadone. However, no fatal opioid overdoses were observed in buprenorphine or naltrexone patients during this period. Following the first 28 days, buprenorphine was shown to be protective, particularly in terms of non-fatal opioid overdoses. After the cessation of treatment, rates of fatal and non-fatal opioid overdoses were similarly between the groups, with the exception of lower rates of non-fatal opioid overdose in the naltrexone treated patients compared with the methadone treated patients.

After the commencement of treatment, gender, and hospitalisations with a diagnosis of opioid poisoning, cardiovascular and mental health hospitalisations were significant predictors of subsequent fatal opioid overdose.

**Conclusions:** Induction on an opioid pharmacotherapy is associated with a high risk of opioid overdose, particularly in methadone treated patients where the outcome is often fatal. Gender
and prior cause specific hospitalisations can be used to identify patients at a high risk of fatal opioid overdose.

**Introduction**

Opioid overdoses are typically the result of opioid induced respiratory depression, resulting in hypoxia and in some instances death. Respiration is controlled principally through the medulla (ventral and dorsal respiratory group) and the pons (pneumotaxic and apneustic centre), with input from chemoreceptors, which respond to changes in blood gases (carbon dioxide, oxygen) and pH. Rhythmic respiration requires the phasic activation and inhibition. In the ventral respiratory group, excitation is mediated by excitatory amino acids such as glutamate [25], while inhibition is mediated by GABA receptors [26]. A number of other neurotransmitters have also been associated with changes in respiratory rhythm, including serotonin [27, 28], substance P [29, 30] and opioid peptides [31, 32]. Opioid peptides have largely been found to have an inhibitory effect on respiratory, likely due to a reduction in glutamate induced excitation [310].

It is generally presumed that opioid poisoning occurs as a result of the excessive consumption of opioids. However, while this may be the case in a small proportion of deaths, toxicological analysis has repeatedly found blood morphine levels in fatal opioid poisoning are similar to individuals who have recently used opioids but died of alternative causes [33-35]. Similarly, while suicide is not uncommon in opioid dependent patients, suicide as a result of opioid poisoning appears to be relatively rare. A study by Heale et al. (2003), interviewed 256 heroin overdose survivors who were successfully revived by paramedics finding that only 9 survivors (3.5%) had intentionally attempted to overdose [36].

The occurrence of opioid poisoning has repeatedly been associated with changes in tolerance. Tolerance to opioids develops quickly, with evidence of tolerance to morphine exhibited as early as 8 hours during continuous intravenous infusions in rats [42, 43]. Following periods of abstinence, the tolerance built over periods of use is reversed and the opioid system up-regulates and re-sensitizes to an approximate pre-opioid use level. Such changes can occur within several days, with an abstinence period of 5.4 days required to regenerate 50% of the intrinsic responsivity lost during the development of tolerance in fully tolerant morphine rats [44]. Upon return to use, opioid users may fail to reduce their opioid dose to accommodate reduced tolerance, resulting in overdose. Such changes account for significant increases in opioid poisoning mortality following release from prison and in-patient rehabilitation [45-47].
In addition, it appears that an individual’s tolerance to the respiratory depressant effects of opioids does not necessarily develop at the same rate as tolerance to its euphoric and analgesic effects, making it harder for returning opioid users to calculate a safe dose [49].

While opioids alone cause sufficient respiratory depression to cause hypoxia, the co-ingestion of other drugs such as alcohol and benzodiazepines has been found to play a significant role in a large percentage of opioid overdoses [39, 51]. Alcohol both suppresses the release of glutamate and stimulates the GABA binding, while drugs such as benzodiazepines and barbiturates also facilitate GABA binding. As such in an examination of 953 heroin-related fatalities, 46% of cases had alcohol present, while benzodiazepines were present in 27% [34].

The pharmacotherapies used to treat opioid use disorders have also been linked to opioid poisoning. The long acting opioid agonist methadone has been associated with high rates of opioid poisoning in the first two weeks following induction onto treatment and the first two weeks following cessation of treatment, as changes in dose and tolerance occur [94-96]. Similarly the opioid antagonist naltrexone has been associated with high rates of opioid poisoning mortality following the cessation of treatment due to a reduction of opioid tolerance during treatment and a rapid unblocking of mu opioid receptors following cessation of oral dosing [296].

A number of pre-existing health conditions are also likely to be influential factors associated with the occurrence of opioid poisoning, including hepatic and respiratory disease/disorders. It is hypothesised that hepatic diseases would result in reduced hepatic clearance of opioids in patients with liver damage, resulting in prolonged exposure to increased levels of opioids [311], while respiratory disease/disorders may increase the risk overdoses given the role of the respiratory system [312].

The aim of this study is to examine the characteristics of both fatal and non-fatal opioid poisoning in opioid dependent patients following entry into an opioid pharmacotherapy. Additionally, the study aims to examine the risk factors associated with fatal opioid poisoning, including previous opioid and non-opioid poisoning, suicide, cardiovascular and respiratory hospital admissions.
Methods

Design

The study was a naturalistic follow up of patients routinely treated with methadone, buprenorphine or implant naltrexone using state health hospital and mortality data sets.

Subjects

The study was comprised of 5646 opioid dependent patients, with 3515 treated with methadone, 3250 treated with buprenorphine and 1461 treated with implant naltrexone. These patients had been treated for the first time in Western Australia (WA) between 2001 and 2010 inclusive. Subjects were required to be at least 18 years of age at the time of first treatment and residing in WA. Subjects treated with methadone and buprenorphine were obtained from the Monitoring of Drugs of Dependence System, managed by the WA Department of Health. Subjects treated with implant naltrexone were obtained from patient treatment lists from a drug and alcohol clinic. Demographics of the cohort are reported in section 5.2.

Data linkage

Identifying subject information was provided to the WA Data Linkage Branch, where it was linked with state hospital, emergency and mortality datasets. The data was then de-identified and provided to the research team.

Data analysis

ICD-10-AM codes assigned to hospital and mortality records were used to identify events that occurred as a result of an opioid poisoning (T40.0–T40.4). Rates of fatal and non-fatal (requiring hospital admission) opioid poisoning were calculated for each group and expressed per 1000 patient years (ptpy). Comparisons of rates of fatal opioid poisoning between the three groups was carried out using univariate Cox Proportional Hazard Regression, while rates of non-fatal opioid poisoning were compared using Generalised Estimating Equations, with a negative binomial distribution and a log link. Pre- and post-treatment incidence rates of hospitalisation with a diagnosis of opioid poisoning were compared using Generalised Estimating Equations.
Rates of fatal and non-fatal opioid overdoses and the ratio of the two were also calculated for patients during the ‘induction’, ‘on treatment’ and ‘off treatment’ periods. The ‘induction’ period was defined as the first 28 days after commencing treatment, while the ‘on treatment’ period followed on from the induction period to the cessation of treatment. For patients treated with implant naltrexone, the treatment was deemed to have ceased at 182 days following the initial treatment, fitting with pharmacokinetic and efficacy studies [145, 146]. However, due to patient variation in metabolism of naltrexone, if a patient transitioned onto methadone or buprenorphine between 121 and 181 days, this was used as the treatment period, as it was assumed that to transition onto either treatment naltrexone levels would need to be negligible. In two fatalities, methadone was present at therapeutic doses within a week of the patients having ceased methadone. However the treatment data suggested they only received one day of treatment. It was deemed most likely that these patients were still on treatment at the time of death. For all three treatments, ‘off’ treatment was calculated from the cessation of the ‘on’ treatment period to the commencement of a subsequent treatment or 31/Dec/2012.

Characteristics of fatal and non-fatal opioid overdose were ascertained from mortality and hospital records and collated for each treatment (overall, on and off treatment) and expressed ptpy. Characteristics examined include gender, diagnosis of non-opioid drug poisoning (T36-39.9, T40.5 - 51), suicide (X60–X84, Y87.0), respiratory disease (J00 – J99) or cardiovascular disease (I00 – I99). Simple logistic regression was used to compare the prevalence of these characteristics in each treatment group.

Univariate and multivariate Cox proportional hazard regression was used to identify potential risk factors for fatal opioid overdose. Risk factors examined included gender, age at first treatment, hospital attendances for opioid overdose, non-opioid drug overdose, suicide, cardiovascular or respiratory hospital admission in the two years prior to initial treatment and following the commencement of initial treatment (time varying covariate).

Results

Cohort characteristics

Patients treated with the methadone, buprenorphine and naltrexone were predominantly male and aged in their early 30’s at the commencement of treatment (Table 13). In the 12
months prior to admission to any opioid pharmacotherapy, rates of non-fatal opioid overdoses were not significantly different between the three groups. Mortality rates in this cohort of patients has been previously presented in Section 5.2.

Table 13: Opioid dependent patients treated with methadone, buprenorphine or implant naltrexone for the first time between January 2001 and December 2010 in Western Australia.

<table>
<thead>
<tr>
<th></th>
<th>Methadone</th>
<th>Buprenorphine</th>
<th>Naltrexone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>3515</td>
<td>3250</td>
<td>1461</td>
</tr>
<tr>
<td>Male (%)</td>
<td>66.7</td>
<td>65.5</td>
<td>64.4</td>
</tr>
<tr>
<td>Start age ± st dev.</td>
<td>31.9 ± 8.4</td>
<td>31.5 ± 8.3</td>
<td>30.3 ± 7.9</td>
</tr>
<tr>
<td>Average follow-up</td>
<td>5.5 ± 3.3</td>
<td>4.5 ± 3.4</td>
<td>4.9 ± 3.3</td>
</tr>
<tr>
<td>Pre-treatment opioid poisoning (ptpy)</td>
<td>18.5</td>
<td>24.0</td>
<td>20.5</td>
</tr>
</tbody>
</table>

1. Rate of hospital admissions for opioid poisoning in the 12 months prior to commencing any opioid pharmacotherapy.
St dev = standard deviation, ptpy = per 1000 patient years

Overall 117 deaths and 658 hospital admission were assigned a diagnosis of opioid poisoning. Of the hospital admissions, the death of the patient occurred in 14 admissions (2.1%). Comparisons of pre- and post-treatment rates of opioid poisoning requiring hospital admission (including fatal admissions) showed a statistically significant reduction in patients treated with buprenorphine (RR: 0.66, CI: 0.51 – 0.84). While reductions in rates of hospitalisation were observed in methadone (RR: 1.08, CI: 0.85 – 1.37) and naltrexone patients (RR: 0.75, CI: 0.50 – 1.12), the reduction was not statistically significant.

Overdose characteristics of fatal and non-fatal opioid poisoning

Fatal overdose

Overall 117 fatalities involving opioid poisoning were observed, equating to 2.8 deaths per 1000 patient years (ptpy), with no significant difference in the rate of fatal opioid poisoning in patients treated with methadone, buprenorphine or implant naltrexone (Table 14). The most common co-diagnoses included a poisoning with a non-opioid drug (69.2%), respiratory diagnosis (12.0%), suicide (8.5%) and cardiovascular diagnosis (6.0%). The presence of co-diagnoses did not differ significantly between the three opioid pharmacotherapies overall,
with the exception of lower rates of non-opioid drug poisoning in fatalities in patients treated with buprenorphine compared with methadone (p = 0.040). Fatalities occurring in hospital (including emergency department) made up only a small proportion of fatalities, with only 8.2% of methadone, 14.3% of buprenorphine and 7.7% of naltrexone patients.

Non-fatal overdoses

In comparison, 644 non-fatal opioid poisonings were observed, equating to 15.6 ptpy and 5.70 non-fatal opioid poisonings for every fatal poisoning. Of opioid overdose admission, 10.4% required admission to ICU staying an average of 2.2 days (range: 1 – 18 days). The average hospital length of stay was 3.8 days (range: 1 – 137 days). As per fatal opioid overdoses, there was no significant difference in the rate of non-fatal opioid poisoning in the three treatment groups. The most common co-diagnoses were non-opioid drug poisoning (55.4%), suicide (48.0%), respiratory disorder (7.8%) and cardiovascular disorder (6.1%). The presence of co-diagnoses did not differ significantly between methadone and naltrexone, however buprenorphine had fewer overdoses involving non-opioid drug poisoning (p = 0.048) and attempted suicide (0.045).
Morbidity and mortality in patients with opioid use disorders and their children following treatment/exposure to implant naltrexone

Table 14: Co-diagnoses associated with fatal and serious but non-fatal opioid overdoses in opioid dependent patients treated with methadone, compared with those treated with buprenorphine or implant naltrexone.

<table>
<thead>
<tr>
<th></th>
<th>Methadone</th>
<th></th>
<th>Buprenorphine</th>
<th></th>
<th>Naltrexone</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fatal</td>
<td>Non-fatal</td>
<td>Ratio</td>
<td>Fatal</td>
<td>Non-fatal</td>
<td>Ratio</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>2.5</td>
<td>16.8</td>
<td>6.67</td>
<td>2.9</td>
<td>14.5</td>
<td>5.10</td>
</tr>
<tr>
<td>% Non-opioid drugs</td>
<td>79.6</td>
<td>59.0</td>
<td>0.74</td>
<td>59.5*</td>
<td>53.3*</td>
<td>0.89</td>
</tr>
<tr>
<td>% Suicidal behaviour</td>
<td>10.9</td>
<td>52.3</td>
<td>4.81</td>
<td>7.3</td>
<td>43.5*</td>
<td>5.94</td>
</tr>
<tr>
<td>% Cardiovascular</td>
<td>6.5</td>
<td>6.1</td>
<td>0.94</td>
<td>5.6</td>
<td>7.3</td>
<td>1.15</td>
</tr>
<tr>
<td>% Respiratory</td>
<td>17.4</td>
<td>7.3</td>
<td>0.42</td>
<td>7.3</td>
<td>8.4</td>
<td>1.15</td>
</tr>
<tr>
<td><strong>Induction (0 – 28 days)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate</td>
<td>16.2</td>
<td>28.3</td>
<td>1.75</td>
<td>0.0</td>
<td>28.9</td>
<td>-</td>
</tr>
<tr>
<td>% Non-opioid drugs</td>
<td>50.0</td>
<td>42.9</td>
<td>0.86</td>
<td>0.0</td>
<td>64.3</td>
<td>-</td>
</tr>
<tr>
<td>% Suicidal behaviour</td>
<td>12.5</td>
<td>28.6</td>
<td>2.29</td>
<td>0.0</td>
<td>57.1</td>
<td>-</td>
</tr>
<tr>
<td>% Cardiovascular</td>
<td>12.5</td>
<td>7.1</td>
<td>0.57</td>
<td>0.0</td>
<td>0.0</td>
<td>-</td>
</tr>
<tr>
<td>% Respiratory</td>
<td>12.5</td>
<td>7.1</td>
<td>0.57</td>
<td>0.0</td>
<td>0.0</td>
<td>-</td>
</tr>
<tr>
<td><strong>On-treatment (+29 days)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate</td>
<td>1.5</td>
<td>10.5</td>
<td>6.77</td>
<td>0.7</td>
<td>6.6*</td>
<td>9.25</td>
</tr>
<tr>
<td>% Non-opioid drugs</td>
<td>76.9</td>
<td>58.0</td>
<td>0.75</td>
<td>50.0</td>
<td>51.4</td>
<td>1.03</td>
</tr>
</tbody>
</table>
Morbidity and mortality in patients with opioid use disorders and their children following treatment/exposure to implant naltrexone

<table>
<thead>
<tr>
<th></th>
<th>% Suicidal behaviour</th>
<th>% Cardiovascular</th>
<th>% Respiratory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Off-treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate</td>
<td>2.6</td>
<td>4.5</td>
<td>10.2</td>
</tr>
<tr>
<td>% Non-opioid drugs</td>
<td>89.3</td>
<td>60.4</td>
<td>38.5</td>
</tr>
<tr>
<td>% Suicidal behaviour</td>
<td>10.7</td>
<td>56.0</td>
<td>1.87</td>
</tr>
<tr>
<td>% Cardiovascular</td>
<td>3.6</td>
<td>6.7</td>
<td>0.87</td>
</tr>
<tr>
<td>% Respiratory</td>
<td>7.1</td>
<td>6.2</td>
<td>7.9</td>
</tr>
</tbody>
</table>

* p < 0.05, ** p < 0.001 (compared with naltrexone-treated patients, no adjustment has been made for multiple comparisons)
Gender

No significant reduction in non-fatal opioid overdoses were observed in male patients treated with methadone (RR: 1.07, CI: 0.73 – 1.57), buprenorphine (RR: 0.77, CI: 0.55 – 1.09) or naltrexone (RR: 1.25, CI: 0.62 – 2.51). However, in female treated patients, there was a significant reduction in patients treated with buprenorphine (RR: 0.49, CI: 0.34 – 0.71) and naltrexone (RR: 0.52, CI: 0.32 – 0.87), but not methadone (RR: 0.93, CI: 0.67 – 1.30).

Rates of fatal opioid overdose were significantly elevated in male patients treated with naltrexone compared to those treated with methadone (HR: 1.80, CI: 1.06 – 3.06), however rates of opioid overdose in male patients treated with buprenorphine were not significantly different to methadone (HR: 1.24, CI: 0.77 – 1.99). In female patients, rates of fatal opioid overdose in methadone treated patients were not significantly different to either buprenorphine (HR: 0.92, CI: 0.39 – 2.16) or naltrexone (HR: 0.80, CI: 0.26 – 2.44). No significant difference was observed in terms of non-fatal opioid overdoses in either males or females (Table 15).

Table 15: Gender difference in rates of fatal and non-fatal opioid poisoning in opioid dependent patients treated with methadone (MMT), buprenorphine (BUP) and naltrexone (NTX) (per 1000 patient years).

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
<th></th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MMT</td>
<td>BUP</td>
<td>NTX</td>
<td>MMT</td>
<td>BUP</td>
</tr>
<tr>
<td>Pre-treatment</td>
<td>13.6</td>
<td>19.3</td>
<td>9.6</td>
<td>28.2</td>
<td>33.0</td>
</tr>
<tr>
<td>Post-fatal</td>
<td>2.8</td>
<td>3.4</td>
<td>5.0*</td>
<td>2.0</td>
<td>1.8</td>
</tr>
<tr>
<td>Post-non-fatal</td>
<td>14.4</td>
<td>14.4</td>
<td>11.5</td>
<td>21.6</td>
<td>14.8</td>
</tr>
</tbody>
</table>

* P < 0.05 (compared with methadone-treated patients, no adjustment has been made for multiple comparisons)

Treatment periods

Induction

During the induction period (first 28 days after commencing treatment), rates of hospital admissions for non-fatal opioid poisoning were consistent across the three treatments and were approximately double that of patients while ‘on treatment’ (after the first 28 days of treatment). While no opioid fatalities were observed in the induction period in patients
treated with buprenorphine or implant naltrexone, high rates of fatal opioid poisoning were observed in patients treated with methadone (16.2 ptpy). In the methadone cohort, for every 1.75 hospitalisations for opioid poisoning 1 patient died of the same cause.

Although the naltrexone cohort was comprised on 64.4% males, males only made up 16.7% of the patients who were admitted to hospital with a non-fatal opioid poisoning. In contrast, males made up 78.6% and 64.3% of patients admitted to hospital in the methadone and buprenorphine cohorts respectively.

On-treatment

While on treatment, buprenorphine was shown to be protective against opioid poisoning with 9.25 non-fatal opioid poisoning admissions for every fatal opioid poisoning, compared with 6.77 for methadone and 6.50 for naltrexone. Buprenorphine also had significantly fewer admissions for non-fatal opioid poisoning (p = 0.018) compared with methadone.

In patients on treatment, attempted suicide appeared to play a significant role in the occurrence of non-fatal poisoning overdoses however was rare as a co-diagnosis of fatal opioid overdoses. Respiratory disease/disorder was a common co-diagnosis in fatalities involving opioid poisoning in patients on methadone treatment (38.5%), however was absent in fatalities in patients on buprenorphine or naltrexone.

Off-treatment

Rates of fatal opioid poisoning were not significantly different between the three groups, however rates of non-fatal opioid poisoning were significantly lower in naltrexone treated patients than in methadone treated patients following treatment (p < 0.001). Following treatment, non-fatal opioid overdoses in naltrexone treated patients were comprised of fewer overdoses involving non-opioid drugs (p = 0.017) and suicide attempts (p = 0.026) compared with methadone treated patients. Non-fatal opioid overdoses in buprenorphine patients had fewer non-fatal overdoses with a co-diagnosis of suicide (p = 0.008) and fewer fatal overdoses involving non-opioid drugs (p = 0.026) compared with methadone.

Factors associated with risk of fatal opioid overdose

Univariate analysis found a significantly lower risk of fatal opioid overdose in female patients compared with males, with females dying at half the rate (Table 15). In terms of pre-treatment
hospital admissions, an opioid overdose in the two years prior to treatment was associated with significant increase of experiencing a fatal opioid overdose following the commencement of treatment ($p < 0.001$). Similarly, pre-treatment drug overdose, and cardiovascular admissions were also associated with increased mortality as a result of opioid overdoses. However, in the multivariate model only gender (HR: 0.53, CI: 0.34 – 0.82), and pre-treatment opioid overdose (HR: 4.46, CI: 2.45 – 8.11) were statistically significant.

Univariate analysis of post-treatment admissions, observed an increased risk of fatal opioid overdose in patients following an opioid overdose, a non-opioid drug overdose, suicide, mental health, cardiovascular and respiratory hospital admission (Table 16). In the multivariate model, gender (HR: 0.50, CI: 0.33 – 0.78), opioid poisoning (HR: 5.07, CI: 3.12 – 8.26), cardiovascular (HR: 2.32, CI: 1.38 – 3.91) and mental health hospitalisations (HR: 1.91, CI: 1.22 – 2.97) were significant predictors.
Table 16: Univariate hazard ratios associated with potential risk factors for opioid overdose following the commencement of treatment.

<table>
<thead>
<tr>
<th></th>
<th>Hazard ratio</th>
<th>Confidence Interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>0.55</td>
<td>0.36 – 0.85</td>
<td>0.007</td>
</tr>
<tr>
<td>Age of first treatment</td>
<td>1.00</td>
<td>0.98 – 1.02</td>
<td>0.765</td>
</tr>
<tr>
<td><strong>Pre-treatment admission (2 years prior)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opioid overdose</td>
<td>4.16</td>
<td>2.29 – 7.57</td>
<td><strong>0.000</strong></td>
</tr>
<tr>
<td>Non-opioid drug overdose*</td>
<td>2.17</td>
<td>1.22 – 3.86</td>
<td><strong>0.009</strong></td>
</tr>
<tr>
<td>Attempted suicide</td>
<td>1.82</td>
<td>0.98 – 3.38</td>
<td>0.059</td>
</tr>
<tr>
<td>Mental health</td>
<td>1.46</td>
<td>0.88 – 2.41</td>
<td>0.142</td>
</tr>
<tr>
<td>Cardiovascular admission</td>
<td>2.42</td>
<td>1.07 – 5.51</td>
<td><strong>0.035</strong></td>
</tr>
<tr>
<td>Respiratory admission</td>
<td>1.71</td>
<td>0.75 – 3.88</td>
<td>0.202</td>
</tr>
<tr>
<td><strong>Post treatment (TVC)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opioid overdose</td>
<td>7.71</td>
<td>4.99 – 11.91</td>
<td><strong>0.000</strong></td>
</tr>
<tr>
<td>Non-opioid drug overdose*</td>
<td>4.78</td>
<td>3.17 – 7.21</td>
<td><strong>0.000</strong></td>
</tr>
<tr>
<td>Attempted suicide</td>
<td>3.59</td>
<td>2.30 – 5.59</td>
<td><strong>0.000</strong></td>
</tr>
<tr>
<td>Mental health</td>
<td>2.99</td>
<td>2.02 – 4.43</td>
<td><strong>0.000</strong></td>
</tr>
<tr>
<td>Cardiovascular event</td>
<td>3.90</td>
<td>2.39 – 6.38</td>
<td><strong>0.000</strong></td>
</tr>
<tr>
<td>Respiratory event</td>
<td>3.13</td>
<td>1.90 – 5.15</td>
<td><strong>0.000</strong></td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>2.38</td>
<td>0.87 – 6.50</td>
<td>0.091</td>
</tr>
</tbody>
</table>

* includes opioid overdoses were non-opioid drugs were involved

TVC = time varying covariate

**Discussion**

**Opioid pharmacotherapies**

Of the three treatments, buprenorphine appeared to be the safest treatment in terms of both fatal and non-fatal opioid overdose. Compared with pre-treatment measures, rates of opioid poisoning hospitalisation decreased by 39.6% following induction onto buprenorphine. During induction onto treatment, rates of non-fatal opioid overdoses were high compared with pre-treatment values but comparative to both methadone and naltrexone, however unlike methadone no fatal opioid overdoses were observed. Following the first 28 days, rates of non-
fatal opioid overdoses were lower than both methadone and implant naltrexone patients and post-treatment the three were comparable in terms of both fatal and non-fatal opioid overdoses. Buprenorphine’s superiority to methadone in terms of opioid overdoses is most likely the result of methadone’s increased ability to cause respiratory depression.

Implant naltrexone was also associated with positive opioid overdose outcomes. Although not statistically significant, following the commencement of treatment there was a 28.3% reduction in the rate of hospitalisation for opioid poisoning. As per buprenorphine, while high rates of non-fatal opioid overdoses were observed in the first 28 days of treatment, no fatal opioid overdoses were observed. While on treatment, rates of both fatal and non-fatal opioid overdose were comparable to methadone, however once treatment had ceased, rates of non-fatal opioid overdose were lower in the naltrexone cohort. Unlike methadone and buprenorphine, naltrexone does not cause respiratory depression, in fact, it blocks the effects of other opioids which may induce respiratory depression. However, it is unclear why naltrexone did not perform as well as buprenorphine, with no evidence to suggest a difference in the type of opioid overdoses observed (i.e. difference in the frequency of co-diagnoses of suicide or non-opioid drug poisoning).

Methadone did not perform as well as buprenorphine or naltrexone, primarily as a result of very high rates of fatal opioid overdose in the first 28 days of treatment (14.1 deaths ptpy in methadone compared with 0 ptpy in both buprenorphine and implant naltrexone patients). Methadone had the smallest change in crude rates of hospital admission for opioid poisoning, with only 9.2% reduction. Similarly rates of non-fatal opioid overdose were high compared with buprenorphine patients in the on treatment period and higher than naltrexone patients following the cessation of treatment. High rates of fatal opioid overdose during induction onto methadone have been previously reported [94-96].

Gender differences

While male patients entering treatment looked similar in terms of pre-treatment opioid poisoning, female patients prior to commencement of naltrexone treatment had high rates of non-fatal opioid overdoses. However, following the commencement of treatment both naltrexone and buprenorphine, rates of opioid overdose were approximately halved in female patients, while rates in male patients entering any treatment and female patients on methadone remained unchanged. In the same cohort, women treated with naltrexone were found to have significantly reduced mortality rates compared with women treated with
methadone and buprenorphine, while mortality rates in males were comparable in the three treatments (section 5.2). Gender differences in the effectiveness of naltrexone have been previously observed. Pettinati et al (2008), found that while high dose naltrexone was associated with reduction in cocaine and alcohol use in males, the same was not true for female patients [313]. Such a difference in gender response may be attributable to gender based difference in bioavailability, distribution, metabolism and elimination of the naltrexone or potentially a difference in sensitivity of the opioid pathways [313].

Treatment periods

The first 28 days following the commencement of treatment was shown to be a highly risky period in terms of opioid overdose, particularly in patients treated with methadone where fatalities were high. However, regardless of treatment, the first month of treatment should be viewed as an increased risk period for opioid poisoning in stabilising illicit opioid users with steps taken to identify and intervene with high risk individuals.

Opioid poisoning co-diagnoses

Both fatal and non-fatal opioid overdoses were commonly associated with the use of other non-opioid drugs (67.3% and 55.4% respectively). The presence of non-opioid drugs is common in opioid overdoses in Australia and similarly in a review of 200 opioid overdoses, two or more different drugs were found in 71% of autopsies, with alcohol found in 45% of cases and benzodiazepines found in 26%. In addition to depressing respiratory function itself, low doses of alcohol have also been shown to reverse respiratory depressant effects of morphine, further accounting for the high rates of opioid-alcohol co-diagnosis [48]. Further investigation is required to examine what drugs were present in this cohort and at what concentrations.

While intentional self-harm was a common co-diagnosis in non-fatal opioid overdoses, occurring in almost half of the opioid overdose admissions (48.0%), it was only listed as a co-diagnosis in 6.3% of fatal opioid overdoses. Suicide may have been underreported in fatal overdoses and may have been easily mistaken for an unintentional overdose, particularly as blood morphine levels are not accurate indicators of intent [33-35].

Respiratory and cardiovascular diagnoses were commonly associated with opioid overdose. Respiratory co-diagnosis was most prevalent in fatal opioid overdose in methadone patients, particularly while on treatment. This may be attributed to methadone’s ability to depress respiratory function.
Factors associated with risk of fatal opioid overdose

Hospitalisation for an opioid overdose in the two years prior to treatment and following initial treatment were associated with a significant increase in the risk of dying of an opioid overdose. As such, strategies to reduce the rates of fatal opioid overdoses could be implemented by both drug and alcohol treatment services at the commencement of treatment and at hospitals following admission for an opioid overdose. This is in keeping with previous research by Stoove et al (2009) that found individuals who experience more than two opioid overdoses attended by an ambulance were at a more than a 7 fold increase in risk of dying of an opioid overdose compared with individuals who experience just a single opioid overdose [314].

Unsurprisingly, as described previously, male patients were at a high risk of fatal opioid poisoning, with males dying of opioid poisoning at twice the rate of female patients in both models. Such has traditionally been associated with increased risky behaviour in males [20, 154, 288]. Interestingly, post-treatment hospital admission with a cardiovascular diagnosis was associated with a significant increase in fatal opioid overdose. Opioid use disorders have been associated with high rates of cardiovascular disease and cardiovascular abnormalities in both illicit opioid user and those on opioid pharmacotherapies such as methadone [97, 99] and represents a major cause of death in opioid dependent patients, accounting for between 1.0 to 18.9% of all deaths, or approximately 0.9 deaths per 1000 patient years (ptpy) [20]. Prior hospitalisations with cardiovascular diagnoses may be indicative of cardiovascular damage or susceptibility, making a patient less resilient to opioid overdoses.

Following the commencement of treatment, hospitalisation for a mental health event was also positively associated with an increased risk of opioid poisoning. One possible explanation may be that patients with a mental health associated hospital admission may be more likely to attempt suicide using opioids or be more likely to combine opioids with other illicit or licit drugs.

Rates of fatal opioid overdose were not significantly different in patients diagnosed with HCV compared with those not diagnosed with HCV. While HCV is a common cause of hepatic damage in intravenous drug users, the effects of HCV are highly variable with most patients initially experiencing minimal or no symptoms, with significant liver impairment often taking decades to develop [315].
Limitations

Rates of non-fatal opioid poisoning were limited to those requiring hospital admission, and thus did not including opioid poisoning that required only emergency department attendance, or those who did not seek medical assistance. As such, ratios of fatal to non-fatal opioid overdoses in this study were much lower than previous studies. For example, in a study by Darke et al (2003) ratio of fatal to non-fatal opioid overdoses were reported as 1:31 based on self-reported accounts of non-fatal opioid overdoses [316]. Similarly, in a prospective study, Neale (2003) using self-reported opioid overdoses calculated a ratio of fatal to non-fatal overdose of 1:26 [317]. Additionally, as the study used only state wide datasets, both fatal and non-fatal opioid overdoses that occurred interstate or overseas may not have been included in the study.

The study has a naturalistic design, with patients having self-selected their own treatment. The lack of randomisation may result in some bias, with certain patient groups more likely to select certain treatments. Research using this patient cohort and examining the patient’s first treatment, found some evidence to suggest that restrictions placed on patients entering methadone and buprenorphine programs may have resulted in patients with more severe health problems entering implant naltrexone treatment, where barriers to treatment are minimal (Section 5.3).

Conclusions

Induction on an opioid pharmacotherapy is associated with an increased risk of opioid overdose, particularly in methadone treated patients where the outcome is often fatal. Hospital data could be used to identify opioid dependent patients at a high risk of opioid overdose death.
5.5. **Paper 5: Self-injuring behaviour and mental illness in opioid dependent patients treated with implant naltrexone, methadone and buprenorphine**

**Abstract**

**Aims:** To compare rates of intentional self-harm (ISH) and other mental illness events in opioid dependent patients treated implant naltrexone, with those treated with methadone or buprenorphine.

**Methods:** Patients treated between 2001 and 2010 were cross-matched with hospital, emergency (ED), out-patient mental health and mortality records. Rates of health events were compared between the three groups using survival analysis and generalized estimating equations.

**Results:** ISH and other mental illness were significant contributors to the burden of disease accounting for 7.0% and 28.3% of hospital admissions respectively and 14.3% of all fatalities. Rates of suicide and ISH in patients following the commencement of treatment with implant naltrexone were comparable to patients treated with methadone or buprenorphine. Rates of mental health and psychiatric hospital admissions, ED attendances and out-patient mental health events were significantly lower in patients treated with methadone compared with naltrexone. Buprenorphine patients had higher rates of psychiatric admission, but lower rates of ED and out-patient mental health events compared with naltrexone patients. The difference in mental health events appeared to be associated with high rates of pre-treatment events in female naltrexone patients.

**Conclusions:** Naltrexone was associated with high rates of mental health events, however further controlled research is required.

**Introduction**

Endogenous opioids have euphoric properties and have been linked to mood modulation [318]. As such, dysfunction and abnormalities in the opioid system have been linked to non-suicidal self-injuring (NSSI), suicidal behavior (SB) and a number of mental health disorders including depression, anxiety and schizophrenia [319-322].
The opioid system has been proposed as a mechanism behind NSSI based on (i) the use of opioid antagonists such as naltrexone in the partial reversal of symptoms [169], (ii) reduced levels of beta-endorphin and met-encephalin in the CSF of NSSI individuals compared with controls [323], and (iii) reports of reduced pain sensitivity [324, 325]. In suicidal patients, changes to the affinity and distribution of the mu-opioid receptor have been observed [321, 326-328].

Genetic variation in the neutral endopeptidase gene involved in the metabolism of encephalin has also been associated with phobic anxiety, obsessive compulsivity, and general anxiety [329]. Consistent with this, the removal of the delta opioid receptor in knock-out mice was shown to result in increased levels of anxiety and depression [330]. Similarly, examination of serum β-endorphin levels, found that high levels may be associated major depression [319], and more severe anxiety, phobia and compulsivity in depressed patients [331]. Additionally, alterations to the opioid system have been observed in patients with schizophrenia [332], and post-traumatic stress disorder [333, 334].

High rates of self-harming behavior and other mental health disorders have been observed in opioid dependent patients [335, 336]. This may be the result of an attraction of individuals with such behaviors to opioid use as a form of self-medication, the contribution of continual opioid use to the neuroadaptation of structures in the brain that contribute to mood homeostasis [318], a shared genetic influence/vulnerability or shared environmental triggers [337] or a combination of these factors.

While opioids may precipitate the occurrence of some mental health disorders, opioids have also been used in the treatment of anxiety and depression for thousands of years [164]. However, conversely, as noted above, treatment with naltrexone, an opioid antagonist, has shown to reduce NSSI behavior in affected patients [169]. More recently, the use of buprenorphine, a partial opioid agonist/antagonists has been found to significantly reduce depressive symptoms in both opioid and non-dependent patients [165, 166, 338].

Given the significant role endogenous opioids likely play in mood stabilization, and the high rates of mental health disorders in opioid dependent patients, concerns have arisen regarding the use of opioid antagonists in the treatment of opioid use disorders. In non-dependent controls, the use of the short acting opioid antagonist naloxone was shown to dose dependently increase self-ratings of both tension-anxiety and anger-hostility [339, 340]. However in opioid dependent patients, preliminary evidence suggests the use of naltrexone is
not associated with increase rates of depression [276] or mental health related hospitalization [167]. However, given the significant role endogenous opioids likely play in mood stabilization the use of methadone a full opioid agonist, or buprenorphine, a partial agonist regularly used to management heroin dependence might also influence the occurrence of mental health events in at risk individuals.

This study examined changes in the occurrence of serious self-injuring behavior and other mental health events in opioid dependent patients following treatment with implant naltrexone, compared with patients treated with methadone, or buprenorphine.

**Methods**

**Participants**

The study included all opioid dependent patients treated for the first time with methadone, buprenorphine or implant naltrexone in Western Australia (WA) between January 2001 and December 2010. All included patients were over the age of 18 years at the time of first treatment. Further details of the study cohort are outlined in section 5.3.

**Data linkage**

Data on study participants treated with methadone or buprenorphine were obtained from the WA Department of Health Monitoring of Drug of Dependence System (MODDS). Data on participants treated with implant naltrexone were obtained from clinic treatment records. Participant information was provided to the WA Data Linkage Branch, where it was linked with data from the Hospital Morbidity Data System (HMDS), the Emergency Department Data Collection (EDDC), the Mental Health Information System (MHIS), and the WA Death Registry (WADR). Records from the HMDS, MHIS, and WADR were provided from 1999 to 2012, however ED data was only available from 2002 onwards.

**Analysis**

Hospitalizations and fatalities involving ISH or suicide were ascertained from the assigned ICD-10 code for each event (ICD-10: X60 – 84 / Y87), both primary and additional diagnoses, with hospital events having up to 20 diagnostic codes and fatalities up to 9. At present, ICD-10 codes do not distinguish between NSSI and SB, thus the two categories of were combined. Rates of suicide and hospitalizations with a diagnosis of ISH were calculated for the three
groups and expressed per 1000 patient years (ptpy). ED data was not utilized in examining ISH, as only one diagnosis code is used per admission and this usually described the injuries rather than the cause.

Similarly hospital and ED attendances with a mental health diagnosis were identified using ICD-10 codes (F01 – 9; F20 - 99). Rates of hospital admissions and ED attendances with a mental health disorder were calculated and expressed ptpy. Additionally rates of hospital admissions in which the patient was admitted to a psychiatric ward (in-patient) were calculated as a further indicator of the mental health of the three cohorts. Rates of out-patient mental health events were also calculated and expressed ptpy.

Rates of ISH and other mental illnesses were calculated for the induction period (0 – 28 days), on treatment (29 – cessation of treatment) and off treatment (cessation to the commencement of a new treatment or 31st of December 2012). With the exception of fatalities, pre-treatment rates of ISH and mental illness were also calculated (12 months prior to the commencement of the first treatment)

Rates of fatalities involving ISH were compared using Cox proportional hazard regression models, while rates of non-fatal events, with the exception of pre-treatment events, were compared using Generalized Estimating Equations with a negative binomial distribution and a log link. Rates of pre-treatment events and gender were factored into the analysis of non-fatal events. Patients may have been treated with more than one treatment, and changing treatments was accounted for in the analysis, however treatments were excluded if the patient was on more than one treatment at that time.

Results

Demographics

The study consisted of 5646 opioid dependent patients, of whom 1461 had been treated with implant naltrexone, 3515 had been treated with methadone and 3250 had been treated with buprenorphine. The participant and treatment details have been outlined in section 5.3.
**Intentional self-harm**

Of the 314 deaths observed in the opioid dependent patient cohort, 45 deaths (14.3%) were classified as suicide, equating to 1.1 deaths per 1000 patient years (ptpy). Fatalities involving suicide were predominantly the result of hanging/strangulation/suffocation (48.9%), poisoning (24.4%) and exposure to gases and vapors (11.1%).

Overall rates of suicide were not significantly different between patients treated with implant naltrexone, methadone or buprenorphine. However, while on treatment rates of suicide were significantly elevated in patients treated with implant naltrexone compared with those treated with buprenorphine (p = 0.039). During the induction period (first 28 days of treatment) and following the cessation of treatment there was no significant difference between the three groups in rates of suicide.

Of the 20,066 hospital admissions, 1401 were assigned a diagnosis associated with ISH (7.0%), equating to 34.0 admissions ptpy. Of these ISH admissions, 8 resulted in the death of the patient (0.6%). For every fatal suicide, there were 30.9 admissions to hospital with a diagnosis of ISH. The most common method of ISH resulting in hospitalization was poisoning (76.4%), injury with a sharp object (5.1%), and hanging/strangulation/suffocation (1.8%).

Prior to treatment entry, persons who entered implant naltrexone treatment had the highest rate of ISH (63.0 admissions ptpy), followed by buprenorphine (48.8 ptpy) and methadone (47.5 ptpy) Table 17. Considering the total period following treatment entry and exit, rates of ISH in patients treated with implant naltrexone were not significantly different to those treated with methadone (RR: 0.92, CI: 0.77 – 1.09) or buprenorphine (RR: 0.86, CI: 0.72 – 1.02). Similarly there was no difference in the number of patients in each cohort with 1 or more ISH admissions (9.9% naltrexone, 8.7% methadone and 7.2% buprenorphine). Rates of ISH hospitalization were highest in naltrexone treated patients during the induction period and were significantly elevated in comparison to methadone (RR: 0.26, CI: 0.14 – 0.51) and buprenorphine (RR: 0.57, CI: 0.33 – 0.99). Rates of ISH hospitalization were also significantly elevated in naltrexone treated patients while on treatment in comparison to methadone (RR: 0.54, CI: 0.40 – 0.73) and buprenorphine (RR: 0.38, CI: 0.27 – 0.53). However following the cessation of treatment, rates of ISH were significantly lower in patients treated the naltrexone compared with both methadone (RR: 1.35, CI: 1.10 – 1.67) and buprenorphine (RR: 1.28, CI: 1.03 – 1.59).
Table 17: Rates of mortality and hospital admissions involving self-injuring behaviour in patients treated with implant naltrexone, methadone, or buprenorphine.

<table>
<thead>
<tr>
<th></th>
<th>Naltrexone</th>
<th>Methadone</th>
<th>Buprenorphine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fatalities</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post treatment</td>
<td>1.3</td>
<td>1.2</td>
<td>0.9</td>
</tr>
<tr>
<td>- Induction</td>
<td>4.3</td>
<td>4.0</td>
<td>4.1</td>
</tr>
<tr>
<td>- On treatment</td>
<td>2.5</td>
<td>0.8</td>
<td>0.4*</td>
</tr>
<tr>
<td>- Off treatment</td>
<td>0.9</td>
<td>1.3</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>Hospitalization</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-treatment</td>
<td>63.0</td>
<td>47.5</td>
<td>49.8</td>
</tr>
<tr>
<td>Post-treatment</td>
<td>40.9</td>
<td>35.1</td>
<td>29.3</td>
</tr>
<tr>
<td>- Induction</td>
<td>164.8</td>
<td>28.3***</td>
<td>64.0*</td>
</tr>
<tr>
<td>- On treatment</td>
<td>60.4</td>
<td>24.5***</td>
<td>18.9***</td>
</tr>
<tr>
<td>- Off treatment</td>
<td>31.5</td>
<td>43.8**</td>
<td>34.1*</td>
</tr>
</tbody>
</table>

* p < 0.05, ** p < 0.01, *** p < 0.001 (compared with naltrexone-treated patients, no adjustment has been made for multiple comparisons)

Mental health presentations

Of the 20 066 hospital admissions observed in the opioid dependent cohort, 5 671 hospital admissions were assigned a mental health diagnosis (28.3%) and 4788 admissions involved admission to a psychiatric ward (23.9%), equating to 137.7 and 116.2 admissions ptpy respectively. While mental health and psychiatric admissions largely overlapped, not all psychiatric admissions were counted as mental health admissions and vice versa. Psychiatric admissions included patients admitted to a psychiatric ward for substance use issues (ICD-10 F10 – F19), while mental health disorders associated with substance use were excluded from hospital admissions with a mental health diagnosis.

Prior to treatment entry, persons who entered implant naltrexone had higher rates of hospital admissions with a mental health diagnosis, and rates of psychiatric admissions compared with methadone and buprenorphine. Similarly, rates of both mental health and psychiatric hospital admissions were significantly elevated in implant naltrexone patients compared with methadone following the commencement of treatment, however compared with buprenorphine only rates of psychiatric admission were significantly higher (Table 18).
Table 18: Rates of hospital, ED and out-patient mental health events in opioid dependent patients treated with implant naltrexone, compared with methadone and buprenorphine.

<table>
<thead>
<tr>
<th></th>
<th>Naltrexone</th>
<th>Methadone</th>
<th>Buprenorphine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hospitalization – mental health diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-treatment</td>
<td>183.4</td>
<td>129.7</td>
<td>135.4</td>
</tr>
<tr>
<td>Post-treatment</td>
<td>169.3</td>
<td>112.3***</td>
<td>156.2</td>
</tr>
<tr>
<td>- Induction</td>
<td>316.5</td>
<td>193.8*</td>
<td>224.9</td>
</tr>
<tr>
<td>- On treatment</td>
<td>138.8</td>
<td>92.4</td>
<td>141.8*</td>
</tr>
<tr>
<td>- Off treatment</td>
<td>169.0</td>
<td>124.0***</td>
<td>176.4*</td>
</tr>
<tr>
<td><strong>Hospitalization – admission to a psychiatric ward</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-treatment</td>
<td>160.2</td>
<td>83.1</td>
<td>88.9</td>
</tr>
<tr>
<td>Post-treatment</td>
<td>130.9</td>
<td>90.8***</td>
<td>142.8*</td>
</tr>
<tr>
<td>- Induction</td>
<td>199.5</td>
<td>171.6</td>
<td>233.2</td>
</tr>
<tr>
<td>- On treatment</td>
<td>92.3</td>
<td>67.6</td>
<td>150.6***</td>
</tr>
<tr>
<td>- Off treatment</td>
<td>162.9</td>
<td>105.5***</td>
<td>169.5</td>
</tr>
<tr>
<td><strong>Emergency department – mental health attendances</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-treatment</td>
<td>94.6</td>
<td>81.3</td>
<td>70.9</td>
</tr>
<tr>
<td>Post-treatment</td>
<td>87.2</td>
<td>57.8**</td>
<td>43.8***</td>
</tr>
<tr>
<td>- Induction</td>
<td>176.6</td>
<td>57.0***</td>
<td>51.6***</td>
</tr>
<tr>
<td>- On treatment</td>
<td>79.6</td>
<td>44.4**</td>
<td>29.5***</td>
</tr>
<tr>
<td>- Off treatment</td>
<td>68.2</td>
<td>55.2</td>
<td>48.9*</td>
</tr>
<tr>
<td><strong>Out-patient mental health attendance</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-treatment</td>
<td>1482.5</td>
<td>1515.2</td>
<td>1505.2</td>
</tr>
<tr>
<td>Post-treatment</td>
<td>2027.9</td>
<td>1644.8***</td>
<td>1796.6***</td>
</tr>
<tr>
<td>- Induction</td>
<td>2207.0</td>
<td>1922.3***</td>
<td>1816.0***</td>
</tr>
<tr>
<td>- On treatment</td>
<td>1791.8</td>
<td>1462.0</td>
<td>1547.7***</td>
</tr>
<tr>
<td>- Off treatment</td>
<td>2040.7</td>
<td>1777.1</td>
<td>1954.9*</td>
</tr>
</tbody>
</table>

* p < 0.05, ** p < 0.01, *** p < 0.001 (compared with naltrexone-treated patients, no adjustment has been made for multiple comparisons)

1. Hospital admission exclude admissions in which the patient was admitted as an in-patient to a psychiatric ward

Personality disorders were the most common mental health diagnosis associated with hospital admissions, accounting for around a third of all mental health admissions (Table 19), followed by depression, anxiety, schizophrenia and bipolar. Compared with the naltrexone cohort, there
were fewer patients in the methadone cohort with a hospital admission with a bipolar diagnosis, and fewer patients in the buprenorphine cohort with a hospital admission with a personality disorder diagnosis.

Table 19: Rates of type specific mental health hospital admissions in opioid dependent patients treated with implant naltrexone, methadone or buprenorphine.

<table>
<thead>
<tr>
<th></th>
<th>Naltrexone</th>
<th>Methadone</th>
<th>Buprenorphine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rate (ptpy)</td>
<td>% of pt</td>
<td>Rate (ptpy)</td>
</tr>
<tr>
<td>Mental health</td>
<td>169.3</td>
<td>18.1</td>
<td>112.3***</td>
</tr>
<tr>
<td>Anxiety</td>
<td>11.8</td>
<td>3.1</td>
<td>18.1**</td>
</tr>
<tr>
<td>Bipolar</td>
<td>24.1</td>
<td>2.3</td>
<td>4.8***</td>
</tr>
<tr>
<td>Depression</td>
<td>35.9</td>
<td>3.4</td>
<td>22.0***</td>
</tr>
<tr>
<td>Personality disorder</td>
<td>52.8</td>
<td>6.7</td>
<td>41.5**</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>45.9</td>
<td>2.0</td>
<td>17.5***</td>
</tr>
</tbody>
</table>

* p < 0.05, ** p < 0.01, *** p < 0.001 (compared with naltrexone-treated patients, no adjustment has been made for multiple comparisons)

Ptty = per 1000 patient years

Of the 28 832 ED attendances, 1490 were assigned a mental health diagnosis (5.2%) equating to 57.7 attendances ptty. As per mental health hospital admission, rates of pre-treatment mental health ED attendances were highest in patients treated with implant naltrexone (94.6 admissions ptpt), followed by methadone (81.3 ptty) and buprenorphine (70 ptty). Following the commencement of treatment, rates of ED attendance with a mental health diagnosis in patients treated with implant naltrexone was elevated compared with methadone and buprenorphine, particularly during induction period and while on treatment.

Overall 72 665 out-patient mental health events were recorded (1764.2 ptty), with a median contact time of 30 mins (IQR: 15 – 60 mins). Post treatment rates of out-patient mental health events in naltrexone treated patients were significantly elevated compared with both methadone and buprenorphine patients, however the percentage of patients attending mental health out-patient events in each treatment was not significantly different (naltrexone: 29.8%, methadone: 33.1% and buprenorphine 27.2%).

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Gender differences

Rates of mental health events in male patients in the three groups were comparable with the exception of high rates of mental health out-patient attendances in naltrexone patients compared with both methadone and buprenorphine patients. In contrast, females in the naltrexone cohort had very high rates of mental health events across all measures compared with methadone and buprenorphine patients, but showed substantial reductions following treatment with the exception of out-patient mental health events which increased following treatment (Figure 4).
Figure 4: Rates of mental health events before treatment (solid) and after treatment (diagonals) in opioid dependent patients treated with naltrexone (NTX), methadone (MMT) or buprenorphine (BUP) by gender.
Discussion

Prior to treatment there were differences in severity and/or prevalence of ISH and other mental illness in patients entering the three treatments. In particular, female patients receiving naltrexone implant treatment had very high rates of mental health events compared with methadone and buprenorphine. Despite poorer initial mental health pre-treatment, female patients treated with implant naltrexone showed a reduction in rates of hospital and ED attendances with a mental health diagnosis. Consistent with this improvement and stabilisation, rates of out-patient mental health events amongst females treated with implant naltrexone increased, while remaining relatively unchanged in methadone and buprenorphine patients of both sex. Increases in the rates of out-patient mental health events may not be associated with increases in mental illness, but rather better monitoring and management of mental health conditions and integration into mental health services.

The study raises concerns about the equity and access to service delivery to opioid dependent patients with mental health comorbidity. Those with the most severe mental health histories, particularly female patient with severe mental illness, are less likely to be afforded the opportunity to enter methadone or buprenorphine maintenance. One possible explanation is that the criteria for entering methadone and buprenorphine treatment in WA is more stringent than for implant naltrexone, with patients with a psychiatric illness (including patients at risk of suicide or ISH) either considered unsuitable for treatment, or unable to comply with the assessment procedure which might include time delays and multiple appointments. Notwithstanding, this lack of equitable access to publicly available treatment services requires urgent investigation and addressing.

While the rates of hospital admissions for different mental illnesses fluctuated between treatments, the percentage of patients attending hospital one or more times for a single illness was far more comparable. Rates of individual rates of mental illness were less reliable due to the skewed nature of the data and several outliers. Taking into account pre-treatment admission, there was significantly lower rates of patients admitted to hospital with a bipolar diagnosis in methadone treated patients compared with naltrexone patients. Similarly, fewer patients in the buprenorphine cohort were admitted to hospital with a personality disorder diagnosis compared with naltrexone patients. Further research is required to compare mental health outcomes by diagnosis.
During induction onto all pharmacotherapies rates of suicide were high, however in methadone and buprenorphine cohorts this was not associated with high rates of hospitalisation for ISH, while in naltrexone patients hospitalisation for ISH were significantly elevated compared with methadone and buprenorphine. Overall rates of other mental health events were also generally elevated in naltrexone treated patients compared with methadone and buprenorphine. It is thought that this may be attributable in some part to the co-occurrence of opioid detoxification/withdrawal in patients treated with naltrexone who were using opioids until the time of treatment. In contrast, patients can be transitioned onto methadone or buprenorphine from other opioids with minimal (if any) withdrawal symptoms.

On treatment, rates of suicide were higher in patients treated with implant naltrexone compared with patients treated with buprenorphine. Rates of hospitalisation for ISH, mental health disorders and psychiatric admissions were also elevated in naltrexone treated patients compared with both methadone and buprenorphine patients. While it is possible this difference may be attributable to the involved pharmacotherapies, it is likely that the difference is primarily associated in pre-treatment difference in the three cohorts. Importantly, while on treatment, rates of hospitalisation for ISH and mental health disorders were less while on treatment in all three pharmacotherapies as compared with pre-treatment levels.

Once patients were off treatment, rates of suicide and hospitalisation for intentional self-harm were not significantly different. Similarly, hospitalisation for mental health disorders and admissions to the psychiatric ward in patients treated with implant naltrexone were not significantly different to patients treated with buprenorphine, however rates in methadone patients were significantly less than naltrexone patients.

The methods used to commit suicide were consistent with previously published Australian data [341], with approximately half the result of strangulation/hanging and quarter the result of poisoning. In contrast, three quarters of non-fatal ISH was the results of poisoning, with only 1.8% occurring as a result of strangulation/hanging.

Female patients had higher rates of hospital and ED attendances for ISH and other mental health diagnoses. Gender differences in rates of mental illness have been previously observed, with difference dependent on the type of mental illness [342]. In a US study of 43,093 persons, women had higher rates of mood and anxiety disorders, while men had higher rates of anti-social personality and substance use disorders [343]. The study hypothesised that women had higher mean levels of internalising, while men showed higher mean levels of externalising,
corresponding with varying levels of internalising (mood and anxiety) and externalising (anti-social and substance use) disorders. Hospital and emergency department attendances related to anti-social and substance use disorders may be less likely to be identified or present as a mental health disorder compared with mood or anxiety disorders, accounting for the gender differences in this study.

Clinical implications

While ISH and other mental illness contribute significantly to the burden opioid use disorders places on health services, only around 1 in 12 patients were admitted to hospital for ISH and 1 in 6 for a mental illness following the commencement of treatment. Thus to be effective, this subset of patients should be targeted to reduce mental health morbidity.

Limitations

One of the limitations of the data used is the grouping of NSSI and SB in the ICD-10 coding of hospital and ED attendances. Although both NSSI and SB involve self-injuring behaviour, there is generally substantial difference in the intention, frequency and lethality of the behaviour.

The study was a retrospective cohort study, thus patients selected the treatment they deemed most suitable. The lack of randomisation may have resulted in particular patient groups choosing certain treatment type.

Rates of health events should be considered a minimum, as the project was only able to collect health events that occurred within WA. Additionally, a significant portion of fatalities, hospital, ED attendances and mental health out-patient events were not assigned a diagnosis.

Conclusions

ISH and mental illness were large contributors to morbidity and mortality in opioid dependent patients on treatment, however the majority of patients had no ISH or mental health events. Implant naltrexone appears to be associated with high rates of mental illness, however this may be attributable to the high rate of mental health service utilization in female patients prior to entering naltrexone treatment.
6. Pregnancy in Opioid Dependent Women Treated with Implant Naltrexone, Methadone and Buprenorphine

6.1. Forward

The final research chapter examines the use of naltrexone as a treatment for opioid dependent women during pregnancy and compares outcomes using pregnancy, birth and early childhood, with opioid dependent women treated with methadone and buprenorphine. The study also compares outcomes in women treated with naltrexone and their exposed controls with non-dependent controls and their children. Specifically, the study wished to answer the following questions:

- Are birth rates in naltrexone treated women comparable to women treated with methadone or buprenorphine, and non-dependent controls?
- What are the obstetric, neonatal and childhood risks associated with the use of sustained release naltrexone during pregnancy and how do they compare to methadone, buprenorphine and non-dependent controls?

These questions are addressed in the three following papers. The first paper examines maternal outcomes and outcomes during pregnancy, the second paper looks at the health of the exposed neonate, while the third follows the health of the exposed neonate into early childhood.
6.2. **Paper 6: A retrospective cohort study of obstetric outcomes in opioid dependent women treated with implant naltrexone compared with methadone, buprenorphine and non-dependent controls**

**Abstract**

*Background:* Opioid pharmacotherapies play an important role in the treatment of opioid dependent women, however very little is known about the safety of naltrexone in pregnant patients.

*Objective:* This study examined the obstetric health of opioid dependent women who were treated with implant naltrexone during pregnancy, and compare them with women treated with methadone, buprenorphine and a cohort of non-opioid dependent controls.

*Methods:* Women treated with implant naltrexone, oral methadone or sublingual buprenorphine between 2001 and 2010, along with a cohort of age matched controls were linked with midwives, hospital, and emergency department (ED) records and the death registry to identify pregnancy and health events that occurred during pregnancy and in the post-partum period.

*Results:* Overall rates of pregnancy loss (requiring hospital or ED attendance) were significantly elevated in naltrexone-treated women compared with buprenorphine treated women (p = 0.018) and controls (p < 0.001), however were not statistically different to methadone-treated women (p = 0.210). Birth rates in women on naltrexone implant treatment were significantly higher than all three comparison groups (p < 0.001). Rates of hospital and ED attendances during pregnancy in the naltrexone-treated women were not statistically different to either methadone or buprenorphine groups, as were overall complications during pregnancy and labour. Overall rates of complications during pregnancy were significantly higher in the naltrexone-treated women as compared to the controls.

*Conclusion:* Opioid-dependent women treated with naltrexone implant had higher rates of birth compared with the other three groups (methadone- or buprenorphine-treated women, or age-matched controls). Overall rates of complications during pregnancy were elevated in
naltrexone-treated women when compared with the control group, but were generally not significantly different to rates in methadone- or buprenorphine-treated women.

**Introduction**

Naltrexone is an opioid antagonist, used in the treatment of opioid use disorders. While pharmacologically effective, the clinical efficacy of naltrexone has been problematic due to non-compliance issues with the oral formulation [126]. The development of sustained release naltrexone preparations to overcome non-compliance has resulted in superior clinical efficacy [146]. However, the use of these preparations has generated a number of clinical questions in regards to safety outcomes in pregnancy and fertility.

With sustained release naltrexone preparations becoming more readily available, concerns have arisen regarding the potential for women to become pregnant on treatment. Some clinical observations, suggest that the incidence of pregnancy may increase following naltrexone treatment, potentially due to the cessation of opioids (and thus the restoration of normal menstruation), increased sex drive, re-establishment of relationships, and increased self-care (nutrition, hygiene etc.). Alternatively, the increased incidence may be directly attributable to naltrexone, with naltrexone shown to simulated luteinising hormone (LH) and follicle stimulating hormone (FSH) during the early follicular phase of the menstrual cycle [212, 213]. As such, clinically naltrexone has been found to induce ovulation and re-instate normal menstruation in non-opioid dependent women with weight loss associated and hypothalamic, amenorrhea and polycystic ovarian disease [105, 174, 214]. Notwithstanding, rates of pregnancy and birth in naltrexone-treated opioid dependent women has not been reported.

Increased rates of pregnancy are a concern as the effects of naltrexone on the developing fetus and the pregnant mother are not fully understood [215]. Clinically the use of naltrexone has only been presented in a small number of case studies and a brief report on a case series [211, 216, 344], with generally unremarkable outcomes. However, the scope of these studies has generally been limited to basic neonatal outcomes (birth weight, gestation length, apgar scores). Similarly non-clinical studies of the use of naltrexone in pregnancy have focused on neonatal health rather than maternal health [111].

In addition to concerns regard the direct effects of naltrexone on maternal and fetal safety, concerns have also arisen about the requirement for opioid withdrawal prior to induction on to naltrexone potentially resulting in intrauterine abstinence syndrome, which may have
detrimental effects on the fetus [345, 346]. Similarly concerns have arisen regarding the use of oral naltrexone during pregnancy and the potential for treatment drop out, relapse and opioid overdose, possibly resulting in both maternal and fetal harm [211]. Additionally, high rates of fatal and non-fatal opioid overdose have been observed in non-pregnant opioid dependent patients following the cessation of oral naltrexone treatment [296, 347]. Additionally, the nature of the depot preparations can make cessation difficult if a patient becomes pregnant during their period of exposure and thus patients may have to remain on treatment for a predefined period.

The aim of this study is to examine rates of birth in women treated with a sustained release naltrexone preparation (an implant) and their health during pregnancy, labour, delivery and post-partum, and compare it with patients treated with methadone or buprenorphine and non-dependent controls.

**Methods**

**Subjects**

The study cohort included all women treated with implant naltrexone (manufactured by Go Medical Industries Pty. Ltd., Subiaco, Western Australia (WA), Australia) who were treated in WA between January 2001 and December 2010. Women treated with implant naltrexone were identified from clinic treatment records from a not-for-profit drug and alcohol clinic located in Subiaco WA. This clinic was the sole provider of this implant formulation in WA at the time. Pregnancies in which the neonate was exposed to naltrexone for more than 30 days were included in the study. The period of exposure following implant naltrexone treatment was considered to be 182 days based on pharmacokinetic and efficacy data [145, 146, 344].

The study also included women treated with oral methadone and sublingual buprenorphine (both buprenorphine alone (Subutex) and in combination with naloxone (Suboxone)) in WA between January 2001 and December 2010. Women treated with methadone and/or buprenorphine were identified via the Monitoring of Drug of Dependence System (MODDS). MODDS is maintained by the WA Department of Health and contains notifications of the prescribing of all schedule 8 and 9 drugs of dependence in WA. Prescribing data obtained from MODDS provided monthly records indicating whether or not the patient had received either treatment in that month. MODDS records were linked to authorization records, which contained the date in which the patient was authorized to commence treatment and the date treatment was terminated. On occasions where the authorization or termination date was
absent, the 15th of the month was used as the commencement date and the last day of the month was used for the termination date. Pregnancies in which the neonate was exposed to methadone and buprenorphine for at least 60 days were included in the study. This period was twice that of naltrexone due to potential inaccuracies in the commencement and termination dates. For methadone, the group was limited to women treated for the first time between January 2001 and December 2010 as a result of the way the data was extracted.

A cohort of age (5 year age bracket) matched non-opioid dependent controls (1:1 ratio with opioid dependent patients) was selected from the electoral roll by the Data Linkage Branch to act as a control group. The control group was matched against opioid treatment records to ensure individuals included had not previously received an opioid pharmacotherapy.

All women included in the study were aged between 18 and 45 years at the time of first treatment and at the time of childbirth. Treatments that occurred after a patient reached 45 were excluded from analysis (no births were observed in women 45 or over).

Data Linkage

The cohorts were linked by the Data Linkage Branch with Hospital Morbidity Data Collection (HMDC), Emergency Department Data Collection (EDDC) and WA Death Registry (WADR) to identify pregnancies that had resulted in maternal or fetal losses. Additionally the women were linked with the Midwives Notification System (MNS) to identify pregnancies that resulted in either a live or stillborn neonate of at least 20 weeks gestation or where gestation was unknown at least 400g birth weight. Women who were identified as having given birth were then re-linked against the HMDC and EDDC to ascertain inpatient hospital admissions and ED attendances that had occurred during the pregnancy and post-partum period. ED data were only available from 1st of January 2002, thus rates of ED attendance were calculated for women who conceived after this time. These women were also linked against the WA Notifiable Infectious Diseases Database (WANIDD) to determine rates of Hepatitis C (HCV) in the pregnant women. Table 20 summaries the dataset used and the source of key variables included in the study.
Table 20: Data sources

<table>
<thead>
<tr>
<th>Data source</th>
<th>Abbrev.</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naltrexone treatment records</td>
<td>-</td>
<td>Implantation dates</td>
</tr>
<tr>
<td>Monitoring of Drugs of Dependence System</td>
<td>MODDS</td>
<td>Monthly methadone/buprenorphine dispensing, medication type, dose</td>
</tr>
<tr>
<td>Authorisation records</td>
<td>-</td>
<td>Commencement and cessation date of methadone and buprenorphine treatment</td>
</tr>
<tr>
<td>WA Electoral Roll</td>
<td></td>
<td>Selection of matched controls</td>
</tr>
<tr>
<td>Midwives Notification Scheme</td>
<td>MNS</td>
<td>Identification of births, includes data on pregnancy and labour complications, use of anaesthetic, estimated gestation, previous pregnancies, maternal age, SEIFA</td>
</tr>
<tr>
<td>WA Death Registry</td>
<td>WADR</td>
<td>Maternal deaths during pregnancy and the post-natal period</td>
</tr>
<tr>
<td>Hospital Morbidity Data System</td>
<td>HMDS</td>
<td>Pregnancy loss and terminations that occurred in hospital</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hospitalisations during pregnancy and the post-natal period</td>
</tr>
<tr>
<td>Emergency Department Data Collection</td>
<td>EDDC</td>
<td>Pregnancy loss that resulted in ED presentation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ED attendances during pregnancy and the post-natal period</td>
</tr>
<tr>
<td>WA Notifiable Infectious Diseases Database</td>
<td>WANIDD</td>
<td>Hepatitis C diagnosis</td>
</tr>
</tbody>
</table>

ED = Emergency Department, SEIFA = Socio-economic index for areas (0 – lowest socio-economic area of residence, 10 – highest socio-economic area of residence), WA = Western Australia

**Outcomes**

The study set out to examine the following outcomes in relation to pregnant opioid dependent women treated with implant naltrexone compared with opioid dependent women treated with methadone and buprenorphine, and non-opioid dependent controls:
• Crude birth rates
• Crude and type specific rates of pregnancy loss (resulting in a hospital or ED attendance)
• Crude rates of hospital admissions during pregnancy and the postpartum period, as well as type specific (opioid, non-opioid drug, mental health, and obstetric) and trimester specific admission rates.
• Crude rates of ED attendances during pregnancy and the postpartum period, as well as type specific (opioid, non-opioid drug, mental health, and obstetric), trimester specific and severity (as indicated by triage categories) rates of ED attendances.
• Rates of type specific complications during pregnancy, labour and delivery as reported at birth.

Data Analysis

Crude birth rates for each cohort were calculated for neonates conceived on treatment (as calculated from estimated length of gestation at birth) and expressed per thousand patient years (ptpy). Rates of birth in the naltrexone cohort were compared to methadone, buprenorphine and the controls using a univariate generalized estimating equations (GEE), with a negative binomial distribution and a log link function. GEE were selected for this analysis as opioid dependent participants may have received more than one treatment, which could be accounted for in the model.

Rates of pregnancy losses identified from hospital and ED records using assigned ICD-10-AM codes and Australian Classification of Health Interventions (ACHI) codes were expressed per 1000 patient years (ptpy). Additionally, rates of type specific pregnancy losses were calculated including ectopic pregnancy (ICD-10-AM: O00), hydatidiform mole (O01), other abnormal product of conception (O02), spontaneous abortion (O03), medical abortions (O04 / ACHI: 90461-00 / 90462-00 / 90463-00 / 90463-01), and other or unspecified abortion (O05 – 06). As per rates of birth, rates of pregnancy loss were compared using a univariate GEE, which allowed for women to be included in more than one treatment group.

For outcomes associated with pregnancy and childbirth, pregnancies in which the neonates were exposed to two or more treatments were excluded from analysis. Additionally multiple births (twins and triplets) were removed. For women who had more than one birth during follow up, only one pregnancy was included in the study. Due to the sample size, priority was given to naltrexone pregnancies, followed by buprenorphine, and then methadone. Where
applicable, the first recorded pregnancy was also used in preference to subsequent pregnancies (Figure 5).

Figure 5: Flow chart of women and their exposed neonates included in the study.

For each pregnancy, maternal demographic information (smoking status, HCV status, maternal age at birth, number of previous pregnancies and socio-demographic status) was compared using univariate generalized linear models, with the exception of socio-demographic status, which was analysed using a Wilcoxon signed rank tests due to its unsuitable distribution. Socio-economic status was taken from assigned Socio-Economic Indexes for Area (SEIFA) scores and rankings. The SEIFA scores are calculated by combining information collected in the 5 yearly Census of Population and Housing. The SEIFA Index of Relative Socio-Economic Advantage/Disadvantage (IRSEAD) for 2006 was used as a crude indicator of socio-economic status. IRSEAD data was used in the form of deciles, with suburbs ranked 1 having the lowest 10% of scores for census collection districts in Australia, while those ranked 10 had the top 10% of scores.

Rates of hospital admissions and ED attendances during pregnancy and the post-partum period (first 42 days following birth) in the naltrexone cohort were compared to the three other groups using generalized linear models with a negative binomial distribution and a log link function. For overall rates, a multivariate analysis was performed taking into account smoking status, maternal age at birth, number of previous pregnancies and socio-demographic status. Univariate analysis was carried out examining rates of hospital admissions and ED attendances within each trimester and the post-partum period (first 42 days following birth),
as well as rates of events with an opioid poisoning (ICD-10-AM: T40.0–T40.4), non-opioid drug and alcohol poisoning (T36-39.9, T40.5 - 51), non-drug mental health (F0 – 10 /F20 – 99) and pregnancy/childbirth diagnosis (O00 – 99). For hospital admission both primary and additional diagnoses were used, while only a primary diagnosis was available for ED attendances (however in many cases no diagnosis was available for ED data). Rates of ED attendances were also divided into severity of attendance using assigned codes from the Australasian Triage Scale [304]. An ED attendance allocated a triage scale of 1 is indicative of an immediately life threatening condition, while a scale of 5 is considered of minimal urgency.

Multivariate linear and logistic regression was use to compare overall rates of complications during pregnancy and delivery. Multivariate analysis factored in smoking status, maternal age at birth, number of previous pregnancies and socio-demographic status. Univariate analysis was used for examining the type specific complications and other variables associated the pregnancy and delivery.

A critical p-value of 0.05 was used, with no adjustment made for multiple comparisons. Data analysis was conducted using STATA/IC 12.1.

**Ethics**

This study protocol was approved by the Department of Health Human Research Ethics Committee (2012/63) and the University of Western Australia Human Research Ethics Committee (RA/4/1/1864).

**Results**

**Demographics**

The study included 1976 opioid dependent women treated with implant naltrexone, methadone and/or buprenorphine and 1976 age matched controls. Women moved readily between the three treatments, with 676 (34.2%) treated with naltrexone, 1204 (60.9%) treated with methadone and 1178 (59.6%) treated with buprenorphine. Following their initial treatment opioid dependent participants were followed up for an average of 7.3 ± 3.0 years, while control participants were followed up for an average of 7.4 ± 3.0 years.

**Birth rates**

Birth rates in women who conceived while on naltrexone treatment were significantly higher than those on methadone (RR: 0.49, CI: 0.37 – 0.63), buprenorphine (RR: 0.53, CI: 0.40 – 0.71)
and the controls (RR: 0.49, CI: 0.38 – 0.63) (Table 21). Of the exposed pregnancies, 83.8% of the naltrexone, 68.3% of the methadone and 79.7% of the buprenorphine-treated women conceived on treatment, while the remainder was treated after becoming pregnant.

Table 21: Rates of birth and characteristics of women treated for opioid dependent with implant naltrexone, compared with women treated with methadone, or buprenorphine, and a cohort of controls.

<table>
<thead>
<tr>
<th></th>
<th>Naltrexone</th>
<th>Methadone</th>
<th>Buprenorphine</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of women</td>
<td>676</td>
<td>1204</td>
<td>1178</td>
<td>1976</td>
</tr>
<tr>
<td>Rx start age (yrs)</td>
<td>29.0 ± 6.6</td>
<td>29.1 ± 6.7</td>
<td>29.5 ± 6.6</td>
<td>28.8 ± 6.9²</td>
</tr>
<tr>
<td>Time on rx /pt (yrs)</td>
<td>1.1 ± 0.8</td>
<td>2.8 ± 2.7</td>
<td>2.0 ± 2.4</td>
<td>NA</td>
</tr>
<tr>
<td>No. of births³</td>
<td>99</td>
<td>300</td>
<td>182</td>
<td>879</td>
</tr>
<tr>
<td>No. conceived on rx</td>
<td>83</td>
<td>205</td>
<td>145</td>
<td>NA</td>
</tr>
<tr>
<td>Crude birth rates (PTPY)</td>
<td>116.2</td>
<td>60.5*</td>
<td>62.6*</td>
<td>60.7*</td>
</tr>
</tbody>
</table>

* p < 0.001 (compared with the implant naltrexone group)

Rx = treatment, Pt = participant, PTPY = per 1000 patient years

1. Participant may have been treated with more than one opioid pharmacotherapy.
2. In the control group, start age was based on the corresponding start date of their matched control
3. Includes neonates with exposed to more than one pharmacotherapy, multiple births (i.e. twins and triplets) and subsequent births.

Maternal death and pregnancy loss

No maternal fatalities were observed during pregnancy or the post-natal period.

Overall rates of abortive outcomes (requiring hospital admission or ED attendance) in naltrexone-treated women were not significantly different to women treated with methadone (RR: 0.80, CI: 0.56 – 1.14) but were higher than those treated with buprenorphine (RR: 0.63, CI: 0.43 – 0.92) and the control group (RR: 0.37, CI: 0.26 – 0.51). Elevated rates in the naltrexone cohort were primarily associated with elevated rates of ectopic pregnancies and medical abortions (Table 22).
Table 22: Rates of pregnancies with abortive outcomes requiring ED attendance or hospital admission in opioid dependent women treated with naltrexone (n = 676) compared with women treated with methadone (n = 1204), buprenorphine (n = 1187) and non-opioid exposed controls (n = 1976), expressed per 1000 patient years.

<table>
<thead>
<tr>
<th></th>
<th>Naltrexone</th>
<th>Methadone</th>
<th>Buprenorphine</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ectopic pregnancy</td>
<td>5.6</td>
<td>0.9*</td>
<td>1.3</td>
<td>1.3**</td>
</tr>
<tr>
<td>Hydatidiform mole</td>
<td>0.0</td>
<td>0.6</td>
<td>0.0</td>
<td>0.1</td>
</tr>
<tr>
<td>Other abnormal product of conception</td>
<td>5.6</td>
<td>2.7</td>
<td>4.3</td>
<td>4.8</td>
</tr>
<tr>
<td>Spontaneous abortion</td>
<td>4.2</td>
<td>13.0</td>
<td>3.5</td>
<td>5.2</td>
</tr>
<tr>
<td>Medical abortion(^1)</td>
<td>43.4</td>
<td>30.1</td>
<td>25.0*</td>
<td>9.0**</td>
</tr>
<tr>
<td>Other/unspecified abortion</td>
<td>0.0</td>
<td>0.6</td>
<td>0.9</td>
<td>0.1</td>
</tr>
<tr>
<td>Failed abortions</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td><strong>Pregnancies with abortive outcomes</strong></td>
<td>58.8</td>
<td>47.8</td>
<td>34.9*</td>
<td>20.7**</td>
</tr>
</tbody>
</table>

\(^*\) p < 0.05, \(^{**}\) p < 0.001 (compared with naltrexone-treated women, no adjustment has been made for multiple comparisons)

ED = Emergency Department

1. Includes both elective and therapeutic abortions

**Demographics of pregnant women at birth (single exposure)**

Of the 1976 women treated with an opioid pharmacotherapy, 68 naltrexone, 199 methadone and 124 buprenorphine exposed infants were born with exposure to a single pharmacotherapy and unique mother (Figure 5). Characteristics of women treated with naltrexone during pregnancy (single exposure) were similar to both methadone and buprenorphine treated women (Table 23). As compared with the control women, naltrexone-treated women were more likely to be younger (26.8 v 29.8 years), have more previous pregnancies (2.4 v 1.2 pregnancies), were less likely to be married or in a de facto relationship (52.9 v 92.3%), were of a lower socioeconomic status (SEIFA 4.9 v 5.9) and were more likely to have smoked during pregnancy (70.2 v 13.0%) and have been diagnosed with HCV (52.9 v 0.4%).

Table 23: Maternal demographics and characteristics of women treated with implant naltrexone during pregnancy compared with those treated with methadone, buprenorphine, and control women.
<table>
<thead>
<tr>
<th></th>
<th>Naltrexone</th>
<th>Methadone</th>
<th>Buprenorphine</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of mothers/pregnancies</td>
<td>68</td>
<td>198</td>
<td>126</td>
<td>569</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never married</td>
<td>45.6%</td>
<td>36.4%</td>
<td>42.1%</td>
<td>5.8%**</td>
</tr>
<tr>
<td>Married (include defacto)</td>
<td>52.9%</td>
<td>56.6%</td>
<td>52.4%</td>
<td>92.3%**</td>
</tr>
<tr>
<td>Divorced/separated/widowed</td>
<td>1.5%</td>
<td>3.0%</td>
<td>4.0%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Unknown</td>
<td>0.0%</td>
<td>2.5%</td>
<td>1.6%</td>
<td>0.5%</td>
</tr>
<tr>
<td>SEIFA</td>
<td>4.9 ± 3.0</td>
<td>4.5 ± 2.5</td>
<td>4.4 ± 2.7</td>
<td>5.9 ± 2.5*</td>
</tr>
<tr>
<td>Diagnosed with hepatitis C</td>
<td>52.9%</td>
<td>63.1%</td>
<td>60.3%</td>
<td>0.4%**</td>
</tr>
<tr>
<td>Previous pregnancies</td>
<td>2.4 (0 – 15)</td>
<td>2.6 (0 –10)</td>
<td>2.2 (0 – 7)</td>
<td>1.2 (0 – 18)**</td>
</tr>
<tr>
<td>Maternal age at birth (range)</td>
<td>26.8 (19 – 40)</td>
<td>27.8 (18 – 42)</td>
<td>27.9 (19 – 40)</td>
<td>29.8 (20 – 43)**</td>
</tr>
<tr>
<td>Smoked during pregnancy</td>
<td>70.2%</td>
<td>76.5%</td>
<td>75.8%</td>
<td>13.0%**</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>47.1%</td>
<td>58.1%</td>
<td>54.8%</td>
<td>50.4%</td>
</tr>
<tr>
<td>Estimated gestation</td>
<td>38.0 ± 2.5</td>
<td>37.7 ± 2.9</td>
<td>38.0 ± 3.0</td>
<td>38.7 ± 2.0*</td>
</tr>
</tbody>
</table>

* p < 0.01, ** p < 0.001 (compared with naltrexone-treated women, no adjustment has been made for multiple comparisons)

ED = Emergency Department, SEIFA = Socio-economic index for areas (0 – lowest socio-economic area of residence, 10 – highest socio-economic area of residence)

Pregnancy complications - hospital admission and ED attendances

Overall, rates of hospital attendances during pregnancy (including the post-natal period) in the naltrexone cohort were not significantly higher than those in either of the three comparison groups. There was no significant difference between rates of hospital admissions in naltrexone-treated women compared with either methadone or buprenorphine during the three trimesters and the post-partum period. Similarly, there was no difference in rates of cause specific admissions, with the exception of increased rates of hospital admissions with a mental health diagnosis in women treated with methadone (RR: 1.68, CI: 1.25 – 2.27).

Compared with the naltrexone group, rates of hospital admission were significantly lower in the control cohort during the second trimester (RR: 0.27, CI: 0.12 – 0.61), and the third trimester (RR: 0.78, CI: 0.63 – 0.96). Rates of obstetric (RR: 0.80 CI: 0.65 – 0.99) and mental health (RR: 0.04, CI: 0.03 – 0.08) admissions were significantly lower in the control women compared with naltrexone treated women.

Overall rates of ED attendances in the naltrexone treated women were not significantly different to both methadone and buprenorphine treated women, as were rates during the
three trimesters of pregnancy or postpartum. Overall rates of ED attendances in the naltrexone group were significantly higher than in the control group (RR: 0.57, CI: 0.33 – 0.97), as were ED attendances during the second trimester (RR: 0.35, CI: 0.18 – 0.66) and during the post-partum (RR: 0.40, CI: 0.16 – 0.99). In addition, obstetric ED attendances and triage codes three (RR: 0.37, CI: 0.19 – 0.73) and five (RR: 0.35, CI: 0.17 – 0.73) were significantly higher in the naltrexone group compared with the control group (Table 24).

Three cases of opioid poisoning were observed in patients attended hospital and/or ED, one occurred in a naltrexone-treated women prior to treatment, and the other two were in women treated with methadone (one while on methadone treatment, the other prior to treatment).

Table 24: Rate of hospital admission and ED attendances per 100 pregnancies (reaching 20 weeks) during the three trimesters of pregnancy and the post-partum period in pregnant women treated with implant naltrexone, as compared with methadone, buprenorphine and a cohort or controls.

<table>
<thead>
<tr>
<th></th>
<th>Naltrexone</th>
<th>Methadone</th>
<th>Buprenorphine</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital Admissions</td>
<td>179.4</td>
<td>186.9</td>
<td>160.5</td>
<td>135.0</td>
</tr>
<tr>
<td>Trimesters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- 1</td>
<td>2.9</td>
<td>9.0</td>
<td>4.0</td>
<td>7.0</td>
</tr>
<tr>
<td>- 2</td>
<td>19.1</td>
<td>23.6</td>
<td>16.1</td>
<td>5.1**</td>
</tr>
<tr>
<td>- 3</td>
<td>152.9</td>
<td>145.7</td>
<td>131.5</td>
<td>119.3*</td>
</tr>
<tr>
<td>- Post-partum</td>
<td>4.0</td>
<td>8.5</td>
<td>8.9</td>
<td>3.1</td>
</tr>
<tr>
<td>Admitted with a</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>diagnoses of:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Opioid poisoning</td>
<td>1.5</td>
<td>1.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>- Non-opioid drug</td>
<td>0.0</td>
<td>1.5</td>
<td>0.8</td>
<td>0.0</td>
</tr>
<tr>
<td>poisoning</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Mental health</td>
<td>76.5</td>
<td>128.6**</td>
<td>87.1</td>
<td>3.7***</td>
</tr>
<tr>
<td>- Obstetric</td>
<td>154.4</td>
<td>158.8</td>
<td>139.5</td>
<td>123.9</td>
</tr>
<tr>
<td>Median length of</td>
<td>4 (1 – 5)</td>
<td>4 (1 – 6)</td>
<td>4 (2 – 6)</td>
<td>4 (1 – 5)</td>
</tr>
<tr>
<td>stay (IQR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emergency Department¹</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attendances</td>
<td>124.5</td>
<td>180.9</td>
<td>179.7</td>
<td>55.8*</td>
</tr>
</tbody>
</table>
Trimesters

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>Post-partum</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>32.1</td>
<td>32.9</td>
<td>40.7</td>
<td>17.0*</td>
</tr>
<tr>
<td>2</td>
<td>43.4</td>
<td>52.0</td>
<td>52.0</td>
<td>15.0***</td>
</tr>
<tr>
<td>3</td>
<td>26.4</td>
<td>43.9</td>
<td>41.5</td>
<td>14.7</td>
</tr>
<tr>
<td>Post</td>
<td>22.6</td>
<td>52.0</td>
<td>45.5</td>
<td>9.1*</td>
</tr>
</tbody>
</table>

Attendances with diagnoses of:

- Opioid poisoning: 0.0 0.6 0.0 0.0
- Non-opioid drug poisoning: 3.8 2.9 0.0 0.0
- Mental health: 1.9 4.0 2.4 0.4
- Obstetric: 18.9 17.9 13.0 5.0**

ED triage code

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.2</td>
</tr>
<tr>
<td>2</td>
<td>3.8</td>
<td>11.6</td>
<td>5.7</td>
<td>2.7</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>34.0</td>
<td>31.8</td>
<td>30.1</td>
<td>12.7**</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>35.8</td>
<td>46.2</td>
<td>44.7</td>
<td>22.2</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>50.9</td>
<td>91.3</td>
<td>99.2</td>
<td>18.1**</td>
<td></td>
</tr>
</tbody>
</table>

* p < 0.05. ** p < 0.01. ***p < 0.001 (compared with naltrexone-treated women, no adjustment has been made for multiple comparisons)

ED = Emergency Department, IQR = interquartile range

1. ED date only available from 2002 onwards, thus only patients conceived after the 1st January 2002 were used in calculation of rates of ED attendances. Naltrexone, n= 53; methadone, n=172; buprenorphine, n=125; control, n=559)

Pregnancy complications - reported at birth

Rates of pregnancy complications reported at birth in naltrexone mothers were not significantly different to methadone (OR: 1.04, CI: 0.57 – 1.89) or buprenorphine (OR: 0.65, CI: 0.34 – 1.24). There was no significant difference between naltrexone and methadone or buprenorphine in any of the cause specific pregnancy complications. Compared with the naltrexone group, the control group had significantly lower rates of pregnancy complications (OR: 0.50, CI: 0.27 – 0.90), and rates of ‘other’ complications (OR: 0.44, CI: 0.23 – 0.83)(Table 25).
Table 25: Complications during pregnancy in opioid dependent women treated with implant naltrexone (n = 68) compared with women treated with methadone (n = 198), buprenorphine (n = 126) and controls (n = 569), as reported at birth in Midwife Notification System.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Naltrexone</th>
<th>Methadone</th>
<th>Buprenorphine</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>55.9%</td>
<td>58.3%</td>
<td>46.8%</td>
<td>35.3%*</td>
</tr>
<tr>
<td>Threatened abortion &lt;20 weeks¹</td>
<td>0.0%</td>
<td>2.0%</td>
<td>3.2%</td>
<td>4.2%</td>
</tr>
<tr>
<td>Threatened pre-term labour &lt;37 weeks</td>
<td>5.9%</td>
<td>4.0%</td>
<td>1.6%</td>
<td>3.4%</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>1.5%</td>
<td>6.0%</td>
<td>6.5%</td>
<td>3.7%</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>1.5%</td>
<td>4.5%</td>
<td>2.4%</td>
<td>3.2%</td>
</tr>
<tr>
<td>Antepartum haemorrhage – placenta praevia</td>
<td>1.5%</td>
<td>1.0%</td>
<td>0.0%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Antepartum haemorrhage – placenta abruption</td>
<td>1.5%</td>
<td>0.5%</td>
<td>0.8%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Antepartum haemorrhage – other</td>
<td>2.9%</td>
<td>7.0%</td>
<td>2.4%</td>
<td>4.2%</td>
</tr>
<tr>
<td>Pre-labour rupture of membranes</td>
<td>8.8%</td>
<td>9.1%</td>
<td>4.0%</td>
<td>3.7%</td>
</tr>
<tr>
<td>Gestational diabetes</td>
<td>5.9%</td>
<td>0.5%</td>
<td>0.8%</td>
<td>3.4%</td>
</tr>
<tr>
<td>Other</td>
<td>35.3%</td>
<td>39.2%</td>
<td>36.3%</td>
<td>16.5%*</td>
</tr>
</tbody>
</table>

* p < 0.05 (compared with naltrexone-treated women, no adjustment has been made for multiple comparisons)

1. Vaginal bleeding with the uterus determined to be the source of bleeding before the 20th gestational week

Characteristics of labour and delivery

Lower rates of spontaneous labour / higher rates of induced labour were observed in buprenorphine-treated women compared with the naltrexone-treated women. Similarly, rates of spontaneous vaginal birth were also significantly higher in naltrexone treated women compared with buprenorphine treated women (Table 26). There was no significant difference between naltrexone-treated women and the other cohorts in their use of anesthetics or analgesics, except higher rates of the use of combined epidural/spinal anesthetic in buprenorphine-treated women.

Rates of delivery complications in naltrexone-treated women were not dissimilar to methadone and buprenorphine. Overall rates of labour complications in the naltrexone-treated women were not significantly different to the non-dependent controls (OR: 0.54, CI:
0.29 – 1.03), although rates of fetal distress were significantly elevated in naltrexone-treated women compared with the control group (OR: 0.29, CI 0.14 – 0.61).

Table 26: Labour and deliver characteristic in opioid dependent women treated with implant naltrexone (n = 68) compared with those treated with methadone (n = 198), buprenorphine (n = 126) and non-dependent controls (n = 569).

<table>
<thead>
<tr>
<th></th>
<th>Naltrexone</th>
<th>Methadone</th>
<th>Buprenorphine</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Onset of labour</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Spontaneous</td>
<td>54.4%</td>
<td>49.3%</td>
<td>38.7%**</td>
<td>48.2%</td>
</tr>
<tr>
<td>- Induced</td>
<td>29.4%</td>
<td>33.7%</td>
<td>45.2%</td>
<td>30.2%</td>
</tr>
<tr>
<td>- No-labour (caesarean)</td>
<td>16.2%</td>
<td>17.1%</td>
<td>16.1%</td>
<td>21.6%</td>
</tr>
<tr>
<td><strong>Intended place of birth</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Hospital</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>96.7%</td>
</tr>
<tr>
<td>- Birth centre</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>3.3%</td>
</tr>
<tr>
<td>Born before arrival</td>
<td>1.5%</td>
<td>1.0%</td>
<td>0.0%</td>
<td>0.4%</td>
</tr>
<tr>
<td><strong>Delivery</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Spontaneous vaginal</td>
<td>63.2%</td>
<td>57.8%</td>
<td>52.4%</td>
<td>49.0%</td>
</tr>
<tr>
<td>- Assisted vaginal</td>
<td>16.2%</td>
<td>18.1%</td>
<td>17.7%</td>
<td>17.1%</td>
</tr>
<tr>
<td>- Breech</td>
<td>1.5%</td>
<td>0.5%</td>
<td>1.6%</td>
<td>0.0%</td>
</tr>
<tr>
<td>- Emergency caesarean</td>
<td>8.8%</td>
<td>14.6%</td>
<td>15.3%</td>
<td>14.8%</td>
</tr>
<tr>
<td><strong>Anesthetics and analgesics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- None</td>
<td>7.4%</td>
<td>8.0%</td>
<td>6.5%</td>
<td>13.4%</td>
</tr>
<tr>
<td>- Epidural</td>
<td>51.5%</td>
<td>46.7%</td>
<td>55.7%</td>
<td>53.6%</td>
</tr>
<tr>
<td>- Spinal block</td>
<td>11.8%</td>
<td>9.1%</td>
<td>5.7%</td>
<td>14.1%</td>
</tr>
<tr>
<td>- Combined epidural/spinal block</td>
<td>8.8%</td>
<td>18.1%</td>
<td>21.8%*</td>
<td>5.8%</td>
</tr>
<tr>
<td>- General</td>
<td>4.4%</td>
<td>7.0%</td>
<td>4.0%</td>
<td>1.9%</td>
</tr>
<tr>
<td>- Nitrous oxide</td>
<td>38.2%</td>
<td>40.2%</td>
<td>41.1%</td>
<td>28.1%</td>
</tr>
<tr>
<td><strong>Complication of labour or delivery</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Any</td>
<td>72.1%</td>
<td>72.4%</td>
<td>76.6%</td>
<td>61.7%</td>
</tr>
<tr>
<td>- Precipitate delivery</td>
<td>7.4%</td>
<td>9.1%</td>
<td>0.8%</td>
<td>4.6%</td>
</tr>
<tr>
<td>- Fetal distress</td>
<td>25.0%</td>
<td>21.6%</td>
<td>27.4%</td>
<td>13.2%**</td>
</tr>
<tr>
<td>- Prolapsed cord\1</td>
<td>0.0%</td>
<td>0.5%</td>
<td>0.8%</td>
<td>0.0%</td>
</tr>
<tr>
<td>- Cord tight around neck</td>
<td>4.4%</td>
<td>2.5%</td>
<td>3.2%</td>
<td>2.3%</td>
</tr>
<tr>
<td>- Cephalopelvic disproporton</td>
<td>0.0%</td>
<td>0.5%</td>
<td>0.0%</td>
<td>2.1%</td>
</tr>
</tbody>
</table>
- Postpartum haemorrhage (≥500mls) 17.7% 23.6% 24.2% 8.4%
- Retained placenta – manual removal 4.4% 1.0% 3.2% 1.6%
- Persistent occipito posterior 0.0% 0.5% 2.4% 2.5%
- Shoulder dystocia 2.9% 2.0% 3.2% 1.6%
- Failure to progress ≤ 3cm 5.9% 8.5% 10.5% 4.0%
- Failure to progress > 3cm\(^1\) 0.0% 3.5% 3.2% 4.9%

* p < 0.05, ** p < 0.01 (compared with naltrexone-treated women, no adjustment has been made for multiple comparisons)

Discussion

Birth rates

Birth rates in women-treated with naltrexone were significantly elevated as compared to all three comparison groups with rates almost double that of women in the other 3 cohorts. The increased rate of birth in naltrexone-treated women may be attributable to the cessation of opioids (and restoration of menstruation) or a direct effect of naltrexone. Given the rates of pregnancy and previous pregnancy, contraception (including the use of long-term contraceptive options such as Implanon\(^*\)) should be an integral part of drug and alcohol service for women, particularly those treated with implant naltrexone.

Maternal mortality

No incidences of maternal death were noted in any of the four cohorts. This is not unexpected given the overall incidence of maternal mortality in Australia between 2006 and 2010 was 6.8 deaths per 100 000 women who gave birth (99 deaths nationally) [348].

Pregnancy loss

Overall pregnancy losses prior to 20 weeks of gestation were significantly elevated in naltrexone- treated women compared to buprenorphine-treated women and controls (but not compared to methadone-treated women). Given that rates of birth in the naltrexone cohort were almost double that of the other three cohorts, it is not unexpected that rates of pregnancy loss would also be elevated. However rates of ectopic pregnancies in naltrexone-treated women occurred at more than 4 times the rates of the three other treatment groups.
Ectopic pregnancies are relatively common, occurring in approximately 1 – 2% of pregnancies in Europe and the USA [349]. In over 98% of ectopic pregnancies, the implantation occurs in the fallopian tube [349, 350]. Ectopic pregnancies are hypothesised to occur as the result of impaired embryo tubal transfer and/or alterations to the tubal environment allowing for early implantation to occur [350]. One pathway in which naltrexone may increase the rate of ectopic pregnancies is via the regulation of nitric oxide (NO). Naltrexone has been shown to increase the activity of nitric oxide synthase (NOS) [351]. It is thought that NO, synthesized by inducible NOS is involved in ciliary beat in the fallopian tubes, with increased levels relaxing the smooth muscle and potentially leading to higher rates of embryo retention[350]. In keeping with this, inducible NOS mRNA and protein levels have been shown to be greater in women with tubal ectopic pregnancies as compared with pseudo-pregnant women [352].

Complications during pregnancy, labour and delivery

Overall rates of complications during pregnancy (reported at birth) were elevated in naltrexone-treated women in comparison to the control groups, however overall rates of hospital attendances, and complications during labour were not significantly different. Reported rates of complications during labour and delivery in the control group were similar to published rates for WA (61.8% for singleton births in 2013) [353]. Notably opioid dependent women had high rates of hospital admissions with a mental health diagnosis compared with non-opioid dependent women, which should be taken into account in the delivery of obstetric services to opioid dependent women.

Naltrexone treated women were generally not significantly different to both methadone and buprenorphine in terms of complication during pregnancy, labour, and delivery. Rates of complications in the three opioid pharmacotherapy groups did not appear to be as high a reported by Dattel et al. (1990), who found up to 6 fold increase in prenatal obstetric complications in narcotic abusers [354].

The use of naltrexone in pregnancy was associated with high rates of spontaneous labour and spontaneous vaginal delivery compared with buprenorphine patients. While not significant, buprenorphine also appeared to have fewer incidences of precipitated delivery (7.4 v 0.8%), pre-labour rupture of membranes (8.8 v 4.8%), threatened pre-term labour (5.9 v 1.6%) and higher rates of failure to progress (5.9 v 13.5%). In contrast, delivery characteristics in methadone-treated women were very similar to naltrexone. Difference in naltrexone and methadone in comparison with buprenorphine in terms of delivery may be attributable to
buprenorphine’s agonist activity on the orphan opioid receptor-like 1 (ORL-1), which is not acted on by either methadone or naltrexone. The ORL-1 and its endogenous ligand, nociceptin (PNOC) have been detected in the uterus of both pregnant and non-pregnant rats, with a moderate increase in PNOC with gestation [355]. PNOC was found to inhibit both KCl and oxytocin evoked rhythmic contractions, thus having a relaxing effect on the uterus. Interestingly, naloxone was found to significantly increase the effects of PNOC on the uterus, however when used alone the effect of naloxone was insignificant. As buprenorphine acts on the ORL-1, it could be assumed that it would also have a relaxing effect on the uterus, explaining the reduction in spontaneous labour, threatened pre-term labour, precipitate delivery and increased rates of failure to progress and induced labour. However further research is required to support these findings.

The risk of opioid poisoning in pregnant women treated with naltrexone has been proposed as a potential problem [215]. Concerns regarding this have arisen from observations of increased rates of both fatal and non-fatal opioid poisoning following the cessation of oral naltrexone treatment in non-pregnant patients [296, 347]. These concerns led to the development of sustained release naltrexone preparations, which slowly dose taper to prevent rapid changes in a patient’s receptor occupancy and opioid tolerance. The move towards long lasting naltrexone preparations has been shown to dramatically reduce opioid poisoning death in non-pregnant patients [296] and, as such, no opioid poisonings were observed in naltrexone-treated patients during pregnancy or in the post-partum period in this study.

Overall naltrexone performed comparably to both methadone and buprenorphine and thus patients who are stable on naltrexone treatment should be allowed to remain on treatment rather than transferred onto an alternative agonist or partial agonist pharmacotherapy. However subsequent research is required to support these findings. For women who do become pregnant while on opioids or an opioid pharmacotherapy, support should be provided taking into account the high rates of young, single women of a low socioeconomic status, high rates of mental health disorder and HCV.

*Strengths and limitations*

The rates of birth and complications reported in this study should be considered a minimum, with events occurring outside of WA not captured by the databases utilized. Additionally ED data was not available prior to 2002, thus pregnancy losses requiring ED attendance (but not
hospital admission), would have not been captured. ED attendances are often not assigned a diagnosis, as it may be unclear.

Rates of pregnancy loss should also be considered only a portion of the actual rates of pregnancy loss with the results not able to encapsulate planned medical abortions that occurred outside of hospital (for example in private clinics) or spontaneous abortions/miscarriages that did not result in the women attending a hospital or ED. In many cases spontaneous abortions occur before a women realizes she is pregnant. The absence of these results significantly underestimates the rates of conception.

It was assumed that patients who had been previously diagnosed with HCV still had the disease at the time of pregnancy and had not been treated. It is expected that treatment for HCV would have been minimal, given that HCV treatment is often restricted for patients who are at a high risk of becoming re-infected (i.e. via relapse to intravenous drug use). In WA, routine screening for HCV is generally carried out during the first trimester, thus the capture of patients with HCV should be high.

Additionally, the study suffers from many of the limitations that occur in most epidemiological cohort studies including a lack of randomization. While the three groups appeared comparable in terms of the measured demographic, the three treatments may appeal to different patient groups in terms of their length of dependence (short versus long term opioid users), motivation for treatment (maintenance versus abstinence) or desired treatment outcome (drug free life versus risk management). Demographic information on a number of important variables was not available, including drug use history, concurrent drug use and use of contraception. Additionally, within each treatment group there was variation between individuals in the length and trimester of exposure.

Comparisons between naltrexone-treated women and the control women should be interpreted with caution. The naltrexone group was significantly different to the control group in terms of a number of measured variables including smoking status, socio-economic status, hepatitis C status and marital status. Additionally, the two groups are likely different in a number of other factors such as alcohol and other drug consumption which would result in different maternal outcomes. For this reason, the difference between naltrexone-treated women and control women cannot be solely attributed to naltrexone.
Conclusions

The use of implant naltrexone in opioid dependent women was associated with a significant increase in birth rates, as compared with methadone, buprenorphine and controls. Overall rates of complications during pregnancy in naltrexone-treated women were elevated compared with control women, but was not significantly different to those seen in methadone- and buprenorphine-treated women.
6.3. **Paper 7: A retrospective cohort study of birth outcomes in neonates exposed naltrexone in utero: A comparison with methadone, buprenorphine and non-opioid exposed neonates**

**Abstract**

*Background:* Naltrexone may provide a suitable alternative to methadone and buprenorphine in the treatment of pregnant opioid dependent women, however little is known about its effects on neonatal morbidity and mortality.

*Objective:* To evaluate the health of neonates exposed to naltrexone in utero, and compare it with outcomes in neonates exposed to methadone, buprenorphine and a non-exposed control group.

*Methods:* Sequential cohorts of Western Australian (WA) opioid dependent women treated with implant naltrexone, oral methadone or sublingual buprenorphine were identified via clinic treatment (naltrexone) and state prescribing records (methadone and buprenorphine). A control cohort of non-opioid dependent women was obtained from the WA electoral roll. Identifying information and treatment records for these women were linked against the Midwife Notification System records to identify exposed children born between 2001 and 2011. Birth characteristics, congenital anomalies and perinatal mortality for all neonates were extracted from state records.

*Results:* The birth characteristics of naltrexone-exposed neonates (n = 68) were superior to methadone-exposed neonates (n = 199) in terms of birth size (birth weight, head circumference and length), hospital length of stay (5.5 v 11.3 days), and rates of neonatal abstinence syndrome (NAS) (7.5 v 51.5%). Naltrexone-exposed neonates were generally not significantly different to buprenorphine-exposed neonates (n = 124) with the exception of significantly lower rates of NAS (7.5 v 41.8%) and shorter hospital length of stay (5.5 v 8.0 days) in naltrexone-exposed neonates. Compared with the control group of neonates (n = 569), naltrexone-exposed neonates were not significantly different in terms of overall rates of congenital anomalies, stillbirths and neonatal mortality, however they were significantly smaller (3137.1 v 3378.0 grams), spent more time in hospital following birth (5.5 v 4.3 days) and had higher rates of NAS (7.5 v 0.2%). Exposure of neonates to prenatal methadone was associated with a high incidence of neonatal mortality (2.0 v 0.2 per 100 live births) and
congenital anomalies (10.6 v 4.4 per 100 births) compared with the control group. Rates of neonatal mortality and congenital abnormalities in buprenorphine-exposed neonates were not significantly different to the control group.

Conclusions: The use of implant naltrexone during pregnancy was not associated with higher rates of negative birth outcomes compared with methadone and buprenorphine-exposed neonates. Significantly, naltrexone and buprenorphine were not associated with the high rates of neonatal mortality or congenital anomalies as seen in methadone-exposed neonates.

Introduction

The use of illicit opioids during pregnancy has been associated with detrimental health outcomes in exposed neonates; however cessation of opioids is generally not recommended [356]. Instead the management of pregnant opioid dependent women is generally centered on the use of opioid maintenance treatments such as methadone or buprenorphine. While the use of such treatments aims to reduce fluctuations in opioid levels and foster a lifestyle conducive to motherhood [357, 358], they have also been associated with many of the complications and poor neonatal outcomes observed in neonates exposed to illicit opioids, including neonatal abstinence syndrome (NAS), low birth weight, small head circumference, respiratory difficulties and seizures [183, 204, 208, 359].

Naltrexone, an opioid antagonist, has been proposed as an alternative treatment to opioid agonists [360]. Thus far the safety of naltrexone in pregnancy has only been examined in a small number of case studies and case series, predominately but not exclusively examining the use of an implant naltrexone formulation [211, 216, 344, 361]. Studies observed an absence of NAS and generally unremarkable neonatal and obstetric outcomes. A brief communication reported on obstetric and neonatal outcomes in 17 pregnant women managed with implant naltrexone, compared with 90 women managed with methadone. In this study, naltrexone and methadone pregnancies were not significantly different in terms of length of gestation, birth weight or APGAR scores at 5 minutes, however naltrexone-exposed neonates (NEN) had significantly higher APGAR scores at 1 minute [216]. While these clinical results are promising, concerns exist as to the consequences of opioid receptor blockade during in utero development [215, 362, 363]. Non-clinical animal research using a rat model has highlighted a number of areas of concern, including change in the pain response and sensitivity [364, 365], the development of physical characteristics and achieving developmental milestones [366], changes to the brain and cerebellar weight, increased number of glial and granule neurons,
and increased cell dendritic length and spine concentration in the hippocampus [111]. The clinical implications of these findings are not currently understood.

The aim of this study is to examine birth outcomes in neonates exposed to naltrexone in utero and compare them to neonates exposed to methadone, buprenorphine and a control group born to non-opioid dependent women.

**Materials and Methods**

*Study Cohort*

Women treated with a sustained release naltrexone implant (Go Medical Industries Pty. Ltd., Subiaco, Western Australia (WA), Australia) between January 2001 and December 2010 in WA were identified from treatment lists provided by a drug and alcohol treatment clinic (Subiaco, WA, Australia). This clinic was the sole provider of this implant formulation in WA during this period. Women treated with methadone or buprenorphine in WA over the same period were identified using the Health Department of WA’s Monitoring of Drugs of Dependence System (MODDS). Eligible women were aged 18 to 45 years at the time of first treatment and at the time of childbirth and were residing in WA at the time of first treatment.

Women and their opioid treatment records were linked with the Midwives Notification System (MNS) to identify neonates exposed to any of the three opioid pharmacotherapies. NEN included in the study were required to have been exposed to naltrexone for more than 30 days. Following implantation, the implant was considered to be active (maintaining blood levels above 1ng/ml) for 182 days, however pharmacokinetic data of the implant suggest that the implant releases at low levels beyond 182 days [145, 344]. Infants exposed to methadone or buprenorphine were required to have been exposed to an average monthly dose of at least 20 mg/day for methadone and 2mg/day for buprenorphine. Dosing records obtained from MODDS provided monthly records indicating whether or not the patient had received methadone during that month. MODDS data were linked with authorization records, containing the date at which the patient was authorized to receive treatment and a termination date. Where authorization data were not available, the 15th of the month was selected as the start date and the last day of the month was selected as the termination date. To account for the inaccuracy in commencement and termination date patients were required to be exposed to methadone and buprenorphine for at least 60 days to be included in the study.
Neonates exposed to more than one opioid pharmacotherapy in utero were excluded from the study, as were twins and triplets. For women who had more than one birth during the follow-up period, only one neonate was included in the study. Where a mother had more than one exposed child, children exposed to naltrexone were included in preference to buprenorphine, and buprenorphine children were included in preference to methadone. Where two children of the same exposure were present, the eldest was selected.

A control cohort of women were selected from the WA electoral roll (1:1 ratio), approximately age matched (5 year age bracket) to those in the three opioid pharmacotherapies. They were also linked with the MNS to produce a non-dependent control group of neonates. Neonates born to mothers under the age 18 years at birth were excluded from the study.

All infants were born between January 2001 and December 2011.

Data Collection

Data collected from the MNS, the Hospital Morbidity Data Collection, the WA Register of Developmental Anomalies and the WA Death Registry were provided by the WA Data Linkage Branch. The MNS provides notification and summary of all births that occur in WA. Births include all live and stillborn neonates of 20 weeks or more gestational age or if gestation unknown, weighing 400 grams or more at birth. Each birth record was accompanied by a number of Socio-economic Indexes for Area (SEIFA) scores and rankings. The SEIFA scores are calculated by combining information collected in the 5 yearly Census of Population and Housing.

The WA Death Registry included all deaths that occurred within WA, including still births. Cause of death was ascertained from assigned ICD-10 codes (both primary and contributing causes). The WA Register of Developmental Anomalies is a record of developmental anomalies in infants and children diagnosed before the age of 6 years. Details regarding the anomalies included and excluded in the register are outlined in Bower et al. (2012)[367].

Hospital admissions for neonates with a diagnosis of NAS (ICD-10-AM P96.1) and infant respiratory distress syndrome (IRDS) (ICD-10-AM P22) were obtained from the Hospital Morbidity Data Collection for the first 28 days following birth (including both primary and additional diagnoses). This collection contains all inpatient hospital records from both private and public hospitals in WA.
Data Analysis

Univariate linear regression and logistic regression was used to compare maternal characteristics: maternal age at birth, number of previous pregnancies, cigarette smoking during pregnancy and socio-economic status. The SEIFA Index of Relative Socio-Economic Advantage/Disadvantage for 2006 was used as a crude indicator of socio-economic status. This indicator was used in the form of deciles, with suburbs ranked 1 having the lowest 10% of scores for census collection districts in Australia, while those ranked 10 had the top 10% of scores.

For rates of birth anomalies and mortality, univariate logistic regression with the control group acting as the reference was used due to low frequencies for the outcomes. Perinatal, stillbirth and neonatal mortality rates were calculated for each cohort and were expressed per 100 births. Crude rates of birth defects were calculated for each of the cohorts and expressed per 100 births. Rates of type specific birth abnormalities were also examined, based on the assigned ICD-9 codes and divided into site categories used by the WA Department of Health. These categories were: nervous system anomalies (74000 - 74299), congenital eye anomalies (ICD-9: 74300 - 74399), congenital anomalies of ear, face and neck (74400-74499), cardiovascular defects (74500 - 74799), respiratory defects (74800 - 74899), gastrointestinal defects (74900 - 75199), urogenital defects (75200 - 75399), musculoskeletal defects (75400 - 75699), congenital defects of integument (75700 – 75799) and chromosome defects (75800 - 75899). Rates of major birth anomalies were also calculated for each group. Birth anomalies were classified as either major or minor by the WA Register of Development Anomalies (based on Centre for Disease Control classification). Major anomalies are classified “a structural change that has significant medical, social or cosmetic consequences for the affected individual; this type of anomaly typically required medical intervention”[368].

For birth outcomes, multivariate generalized linear models were used. Comparisons between groups were made using naltrexone as a reference and taking into account maternal age, number of previous pregnancies, smoking status during pregnancy, and socio-economic status.

To account for difference in gestational age, birth weights were expressed as an average and as a percentage of infants with a birth weight below the 10th percentile for their gestational age. Cut off birth weights for each gestational age bracket were taken from Roberts & Lancaster 1999 [369].
A critical p-value of 0.05 was used, with no adjustment made for multiple comparisons. Data analysis was conducted using STATA/IC 12.1.

Compliance with Ethical Standards

This study protocol was approved by the Department of Health Human Research Ethics Committee (2012/63) and the University of Western Australia Human Research Ethics Committee (RA/4/1/1864). A waiver of consent was approved by both committees.

Results

The study included 68 naltrexone-exposed, 199 methadone-exposed, 124 buprenorphine-exposed and 569 non-opioid exposed neonates (Table 27). Pregnant women receiving implant naltrexone treatment were not significantly different to the pregnant women treated with methadone and buprenorphine in terms of age at birth, number of previous pregnancies, rates of cigarette smoking and socio-economic status. In comparison to non-dependent mothers, naltrexone mothers on average were significantly younger (p < 0.001), had significantly higher numbers of previous pregnancies (p < 0.001), had a higher rate of smoking (p < 0.001) and on average were from a lower socio-economic area (p = 0.001). To account for differences in maternal age, previous pregnancies, smoking status and socio economic status, these variables were factored into the analysis of birth outcomes.
Table 27: A comparison of the demographics of mothers treated with implant naltrexone, with those treated with methadone, buprenorphine and control group during pregnancy (single exposure only).

<table>
<thead>
<tr>
<th></th>
<th>Naltrexone</th>
<th>Methadone</th>
<th>Buprenorphine</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of mothers</td>
<td>68</td>
<td>199</td>
<td>124</td>
<td>569</td>
</tr>
<tr>
<td>Pregnancies conceived</td>
<td>50 (73.5%)</td>
<td>124 (62.3%)</td>
<td>87 (70.2%)</td>
<td>N/A</td>
</tr>
<tr>
<td>on treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On treatment at birth</td>
<td>14 (20.6%)</td>
<td>185 (93.0%)</td>
<td>101 (81.5%)</td>
<td>N/A</td>
</tr>
<tr>
<td>Average length of</td>
<td>129.8 ± 50.7</td>
<td>211.3 ± 70.7</td>
<td>217.4 ± 69.3</td>
<td>N/A</td>
</tr>
<tr>
<td>exposure (days)(± sd)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean exposure dose (mg)(± sd)</td>
<td>N/A</td>
<td>52.2 ± 25.6¹</td>
<td>17.3 ± 10.3²</td>
<td>N/A</td>
</tr>
</tbody>
</table>
| Maternal age at birth   | 26.8 (19 – 40) | 27.8 (18 – 42) | 27.9 (19 – 40) | 29.8 (20 – 43)³**
| (range)                 |            |           |               |         |
| Previous pregnancies    | 2.4 (0 – 15) | 2.6 (0 – 10) | 2.2 (0 – 7)  | 1.2 (0 – 18)²**
| Smoked during pregnancy | 70.2%      | 76.1%     | 75.4%         | 13.0%³***
| SEIFA³                  | 4.9 ± 3.0  | 4.5 ± 2.5 | 4.4 ± 2.7     | 5.9 ± 2.5²**

* p < 0.05, **p < 0.01, ***p < 0.001 (compared with naltrexone-treated women, no adjustment has been made for multiple comparisons)

Sd = standard deviation

1. Range of methadone doses: 20 – 205 mg per day
2. Range of buprenorphine doses: 2 – 58 mg per day
3. Socio-economic Index for Area (SEIFA) scores and rankings. Indication of the socio-economic status (SES) of the area in which participants reside (0 – lowest SES, 10 – highest SES).

**Mortality**

Crude rates of perinatal mortality in the three groups of exposed neonates were not significantly different to the control neonates (CN). While rates of stillbirth and neonatal mortality in NEN and buprenorphine-exposed neonates (BEN) were also not significantly different than the CN, rates of neonatal mortality in the methadone-exposed neonates (MEN) were significantly higher than for the CN (OR: 11.65, CI: 1.29 – 104.78) (Table 28).
Table 28: Rate of mortality in children exposed to naltrexone, methadone or buprenorphine in utero compared with non-exposed children (per 100 births).

<table>
<thead>
<tr>
<th></th>
<th>Naltrexone (n = 68)</th>
<th>Methadone (n = 199)</th>
<th>Buprenorphine (n = 124)</th>
<th>Control (n=569)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stillbirth</td>
<td>1.5 (1)</td>
<td>0.5 (1)</td>
<td>1.6 (2)</td>
<td>0.9 (5)</td>
</tr>
<tr>
<td>Neonatal (0 – 28 days)</td>
<td>0.0 (0)</td>
<td>2.0* (4)</td>
<td>0.0 (0)</td>
<td>0.2 (1)</td>
</tr>
<tr>
<td>Perinatal mortality</td>
<td>1.5 (1)</td>
<td>2.5 (5)</td>
<td>1.6 (2)</td>
<td>1.1 (6)</td>
</tr>
</tbody>
</table>

* p < 0.05 (compared with non-exposed neonates, no adjustment has been made for multiple comparisons)

**Birth Anomalies**

Rates of overall and site specific birth anomalies in NEN were not significantly different to the CN, with the exception of elevated rates of urogenital anomalies (OR: 3.89, CI: 1.16 – 12.99). The urogenital anomalies were observed in four neonates and included an epispadias, an undescended and retracted testicle (requiring surgery), a medullary sponge kidney and an unspecified abnormality of the kidney. All four cases occurred in male infants, were the only present abnormality and were considered ‘major’ anomalies. Two non-urogenital anomalies were observed in NEN, they were an abnormality of the intestine (major) and a ventricular septal defect (minor), each were the only abnormality present in that neonate.

MEN were associated with an overall higher incidence of total (OR: 2.57, CI: 1.40 – 4.70) and major (OR: 2.32, CI: 1.21 – 4.47) birth anomalies compared with the control group (Table 29), with elevated rates of musculoskeletal (OR: 5.15, CI: 1.49 – 17.78) and ‘other’ anomalies (OR: 5.15, CI: 1.49 – 17.78). Additionally, two incidences of chromosomal defects were also observed in the MEN but not in the other three groups. Overall rates of birth anomalies in BEN were not significantly different to the CN, with the exception of an elevated rate of gastrointestinal birth anomalies (OR: 6.29, CI: 1.39 – 28.46).
Table 29: Rate and types of birth abnormalities in children exposed to naltrexone, methadone, and buprenorphine, control groups and a reference group, expressed as abnormalities per 100 births.

<table>
<thead>
<tr>
<th></th>
<th>Naltrexone (n = 68)</th>
<th>Methadone (n = 199)</th>
<th>Buprenorphine (n = 124)</th>
<th>Control(^1) (n = 569)</th>
<th>Rates in WA 2005 - 2009 [367]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rate of infants with abnormalities in the following areas (^2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system</td>
<td>0.0</td>
<td>1.5</td>
<td>0.0</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Congenital anomaly of eye</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.8</td>
</tr>
<tr>
<td>Congenital anomaly of ear, face and neck</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.2</td>
<td>0.4</td>
</tr>
<tr>
<td>Cardiovascular defect</td>
<td>1.5</td>
<td>2.5</td>
<td>0.0</td>
<td>1.1</td>
<td>1.1</td>
</tr>
<tr>
<td>Respiratory system defect</td>
<td>0.0</td>
<td>0.5</td>
<td>0.0</td>
<td>0.2</td>
<td>0.1</td>
</tr>
<tr>
<td>Gastrointestinal defect</td>
<td>1.5</td>
<td>2.0</td>
<td>3.2(^*)</td>
<td>0.5</td>
<td>0.6</td>
</tr>
<tr>
<td>Uro-genital defect</td>
<td>5.9(^*)</td>
<td>2.0</td>
<td>1.6</td>
<td>1.6</td>
<td>1.6</td>
</tr>
<tr>
<td>Musculo-skeletal defect</td>
<td>0.0</td>
<td>3.5(^*)</td>
<td>0.8</td>
<td>0.7</td>
<td>1.4</td>
</tr>
<tr>
<td>Congenital abnormalities of integument</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.4</td>
<td>0.3</td>
</tr>
<tr>
<td>Chromosominal defect</td>
<td>0.0</td>
<td>1.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.1</td>
</tr>
<tr>
<td>Other</td>
<td>0.0</td>
<td>3.5(^*)</td>
<td>0.0</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>Infants with a birth abnormality</td>
<td>8.8</td>
<td>10.6(^**)</td>
<td>4.8</td>
<td>4.4</td>
<td></td>
</tr>
<tr>
<td>Infants with a major abnormality(^3)</td>
<td>7.4</td>
<td>8.5(^*)</td>
<td>4.8</td>
<td>3.9</td>
<td></td>
</tr>
</tbody>
</table>
* p < 0.05, ** <0.01, *** <0.001 (compared with non-exposed controls, no adjustment has been made for multiple comparisons)

1. Comparison with non-exposed controls
2. Infants may have had one or more abnormality in the same area, however multiple abnormalities in the same area have only been counted as a single incidence. Infants may have had one or more abnormalities in different areas and these would have been counted in each area.
3. Major anomalies are those which create a significant medical problem for the patient and/or require specific surgical or medical management.

**Birth Outcomes**

NEN were significantly larger than MEN in birth weight (p = 0.012), length (p = 0.007) and head circumference (p=0.040). However rates of low birth weight (<2500g) (p = 0.123) and low birth weight for gestational age (p = 0.301) were not statistically different. When controlled for gestational age, MEN were still significantly smaller than NEN in terms of weight (p = 0.003), length (p = 0.001) and head circumference (p = 0.018). Gestational length and Apgar scores at 1 and 5 minutes were also not significantly different in NEN and MEN, however rates of NAS (p < 0.001), and hospital length of stay (p < 0.001) were significantly reduced in the NEN (Table 30). NEN and BEN were not significantly different in the majority of measured birth outcomes, with the exception of higher rates of NAS (p < 0.001), longer hospital stay following birth (p = 0.037), and smaller birth length when adjusted for gestational age (p = 0.039) in the BEN.

On average NEN were significantly smaller than CN in terms of weight (p = 0.022), length (p = 0.038) and more NEN were born with a birth weight in the 10th percentile for their gestational age (p = 0.017), however were not different in terms of head circumferences (p = 0.141) (Table 30). Additionally rates of neonates born under 2500g were not significantly different. When controlled for length of gestation, the difference between naltrexone exposed and control neonates in weight and length was no longer significant (p = 0.121 and p = 0.219 respectively). Rates of fetal distress (p < 0.001), length of time spent in hospital (p < 0.001) and special care unit (p < 0.001), and NAS (p < 0.001) were significantly elevated in the NEN as compared with the CN.
Table 30: Health and demographics of neonates exposed to naltrexone in utero compared with neonates exposed to methadone, buprenorphine and control group during pregnancy, labour and birth.

<table>
<thead>
<tr>
<th></th>
<th>Naltrexone</th>
<th>Methadone</th>
<th>Buprenorphine</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of infants</td>
<td>68</td>
<td>199</td>
<td>124</td>
<td>569</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>47.1%</td>
<td>58.3%</td>
<td>55.7%</td>
<td>50.4%</td>
</tr>
<tr>
<td>Birth Weight ± sd (g)</td>
<td>3137.1 ± 629.4</td>
<td>2884.1 ± 658.8*</td>
<td>3035.8 ± 594.5</td>
<td>3378.0 ± 560.1*</td>
</tr>
<tr>
<td>Birth weight &lt;10 percentile for gestational age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth weight &lt;2500g</td>
<td>11.8%</td>
<td>23.1%</td>
<td>12.1%</td>
<td>4.6%</td>
</tr>
<tr>
<td>Body Length ± sd (cm)</td>
<td>48.8 ± 3.6</td>
<td>47.4 ± 4.1**</td>
<td>48.3 ± 3.7</td>
<td>50.0 ± 3.0*</td>
</tr>
<tr>
<td>Head Circumference ± sd (cm)</td>
<td>33.9 ± 2.5</td>
<td>33.1 ± 2.7*</td>
<td>33.6 ± 3.0</td>
<td>34.5 ± 2.0</td>
</tr>
<tr>
<td>Apgar 1 min ± sd</td>
<td>7.9 ± 1.8</td>
<td>7.9 ± 1.7</td>
<td>8.0 ± 1.9</td>
<td>8.3 ± 1.3</td>
</tr>
<tr>
<td>Apgar 5 mins ± sd</td>
<td>8.8 ± 1.5</td>
<td>8.8 ± 1.2</td>
<td>8.8 ± 1.4</td>
<td>9.0 ± 1.0</td>
</tr>
<tr>
<td>% of Apgar score &lt;7 at 5 mins</td>
<td>5.9%</td>
<td>5.0%</td>
<td>4.0%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Estimated gestation ± sd</td>
<td>38.0 ± 2.5</td>
<td>37.7 ± 3.0</td>
<td>38.1 ± 2.6</td>
<td>38.7 ± 2.0</td>
</tr>
<tr>
<td>Rate &lt;37 weeks gestation</td>
<td>16.2%</td>
<td>19.6%</td>
<td>10.5%</td>
<td>7.6%</td>
</tr>
<tr>
<td>Rate &lt;32 weeks gestation</td>
<td>1.5%</td>
<td>3.0%</td>
<td>1.6%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Time to establish unassisted regular breathing* (mins (range))</td>
<td>1.3 (1 – 14)</td>
<td>1.3 (1 – 7)</td>
<td>1.2 (1 – 15)</td>
<td>1.1 (1 – 5)</td>
</tr>
<tr>
<td>Condition</td>
<td>Group 1</td>
<td>Group 2</td>
<td>Group 3</td>
<td>Group 4</td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>Resuscitation required(^2,^3)</td>
<td>41.8%</td>
<td>42.9%</td>
<td>44.3%</td>
<td>29.1%</td>
</tr>
<tr>
<td>Threatened abortion &lt;20 weeks(^4)</td>
<td>0.0%</td>
<td>2.0%</td>
<td>3.2%</td>
<td>4.2%</td>
</tr>
<tr>
<td>Threatened pre-term labour &lt;37 weeks</td>
<td>5.9%</td>
<td>4.0%</td>
<td>1.6%</td>
<td>3.3%</td>
</tr>
<tr>
<td>Fetal distress</td>
<td>25.0%</td>
<td>21.6%</td>
<td>27.4%</td>
<td>13.2%**</td>
</tr>
<tr>
<td>Length of stay (days (range))(^2)</td>
<td>5.5 (0 – 28)</td>
<td>11.3 (0 – 68)***</td>
<td>8.0 (0 – 49)(^7)</td>
<td>4.3 (0 – 93)***</td>
</tr>
<tr>
<td>Special care (days (range))(^2)</td>
<td>2.5 (0 – 28)</td>
<td>8.1 (0 – 68)</td>
<td>4.7 (0 – 49)</td>
<td>0.5 (0 – 93)**</td>
</tr>
<tr>
<td>Admitted with NAS diagnosis(^2,^5)</td>
<td>7.5%</td>
<td>51.5%***</td>
<td>41.8%***</td>
<td>0.2%***</td>
</tr>
<tr>
<td>Admitted with IRDS diagnosis(^2,^5)</td>
<td>1.5%</td>
<td>6.6%</td>
<td>1.6%</td>
<td>1.4%</td>
</tr>
</tbody>
</table>

\(^*\) p < 0.05, \(^**\) p < 0.01, \(^***\) p < 0.001 (compared with naltrexone-exposed neonates, no adjustment has been made for multiple comparisons)

Special care = length of time (days) spent in the special care nursery following birth, IRDS = Infant respiratory distress syndrome, NAS = Neonatal abstinence syndrome,

1. Excluding babies who were intubated and ventilated (an accurate assessment of time was not possible) and those stillborn.
2. Excluding stillborn babies.
3. Resuscitation methods included suction, oxygen therapy, bag and mask, endotracheal intubation, external cardiac massage and ventilation and drugs.
4. Vaginal bleeding with the uterus determined to be the source of bleeding before the 20th gestational week
5. In the first 28 days following birth
Discussion

Mortality

Naltrexone and buprenorphine were not associated with an increased risk of perinatal mortality, stillbirth or neonatal mortality. Methadone however was associated with an increased rate of neonatal mortality. At 2.0%, crude rates of neonatal mortality were more than 10 times that of the control group (0.2%) and surpassed that of a number of high risk groups in Australia including Aboriginal and Torres Strait Islanders (0.5%), women who smoked during pregnancy (0.5%), women with maternal diabetes mellitus (0.5%) or hypertension (0.5%), neonates born weighing 2000-2499g (0.4%) or with an estimated gestation of 32 – 36 weeks (0.5%) [370]. While the underlying cause of this increase could not be attributed to any specific cause of death, the presence of major congenital abnormalities and prematurity/low birth weight are likely to be contributing factors. Rates of still birth and perinatal mortality were not elevated in MEN.

Congenital anomalies

While rates of birth anomalies in NEN were not significantly different to the CN, crude rates were twice that of the CN. The difference was primarily associated with elevated rates of urogenital birth anomalies in NEN, solely in male neonates. The anomalies were not limited to a single type or organ (i.e. kidneys, testes and urethra) and their occurrence requires further investigation. Elevated rates of urogenital birth abnormalities have not been reported previously in either animal or human studies.

Methadone was the only pharmacological treatment associated with a statistically significant overall increase in congenital anomalies compared to the CN. Increases in major, musculoskeletal, and ‘other’ defects were observed. Incident of chromosomal anomalies also appear to be increased in MEN (although statistical comparison was unable to be undertaken due to the absence of any cases in the control group), with rates ten times that of the WA population, and no chromosomal anomalies present in either of the other three groups. In previous research, methadone has not generally considered to be associated with an increased risk of congenital anomalies [371], with no particular type of congenital anomalies associated with in utero methadone exposure. Reported rates of congenital anomalies in MEN have been widely ranging, from 1/248 (0.4%) [232] up to 12/78 (15.4%). A limitation of some studies reporting on congenital abnormalities, is that only congenital abnormalities identifiable at
birth and the neonatal period are reported. In some cases birth abnormalities may not be diagnosed until infancy or early childhood, resulting in under reporting.

Overall rates of congenital anomalies in BEN were in line with previous research [244, 259]. Rates of gastro-intestinal birth anomalies were also significantly elevated in the buprenorphine children. As per methadone, buprenorphine is not considered to be associated with an increased rate of congenital abnormalities [371], and has not been previously been associated an increased incidence of any specific type of congenital abnormality.

Co-exposure to substances including alcohol, cigarettes, illicit drugs and other medications may have also contributed to the presence of congenital anomalies [372-375]

*Birth Outcomes*

At birth, outcomes in naltrexone exposed neonates were significantly better than MEN neonates with significantly increased birth size, reduced length of stay in hospital and a reduced incidence of NAS. NEN were generally not significantly different to BEN in terms of birth outcomes, only differing in terms of lower rates of NAS and length of hospital stay in the NEN.

While NEN were significantly smaller than CN in terms of birth weight, this reduction may be attributable to a slightly shorter period of gestation observed in NEN. Concerns regarding birth weight in NEN infants have arisen with rat studies demonstrating naltrexone to have both an inhibitory (low dose) and stimulatory (high doses) effect on neonatal birth weight [362, 366, 376]. These data suggest that naltrexone infants are not receiving naltrexone at levels sufficient to increase birth weight and yet while smaller than CN, the reduction in birth weight is less than for MEN. Similarly, reductions in birth weight observed in methadone-exposed neonates in this and previous studies has been a concern given the strong relationship between infant mortality and low birth weight [377].

Expectedly, given naltrexone’s antagonist action on the opioid receptors, rates of NAS were reduced in NEN as compared with both MEN and BEN, but not eliminated. This is the first time NAS has been identified in infants exposed to naltrexone prenatally. Notably, NAS is not an opioid specific disorder and refers to withdrawal from drugs of addiction. Thus the presence of NAS may be the result of either return to opioid use or the use of another substance, however this is unclear as the use of opioids and non-opioid drugs during pregnancy was not recorded.
The elevated rates of NAS in NEN compared to CN may additionally contribute to higher rates of hospital and special care length of stay.

Rates of infant respiratory distress (IRDS) were not elevated in the NEN as compared with the CN. Interestingly however rates of IRDS in MEN were approximately 4.7 times that of the CN. Glass et al. found no cases of IRDS in 33 premature neonates (≤37 weeks) of heroin dependent women, compared with rates of 21.1% in the control group [378]. This research was supported by further non-clinical trials in rats and rabbits suggesting in utero exposure to opioids increases lung development, thus decreasing rates of IRDS [379-383]. However recent studies have shown that IRDS is far from absent in opioid exposed children, with a study by Blandthorn et al. finding rates of IRDS comparable with this study, with 5.2% in neonates exposed to either methadone or buprenorphine in utero diagnosed with the disease (n = 97) [384].

**Strengths and limitations**

The lack of randomization in the allocation of pregnant women to treatment may be a confounding issue in this study. However given the nature of the study population and the size required to examine rare events such as neonatal mortality, a randomized controlled trial (RCT) of a similar size would be difficult. Further examination of the use of implant naltrexone in pregnancy using retrospective health data may be enhance by linking clinical data and other datasets to provide additional information about the study population (i.e. maternal drug use, antenatal care, consultations with general practitioners). Methadone and buprenorphine results are consistent with previously published studies [220, 256].

The presented, although limited, demographic information for the mothers showed similarities among the three pharmacotherapies. However, the three cohorts may represent patients with different motivations for treatment (for example: maintenance verses drug free) or be willing to accept different levels of risk (for example: standard treatment versus new treatment). Additionally, information regarding the use of both illicit and licit drugs during pregnancy were unavailable.

Data were only available for infants born in WA and thus neonates born interstate or overseas would not have been included in the study. Movement in and out of WA would be considered to be minimal in comparison to other states and countries, given its isolation. Migration would be prevalent in naltrexone treated women, give that only a single treatment is required for 6
months exposure. In comparison, both methadone and buprenorphine require daily dosing, generally from a pharmacy.

Similarly, rates of congenital anomalies should be considered a minimum, as anomalies can be diagnosed and reported up to 6 years of age. Data on congenital anomalies were available for a minimum of 12 months, but were only available up to 6 years of age for children born before 2006. In a review of age at diagnosis, 86.4% of birth anomalies were diagnosed before 12 months of age [385], which would suggest that majority of birth anomalies would have been captured in the study.

Data on the health of children following the neonatal period have not been presented as it was considered beyond the scope of this paper.

Future research

While this study bridges a number of gaps regarding the use of naltrexone during pregnancy, there are still a number of questions about its long term safety, especially with regards to some of the findings from non-clinical studies showing changes in pain perception, sensitivity to opioids and developmental milestones [364-366]. The results of the study provide substantial supporting data for additional research into the use of implant naltrexone during pregnancy, particularly prospective studies. Future studies should be carefully designed so that all possible confounding factors, including the use of illegal and legal substances, can be documented.

Conclusions

The presented data evoke cautious optimism about the potential for the use of implant naltrexone in pregnant opioid dependent patients, however Further research is needed to more fully answer questions regarding the relative safety and efficacy of naltrexone during pregnancy for the mother, fetus and child.
6.4. Paper 8: A retrospective cohort study of the health of children prenatally exposed to methadone, buprenorphine or naltrexone compared with non-exposed controls.

Abstract

Objective: To compare the health of children exposed to methadone, buprenorphine or naltrexone in utero to non-exposed children born to non-opioid dependent women from birth up to their 5th birthday.

Methods: Children were identified by linking the treatment records of women treated with one of the three opioid pharmacotherapies with midwife notifications. Live born children exposed to methadone (n = 198), buprenorphine (n = 122), naltrexone (n = 67) in utero and non-opioid exposed neonates (n = 564) born between 2001 and 2011 in Western Australia were included in the study. The children were then linked to state mortality, hospital, emergency department (ED), mental health, cancer, and reportable diseases from birth up to their 5th birthday. Incidence of mortality, hospital admissions, ED presentations, out-patient mental health events, cancer diagnoses, and reportable diseases were calculated and compared for children in the four groups.

Results: Overall rates of hospital admission were elevated in all three treatments as compared with the control, while rates of ED attendances were only significantly elevated in the methadone children (p = 0.002). In terms of both hospital and ED attendances, the differences between the exposed and the control children was most apparent in the neonatal period. Rates of mental health out-patient attendances were elevated in buprenorphine children as compared with the control (RR: 14.78, CI: 1.19 – 183.80, p = 0.036). Rates of cancer were comparable between the three opioid pharmacotherapies and the control, as were rates of enteric and vaccine preventable diseases.

Conclusions: The study provides evidence to suggest a disparity in the health of children exposed to opioid pharmacotherapies in utero compared with non-exposed control children.
Introduction

The use of opioids during pregnancy is associated with elevated rates of morbidity and mortality for both the mother and their children. Neonates exposed to opioids in utero have been shown to have higher rates of spontaneous abortion, still birth, fetal growth retardation, infection, neonatal mortality and neonatal abstinence syndrome (NAS) [184, 187, 223].

The treatment of opioid dependent during pregnancy has generally centered around the use of opioid maintenance treatments, such as methadone. Methadone is associated with high levels of compliance and the daily dispensing promotes contact with health professionals, resulting in increased pre-natal care. Compared with illicit opioids, the maternal use of methadone is associated with increased prenatal care, reduced fetal mortality, and decreased growth retardation [187, 188, 203]. However as per illicit opioids, maternal exposure to methadone has also been associated with poor infant outcomes including NAS, small birth size, and increased rates of perinatal mortality as compared with the general population [111, 238, 386].

Buprenorphine (a partial opioid agonist/antagonist) is also commonly used in the treatment of pregnant with an opioid use disorder. In comparison to methadone, buprenorphine has been associated with reduced incidence and severity of NAS, shorter duration of hospital stay, increased birth size (length, weight, head circumference), longer periods of gestation, and reduced medical complications during labour and delivery [208-210], however methadone may be superior in terms of patients retention [208].

Naltrexone (a opioid antagonist) is also used in the treatment of opioid dependent patients, however the clinical data surrounding its safety for use in pregnancy is limited compared with methadone and buprenorphine. In a study of neonatal outcomes, naltrexone-exposed neonates were significantly larger than methadone-exposed neonates, and had significantly lower rates of NAS and spend less time in hospital following birth compared with both methadone and buprenorphine-exposed neonates (Section 6.3). However elevated rates of urogenital birth abnormalities were observed in naltrexone-exposed neonates. Additionally concerns have been raised about women having to undergo opioid detoxification prior to induction on to naltrexone and the potential harm to the fetus that this may cause [215].

While the health of neonates exposed to opioids and opioid pharmacotherapies in utero as a result of maternal dependence has been the focus of numerous studies, research into these
children extending beyond the first few months or even weeks of life are limited. Research that does look beyond this initial period has generally focused on developmental, behavior and mental capacity rather than morbidity and mortality. Additionally studies often fail to sufficiently control for family and social issues that may contribute to poor health. In the few studies that have touched on morbidity and mortality a small number of health issues have been identified. In methadone exposed children including increased incidents of microcephaly, visual abnormalities (including strabismus and nystagmus), elevated systolic blood pressure, acute and chronic inner ear infection [271, 272]. In buprenorphine exposed children, one study reported elevated rates of visual abnormalities (primarily strabismus) and infantile pyloric stenosis [239]. In another study, the oral health of buprenorphine exposed children was poorer compared to a control group, however this was primarily attributed to dental neglect [274]. The effects of naltrexone in utero exposure on the subsequent health of children is yet to be reported.

This study examines health outcomes during the first five years of their life of children exposed to methadone, buprenorphine or naltrexone in utero, and compares them with those of control children selected from the general population.

Materials and methods

Subjects

Children exposed to methadone, buprenorphine or implant naltrexone were identified by linking treatment recorded for their mothers against the Midwives Notification System (MNS) as described in Section 6.2 and 6.3. The mothers of eligible children had been treated with methadone, buprenorphine or implant naltrexone for opioid dependence between January 2001 and December 2010 in Western Australia (WA).

A cohort of control children was included as a comparison group. A cohort of age matched (5 year age bracket) was selected from the Electoral Roll at a ratio of 1:1, for the women treated with methadone, buprenorphine and implant naltrexone. Control women were matched against the MNS for the same period and identified children were included in the study. All children included in the study were born between 2001 and 2011.

Data Linkage

Children included in the study were then matched again the following state wide data bases: Hospital Morbidity Data Collection (HMDC), Emergency Department Data Collection (EDDC),
Mental Health Information System (MHIS), Western Australian Cancer Registry (WACR), Western Australian Notifiable and Infectious Diseases Database (WANIDD), Western Australia Death Registry (WADR). With the exception of the EDDC, data from each set was available for events that occurred from the time of birth to the 31st of December 2012. For the EDDC, the earliest emergency data was available from January 2002. Data linkage was conducted by the Western Australian Data Linkage Branch.

Data Analysis

Mortality rates were calculated for the first year of life (infancy) and early childhood (one to four years of age) and expressed per 1000 patient years (ptpy). Comparisons between the three exposure groups and the control were made using a univariate Cox proportional hazards model.

Rates of hospital attendances, ED attendances, out-patient mental health events, cancer registrations and reportable diseases were calculated for each of the 4 groups and expressed per 100 patient years. Hospital and ED rates divided into age groups: neonatal (0 – 28 days), infants (29 – 365 days), one year, two years, three years, and four years. Cause-specific rates of hospital admissions were also examined using ICD-10-AM codes assigned to the admissions (up to 22 diagnoses were available). Causes include blood and immune (D50 – 89), circulatory (I00 – 99), digestive (K00 – 95), Ear (H60 – 95), Endocrine (E00 – 89), eye (H00 – 59), infection (A00 – 99; B00 – 99), injury (S00 – 99; T00 – 88), musculoskeletal (M00 – 99), mental health (F00 – 09; 20 – 99), nervous system (G00 – 99), respiratory (J00 – 99), skin and subcutaneous (L00 – 99), urogenital (N00 – 99). Rates of health events in the methadone, buprenorphine and naltrexone-exposed children were compared with the control group using univariate generalised linear models.

A critical p-value of 0.05 was used, with no adjustment made for multiple comparisons. Data analysis was conducted using STATA/IC 12.1.

Ethics

This study protocol was reviewed and approved by the Department of Health Human Research Ethics Committee (2012/63) and the University of Western Australia Human Research Ethics Committee (RA/4/1/1864).
Results

The study included 67 naltrexone, 198 methadone, and 122 buprenorphine exposed live born children and 564 live born control children. Methadone children were followed up for an average of 4.2 ± 1.3 years, buprenorphine for 4.0 ± 1.3, naltrexone for 4.3 ± 1.2 and the controls for 4.0 ± 1.3 years. Information on pregnancy, birth and early neonatal health events have been previously reported (Section 6.2 and 6.3).

Mortality

In the first year of life, mortality rates were significantly elevated in children exposed to methadone in utero, with 25.9 deaths ptpy compared with 1.8 deaths ptpy in the control group (HR: 14.41, CI: 1.68 – 123.33, p = 0.015). Rates of mortality were not significantly different in buprenorphine or naltrexone-exposed children compared with the control group, with no deaths in the buprenorphine group and only one in the naltrexone group (15.5 ptpy)(HR: 8.41, CI: 0.53 – 134.48, p = 0.132). During early childhood (1 – 4 years) two additional deaths were observed. Both deaths occurred in children exposed to methadone in utero, equating to 2.9 deaths ptpy.

Hospital Admissions

Rates of hospital admissions in children exposed to the three opioid pharmacotherapies in utero were significantly elevated compared with children born to non-opioid dependent mothers (methadone – RR: 1.76, CI: 1.41 – 2.20, p < 0.001; buprenorphine – RR: 1.61, CI: 1.23 – 2.11, p < 0.001; naltrexone – RR: 1.66, CI: 1.19 – 2.32, p = 0.003). Rates of hospitalization were significantly elevated in all three treatment groups during the neonatal period compared with the control group (methadone - RR 3.60, CI: 2.78 – 4.64, p < 0.001; buprenorphine – RR: 3.27, CI: 2.43 – 4.39, p < 0.001, naltrexone – RR: 2.22, CI: 1.46 – 3.37, p < 0.001). However during infancy, and at the age of one there was no significant difference between the exposed and non-exposed groups. At two years of age, methadone has significantly higher rates of hospitalization (RR: 1.85, CI: 1.09 – 3.14, p = 0.022), however at the same age buprenorphine-exposed children had significantly lower rates of hospital admissions than the control (RR: 0.34, CI: 0.12 – 0.94, p = 0.038). However at 3 and 4 years of age the converse was true, with significantly higher rates of hospitalization in buprenorphine-exposed children compared with the control (Figure 6).
Figure 6: Rates of hospital admission in children prenatally exposed to methadone, buprenorphine, naltrexone and non-exposed controls (per 100 children).

Rates of hospital admissions with a diagnosis of diseases of skin/subcutaneous were elevated in children exposed to all three opioid pharmacotherapies (Table 31). Significantly higher rates of infection were observed in both the methadone (RR: 1.80, CI: 1.11 – 2.93, p = 0.018) and naltrexone-exposed children (RR: 2.34, CI: 1.18 – 4.67, p = 0.015), but not buprenorphine (RR: 1.75, CI: 0.98 – 3.13, p = 0.059). Naltrexone-exposed children also had significantly higher rates of hospital admissions with a diagnosis associated with a disease of the ear (RR: 2.46, CI: 1.02 – 5.92, p = 0.045), the respiratory system (RR: 2.04, CI: 1.09 – 3.82, p = 0.026) and an injury (RR: 2.96, CI: 1.21 – 7.23, p = 0.017).

Eight naltrexone-exposed children were admitted to hospital a total of ten times with an ear related diagnosis. All ten admissions included a diagnosis of otitis media (either chronic mucoid otitis media, nonsupprative otitis media or unspecified otitis media). However, respiratory admissions in naltrexone-exposed children (14 children, 35 admission) were not associated with a single disease or disorder.
Table 31: Cause specific rates of hospital admissions (per 100 patient years) in children exposed to methadone, buprenorphine and naltrexone in utero compared with non-exposed controls.

<table>
<thead>
<tr>
<th></th>
<th>Methadone</th>
<th>Buprenorphine</th>
<th>Naltrexone</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause hospital</td>
<td>37.9***</td>
<td>35.9**</td>
<td>37.7*</td>
<td>22.4</td>
</tr>
<tr>
<td>- Blood and immune</td>
<td>0.7</td>
<td>2.5</td>
<td>0.0</td>
<td>0.2</td>
</tr>
<tr>
<td>- Circulatory</td>
<td>0.1</td>
<td>0.6</td>
<td>0.0</td>
<td>0.1</td>
</tr>
<tr>
<td>- Digestive</td>
<td>2.0</td>
<td>1.0</td>
<td>3.1</td>
<td>2.2</td>
</tr>
<tr>
<td>- Ear</td>
<td>1.9</td>
<td>2.2</td>
<td>3.5*</td>
<td>1.4</td>
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<tr>
<td>- Endocrine</td>
<td>1.4</td>
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<td>1.4</td>
<td>1.9</td>
</tr>
<tr>
<td>- Eye</td>
<td>1.0</td>
<td>0.2</td>
<td>1.0</td>
<td>0.4</td>
</tr>
<tr>
<td>- Infection</td>
<td>5.4*</td>
<td>5.5</td>
<td>7.3*</td>
<td>3.2</td>
</tr>
<tr>
<td>- Injury</td>
<td>1.6</td>
<td>1.8</td>
<td>2.8*</td>
<td>0.9</td>
</tr>
<tr>
<td>- Mental health</td>
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<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>- Musculoskeletal</td>
<td>0.7</td>
<td>1.2</td>
<td>0.0</td>
<td>0.4</td>
</tr>
<tr>
<td>- Nerves</td>
<td>2.3</td>
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<tr>
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<td>15.1</td>
<td>4.3</td>
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</tr>
<tr>
<td>- Skin and subcutaneous</td>
<td>2.8***</td>
<td>3.3***</td>
<td>2.8**</td>
<td>0.7</td>
</tr>
<tr>
<td>All cause emergency</td>
<td>68.8**</td>
<td>48.0</td>
<td>64.4</td>
<td>51.3</td>
</tr>
</tbody>
</table>

* p = 0.05, ** p = 0.01, *** p = 0.001 (compared with naltrexone-exposed children, no adjustment has been made for multiple comparisons)

ED Attendances

Compared with the control group, rates of ED attendances were significantly elevated in methadone exposed children (RR: 1.34, CI: 1.11 – 1.61, p = 0.002), but not buprenorphine (RR: 1.00, CI: 0.79 – 1.27, p = 0.976) or naltrexone-exposed children (RR: 1.23, CI: 0.92 – 1.65, p = 0.155). Statistically higher rates of ED attendances were observed in all three opioid pharmacotherapies during the neonatal period compared with the control (methadone – RR: 2.17, CI: 1.25 – 3.75, p = 0.006; buprenorphine – RR: 2.35, CI: 1.26 – 4.37, p = 0.007; naltrexone – RR: 2.65, CI: 1.22 – 5.74, p = 0.014). Similarly significantly higher rates of ED attendances were also observed in methadone and naltrexone children during infancy (RR: 1.51, CI: 1.17 –
1.94, p = 0.001 and RR: 1.50, CI: 1.02 – 2.21, p = 0.038 respectively), and in one year old methadone children (RR: 1.35, CI: 1.04 – 1.75, p = 0.024) (Figure 7). However at 2, 3 and 4 years of age there was no significant difference between the three exposed groups and the control.

Figure 7: Rates of Emergency Department (ED) attendances in children prenatally exposed to methadone, buprenorphine, naltrexone and non-exposed controls (per 100 children).

**Out-patient Mental Health**

No mental health out-patient events were recorded in children exposed to methadone or naltrexone. Five of the 122 buprenorphine exposed children (4.1%) attended at least one out-patient mental health event, compared with three of the 564 control patients (0.5%). Rates of out-patient mental health events were significantly elevated in buprenorphine exposed children, with 5.3 events per 100 patient years, compared with 0.6 events per 100 patient years in the control group (RR: 14.78, CI: 1.19 – 183.80, p = 0.036).

**Cancer**

A total of four children were diagnosed with cancer (2 in the control group and 2 in the exposed groups). The incidence of cancer were not specific to one groups or one type of cancer.
**Reportable Diseases**

Enteric diseases were the most commonly reported category of reportable diseases found in the study, with 0.7 cases per 100 patient years for the control group, and 0.5, 0.0 and 0.7 cases per 100 patient years for the methadone, buprenorphine and naltrexone groups, respectively. Case of enteric disease included campylobacteriosis, cryptosporidiosis, rotavirus, and salmonella. There was no significant difference rates of enteric diseases between the control and the three exposure groups.

Vaccine preventable diseases, including influenza, pertussis and varicella, were also reported, with 0.3 cases per 100 patient years in the control group, 0.2 in the methadone and buprenorphine-exposed group and 0.7 in the naltrexone exposed group. No significant difference was observed between the control and the exposed groups. No cases of blood borne viruses, vector borne diseases, sexually transmitted diseases or zoonotic diseases were observed.

**Discussion**

**Mortality**

Infant mortality rates were significantly elevated in methadone-exposed children compared with the control group. The increases in mortality in the methadone cohort was most be attributable to high mortality rates in the neonatal period associated with low birth weight, prematurity, and birth anomalies as outlined in Section 6.3. During early childhood, rates of mortality were calculated at 2.9 deaths ptpy for methadone-exposed children, which is well above the national mortality for children aged 1 to 4 of 0.2 deaths ptpy [387].

**Hospital and emergency department presentations**

Rates of hospital admissions were significantly elevated in children exposed to methadone, buprenorphine and naltrexone in utero compared with non-exposed control children, as were emergency department presentations in methadone-exposed children. The difference in hospital and ED admissions were particularly apparent during the neonatal period, which is consistent with the high rates of NAS and low birth weight observed in neonates at birth (section 6.3).

Significantly higher rates of hospital admissions in the exposed groups was also associated with higher rates admissions with a skin/subcutaneous disease or disorder diagnosis and infection
(although short of significance in buprenorphine-exposed children). The increased rates of these admissions across the three treatments is likely the result of demographic or environmental factors rather than the opioid pharmacotherapies.

High rates of respiratory diseases were observed in children exposed to naltrexone in utero. Research has found opioid exposure in utero to be associated with increased lung development [379, 382, 388] and conversely, lung maturation has been shown to be delayed in rabbits treated with the opioid antagonist naloxone [388]. However, incidence of respiratory disease was not restricted to the neonatal or infant period, with a median age of admission of 2 years of age suggesting an on-going effect rather than a delay in development. The pathways and mechanisms involved are not understood and require further research, however a greater understanding of the role of opioids in lung development and may lead to the development of suitable interventions.

Higher rates of hospital admissions with otitis media in naltrexone-exposed children. In children otitis media is commonly co-occur with upper respiratory infection, which were also elevated in naltrexone-exposed children [389]. Although methadone was not associated with an increased rates of otitis media in this study, increased rates have been previously reported [271]. Further investigation of the occurrence of otitis media all children exposed to all three treatments is required.

*Out-patient mental health*

High rates of out-patient mental health events in buprenorphine children (4.1%) provide some evidence to suggest that in-utero exposure buprenorphine may be associated with an increased risk of mental health problems in young exposed children. Similar rates were found in the study by Kivisto et al. (2015), in which 4 of the 102 buprenorphine exposed children (3.9%) were referred to a psychologist or child psychiatrist for behavioural problems by the age of 3 [239]. However the increase in mental health out-patient events was not reflected in increased rates of hospital admissions with mental health diagnoses. Increased rates of mental health events in children exposed to opioid pharmacotherapies in utero would not be unexpected given the increased prevalence of parental mental health issues, domestic violence and sexual assault, unstable home environment, poor parental supervision, and neglect [390, 391]. As such, increases in rates of psychiatric problems have been observed in children exposed to heroin in utero [392]. Incidence of mental health in children neonatally
exposed to methadone, buprenorphine and implant naltrexone needs to be more thoroughly examined.

Cancer

There was no evidence to suggest that rates of cancer are elevated in children exposed to methadone, buprenorphine or naltrexone in utero, however given rare nature of childhood cancer and the sample size available the study was not suitably powered to provide any certainty. Given that naltrexone has been shown to have both stimulatory and inhibitory effects on the development of cancer in animal models [393, 394] and methadone has been associated with both increased and decreased risk of developing certain types of cancer [395, 396], this area should be examined in future research.

Reportable infectious diseases

Rates of reportable diseases in the children exposed to methadone, buprenorphine or implant naltrexone in utero were no significantly different to the non-exposed control group. Given the high rates of blood borne and sexually transmitted diseases in opioid using adults, particularly HCV, it is surprising to note the lack of these diseases in their children. Hepatitis C was diagnosed in approximately 60% of the mothers of exposed children (Section 6.2), with previous studies suggesting vertical transmission of HCV occurs in around 5.8% of children [397]. It would thus be expected that approximately 3.5% or around 14 of the exposed neonates would have been diagnosed with HCV. The lower than expected rate may be due to under diagnosis, with diagnosis not able to be carried out until 18 months of age. Routine testing of HCV and other blood borne viruses in children with mothers who have tested positive to blood borne viruses should be included in routine follow-up of children, possibly facilitated by state health to ensure cases are identified and their associated risks managed.

Strength and Limitations

This study was a non-randomised study, thus differences in the cohorts of women self-selecting each treatment may exist, confounding results of the study. However, given the nature of the study and the participants involved, the conducting of a large scale randomised controlled trial would be largely unfeasible due to the length of time and number of participants required.
The selection of the control group was also a limitation, as the mother of children were only matched based on approximate age. It is likely that the control group is different to the exposure groups in terms of a number of social and demographics characteristics, making it difficult to distinguish between the effects of in utero exposure and other differences such as socio-economic status.

In terms of cause-specific health events, the study only examined events that resulted in hospitalisation. Increases rates of cause-specific hospitalisation may be the result of increased incidence if the disease or difference between the groups in the management of the disease. For example, control children with a specific illness may be more likely to receive early intervention and treatment by a General Practitioner, resulting in fewer hospitalisations, while illnesses in children born to opioid dependent women may be more likely to go untreated, resulting progression of the illness and eventual hospitalisation. The study also did not examine other issues that may arise following in utero exposure to opioid pharmacotherapies such as behavioural and developmental issues.

Additionally, the study only examines the period from birth to the child’s 5th birthday and many health problems may not be apparent until later in life. Similarly, the study only utilises state data sets, thus health events that may have taken place outside of WA would have been missed.

Conclusions

The study provides evidence to suggest that rates of health events are elevated in children exposed to methadone, buprenorphine and naltrexone in utero during the neonatal period. However, after this period, the impact of the exposure on the health of the children is only apparent in certain types of health events and diagnoses. Further research is required to investigate several of these areas and to examine health events beyond the first 5 years of life.
7. Discussion

The aim of this section is to examine how well the collated and analysed data answers the questions (aims) posed in the thesis (2. Aims and Objectives). Additionally this section will make recommendations on the pharmacotherapy treatment of both pregnant and non-pregnant opioid dependent patients based on the presented data, and identify deficiencies in information, and associated future areas for research.

7.1. Thesis Aims

7.1.1. “Does the use of a sustained release naltrexone implant mitigate the high mortality rate associated with oral naltrexone?”

Implant naltrexone was associated with significantly lower rates of mortality compared with oral naltrexone. As per previous studies, high rates of mortality were observed during the first four months following commencement of daily oral naltrexone, likely attributable to elevated rates of opioid overdose following the treatment cessation. Although time at which patients ceased oral naltrexone treatment was not known, previous studies have shown patients commonly remain on treatment for a relatively short period of time [132, 135]. For example, in a study by Preston et al. (1999) 75% of naltrexone patients failed to attend treatment at 2 weeks [135]. Increased risk of a fatal opioid overdose after concluding treatment has been hypothesised to be the results of reduced tolerance and return to pre-treatment/dependence levels of use [118, 150].

In contrast, the use of implant naltrexone was not associated with elevated rates of mortality, both at 0 – 4 and 5 – 8 months post treatment. This is likely due to two pharmacokinetic characteristics of the implant compared to its oral counterpart. Firstly, during the first four months of implant treatment, blood levels are maintained above 2ng/ml (therapeutic levels) [146, 298], avoiding the need to comply with the daily dosing regimen associated with oral naltrexone and providing protection against opioid overdose. Compliance has always been an issue with oral naltrexone, as unlike methadone or buprenorphine, the decision whether or not to take the medication is not associated with any opioid agonist effects to encourage use, or opioid withdrawal symptoms if the daily opioid medication is ceased. Secondly, in the subsequent 4 months (5 – 8 months post implant treatment), blood levels gradually reduce so that protection from opioid overdose is ongoing, although at a reduced level. In contrast,
following the termination of oral naltrexone, patients rapidly lose their opioid antagonist protection against the effects of opioids within days, and are left with little tolerance or protection from opioid overdose.

7.1.2. “Are mortality rates in patients treated with implant naltrexone comparable to mortality rates in patients treated with methadone or buprenorphine?”

While all-cause mortality in patients treated with implant naltrexone was not significantly different to those treated with methadone or buprenorphine when gender was not considered, significantly higher rates of mortality were observed in females treated with methadone compared with those treated with implant naltrexone. This is particularly interesting given the higher rates of mental health morbidity observed in female naltrexone patients prior to entering treatment. One might have expected this group, rather than methadone to be associated with high levels of mortality. This also suggests that the difference in mortality between the two groups may be underestimated given the difference in pre-treatment mental health morbidity. The reduction in mortality was not associated with a particular diagnosis or cause of death.

In the first 28 days following the commencement of methadone, high rates of mortality were observed compared with implant naltrexone, with opioid overdose the major contributing cause. In contrast, rates of mortality during the first 28 days of buprenorphine treatment were comparable to naltrexone. This is consistent with previous studies which have reported high rates of opioid overdose mortality in the first 2 weeks following the commencement of methadone treatment [145, 158, 291, 300]. Non-fatal opioid overdose requiring hospital admission in the two years prior to treatment was a significant predictor of increased risk of fatal opioid overdose following the commencement of treatment, as was gender. These indicators may be used to identify high risk patients, particularly those receiving methadone, to receive suitable interventions or strategies to reduce the rates of opioid overdose.

Following the initial induction period, rates of suicide in naltrexone treated patients were comparable to methadone, but elevated in comparison to buprenorphine patients currently on treatment. However, as already noted, examinations of pre-treatment admission to hospital with a self-harm diagnosis and other mental health diagnoses was higher in naltrexone patients, particularly in female patients, compared with both methadone and buprenorphine patients, indicating that frequency and severity of mental health issues in opioid dependent
patients entering treatment is not evenly distributed between the three treatment groups. Given that pre-treatment rates of mental health events were elevated in naltrexone patients, it is not surprising that post-treatment rates are above that of methadone and buprenorphine.

7.1.3. “How does morbidity compare in patients treated with sustained release naltrexone implant to those treated with methadone or buprenorphine?”

Rates of hospital and ED attendances as an indicator of morbidity were higher in naltrexone treated patients compared to those treated with methadone or buprenorphine. The high rate of morbidity was primarily associated with the first 28 days on treatment, where rates of both hospital and ED attendance spiked well beyond methadone or buprenorphine. These high rates during the induction period was associated with an increased rate of attendances with a mental health diagnosis.

Prior to treatment female patients entering naltrexone treatment had very high rates of mental health events. While pre-treatment these patients looked worse, following treatment they improve substantially. This suggests that the difference in morbidity between the three groups may also be in some part attributable to pre-treatment difference in mental health morbidity. Further research is required using a randomised or matched cohort of patients to more conclusively determine if rates of morbidity in patients treated with implant naltrexone are comparable to methadone and buprenorphine.

Additionally, changes associated with the cessation of illicit opioids facilitated by naltrexone may be associated with factors that may negatively affect mental health, such as isolation from opioid using friends, loneliness, judgement or regret. Similarly, a pre-treatment situation that may have motivated the patient to become opioid free may have also played a role in their post-treatment mental health, for example child custody issues, relationship breakdown, financial strain or family friction.

The high rates of morbidity during the first 28 days of naltrexone implant treatment may be at least partially the result of the co-occurrence of opioid detoxification/withdrawal in patients who were using opioids in the weeks prior to treatment. Common symptoms of withdrawal include anxiety, abdominal cramping, nausea and vomiting, high blood pressure, insomnia, and diarrhoea. For patients commencing methadone or buprenorphine who have been recently using other opioids, only minimal if any withdrawal symptoms would be expected.

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Elevated rates of pregnancy in women treated with naltrexone, may also contribute to increased rates of hospital attendances compared with methadone and buprenorphine women.

7.1.4. “Are birth rates in naltrexone treated women comparable to women treated with methadone or buprenorphine, and non-dependent-controls?”

Birth rates in women treated with naltrexone were significantly elevated as compared to opioid dependent women treated with methadone or buprenorphine, as well as non-dependent women. The elevated rates of pregnancy may be due to the cessation of opioids (and thus the restoration of normal menstruation), increased sex drive and re-establishment of relationships, increased self-care (nutrition, hygiene etc.). Alternatively, the increased incidence may be directly attributable to naltrexone, with naltrexone shown to stimulate luteinising hormone (LH) and follicle stimulating hormone (FSH) during the early follicular phase of the menstrual cycle [212, 213]. As such, clinically, naltrexone has been found to induce ovulation and re-instate normal menstruation in non-opioid dependent women with weight loss associated and hypothalamic, amenorrhea and polycystic ovarian disease [105, 174, 214].

7.1.5. “What are the risks associated with the use of sustained release naltrexone during pregnancy and how do they compare to methadone, buprenorphine and non-dependent controls?”

Obstetric outcomes in women exposed to naltrexone were generally comparable to methadone and buprenorphine exposed women. Compared with methadone and buprenorphine, naltrexone treated women were at an increased risk of ectopic pregnancies. Increases in the rates of ectopic pregnancies in women treated with implant naltrexone were above what would have been expected given the increase in birth rates, with more than 4 times as many ectopic pregnancies compared with methadone women, buprenorphine and control women. In contrast, rates of birth in naltrexone women were approximately 1.9 times greater than the other three groups. Naltrexone may affect the ciliary beat of the fallopian tube, reducing the successful passage of embryos through the fallopian tube, as described in section 6.2.
Neonates and children exposed to naltrexone in utero had higher rates of urogenital birth abnormalities and elevated rates of hospital admissions with a respiratory, ear, or injury diagnosis, compared with control/non-exposed children. In methadone and buprenorphine-exposed children, these health events were not significantly different to the control group. The mechanisms behind these changes in prevalence in the naltrexone-exposed children is unclear. Otherwise children exposed to naltrexone in utero did not exhibit poorer outcomes than those exposed to methadone or buprenorphine.

Naltrexone was associated with a reduction in a number of risks compared with methadone and buprenorphine in both the mother and the children. Specifically:

- Higher rates of spontaneous labour and delivery (compared with buprenorphine mothers).
- Fewer incidence of NAS
- Larger birth size (compared with methadone neonates)
- Shorter length of hospital (compared with both methadone and buprenorphine neonates) and special care length of stay (methadone only).
- No increase in neonatal mortality (as was observed in methadone exposed neonates)
- No increase in overall rates of birth abnormalities (as was observed in methadone exposed neonates)
- No increase in rates of mental health out-patient attendances (as was observed in buprenorphine exposed children)

The difference in neonatal size may be associated with the three treatments’ interaction with the opioid growth factor receptor (OGFr). Opioid growth factor (OGF) has been shown to reduce DNA synthesis in a wide variety of organ systems during prenatal development, which can be reversed and even enhanced by the presence of naltrexone [398]. Exposure to exogenous opioids such as methadone had been postulated to directly interact with the OGF receptor, resulting in slowed development including growth-retardation [111]. As such, methadone exposed neonates were significantly smaller than naltrexone exposed neonates. Exposure to the full agonist methadone appeared to have a greater effect on reducing birth size compared with buprenorphine (partial agonist/antagonist), as has been shown in studies previously [209, 210]. Concerns have arisen that naltrexone may limit the regulation of growth by interfering with OGF, resulting in large body and organ weight [376], however naltrexone neonates were comparable to the control group when adjusted for gestational age.
As would be intuitively thought, naltrexone exposed neonates had a lower rate of NAS compared with both methadone and buprenorphine exposed neonates. For naltrexone patients who conceived on treatment, and remained opioid abstinent throughout pregnancy, neonatal opioid withdrawal following birth would not have occurred. For pregnant patients who commenced treatment while pregnant, withdrawal would have occurred in utero. The low rates of NAS in naltrexone exposed neonates would have also accounted for the difference in hospital and special care length of stay.

Overall rates of perinatal mortality and congenital abnormalities in naltrexone exposed neonates were not significantly different to the control group, while rates of neonatal and early childhood mortality, and congenital abnormalities both were elevated in methadone exposed neonates. This finding while important needs to be viewed in perspective as the sample size of the methadone group was much larger than either the naltrexone or buprenorphine groups, thus the power to detect such differences was also higher. While the results from this study were positive, further research is required to support the safety of naltrexone in terms of perinatal mortality and congenital abnormalities.

The occurrence of out-patient mental health events in 4.1% of the children exposed to buprenorphine before the age of 5 is alarming, given only 0.5% of the control group had also had a mental health out-patient event. Rates are consistent with the study by Kivisto et al. (2015), in which 4 of the 102 buprenorphine exposed children (3.9%) were referred to a psychologist or child psychiatrist for behavioural problems by the age of 3 [239]. This data and events surrounding these admissions are deserving of further investigation and review.

Compared with the control group, naltrexone was associated with an increase in a number of risks, however these also exist in both the methadone and buprenorphine treatment groups. These were:

- Increased rates of complications during pregnancy (reported at birth), and elevates ED attendances during pregnancy and the post-partum period.
- Very high rates of HCV in women
- Higher rates of fetal distress
- Lower average birth weight and length
- Significantly higher rates of NAS in neonates.
- Longer length of stay in hospital and the special care unit following birth.
• Elevated rates of hospital admissions particularly admission with a diagnosis of infection and skin/subcutaneous disease or disorder.
• High rates of ED attendances during the neonatal period

Elevated risks observed in naltrexone, methadone and buprenorphine, compared with the control group could largely be attributed to the lifestyle difference associated with illicit opioid use. Such factors may include low socio-economic status, history of intravenous drug use (ie. Hepatitis C infection), high rates of cigarette and other drug use, lower rates of antenatal care, high rates of mental health issues, poor nutrition, and a lack of meaningful social support [184, 399].

While rates of NAS were reduced in naltrexone exposed neonates, they were not eliminated and were significantly higher than in the control group. The limitation of a NAS diagnosis is that the likely causal drug/s associated with the abstinence syndrome is not specified. The occurrence of NAS in naltrexone exposed neonates may not have been due to the use of opioids (return to opioid use) but rather the result of other substance use. Recording the likely causal drug/s associated with the NAS diagnosis would improve the usefulness of this diagnosis, particularly in measuring the incidence of type-specific drug related harms in pregnancy. Additionally, the addition of drug type would assist researchers in examining the sequelae of in utero drug exposure.

Additionally, concerns regarding the risk of opioid overdose in pregnant opioid dependent treated with naltrexone [215] were not supported by the current data. Opioid overdose requiring hospitalisation was very rare, with only three observed in any of the three treatment groups, with one in the naltrexone (before the commencement of treatment) and two methadone mothers (one while on methadone treatment, the other prior to treatment). Given the extremely low prevalence, the risk of opioid overdose should not be a priority amongst considerations when selecting a suitable treatment.

Similarly concern regarding high rates of reportable infectious disease in children born to opioid dependent mothers was not supported. High rates of reportable infectious diseases including HCV were not observed in children exposed to any of the three opioid pharmacotherapies. Given the high rate of mothers with HCV (~60%) and vertical transmission rates (5.8% of children [397]), it is surprising that no incidence of HCV was identified. It is likely that that lack of HCV cases is due to a lack of follow up and diagnosis rather than an absence of cases.
As outlined in Table 32, the research fills many of the existing gaps in the literature, while directing future research.
Table 32: An overview of the effects of the use/exposure to opioids and opioid pharmacotherapies during pregnancy on maternal and neonatal outcomes (as seen in section 1.5 Pregnancy and Neonatal Outcomes), amended to include results from the study (bold).

<table>
<thead>
<tr>
<th>Mother</th>
<th>Illicit opioids</th>
<th>Methadone</th>
<th>Buprenorphine</th>
<th>Naltrexone</th>
<th>Western Australia (study values)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category AUS/USA</td>
<td></td>
<td>Illicit</td>
<td>C* / C</td>
<td>C / C</td>
<td>B3** / C</td>
</tr>
<tr>
<td>Birth rates</td>
<td>?</td>
<td></td>
<td>60.5</td>
<td>62.6</td>
<td>116.2</td>
</tr>
<tr>
<td>Complications during pregnancy (%)</td>
<td>?</td>
<td></td>
<td>58.3 - 73</td>
<td>46.8</td>
<td>55.9</td>
</tr>
<tr>
<td>Complications during labour/delivery (%)</td>
<td>?</td>
<td></td>
<td>51 – 72.4</td>
<td>31 – 76.6</td>
<td>72.1</td>
</tr>
<tr>
<td>Terminations (%)</td>
<td>?</td>
<td></td>
<td>4.4 [220]</td>
<td>3.3 – 12.8 [220, 221]</td>
<td>?</td>
</tr>
<tr>
<td>Twins (%)</td>
<td>1.16 - 2.9 [223,225]</td>
<td>0.4 - 2.8 [209, 226]</td>
<td>0.0 - 4.3 [209]</td>
<td>1.3</td>
<td>2.7 [219] (1.5)</td>
</tr>
<tr>
<td>Birth Outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stillbirth (%)</td>
<td>3.6 – 7.1 [203, 223, 227-231]</td>
<td>1.1 – 5.8 [220, 226, 229, 231, 232]</td>
<td>0.6 - 3.1 [209, 220, 232, 233]</td>
<td>1.3</td>
<td>0.7 [234] (0.9)</td>
</tr>
<tr>
<td>Neonatal mortality (%)</td>
<td>2.1 – 11.9 [187, 203, 223, 227, 230, 231, 235, 236]</td>
<td>0.5 – 3.4 [187, 203, 226, 231, 236, 237]</td>
<td>0.0</td>
<td>0.0</td>
<td>0.2 [234] (0.2)</td>
</tr>
<tr>
<td>Perinatal mortality (%)</td>
<td>3.0 - 10.7 [203, 227, 235]</td>
<td>2.4 – 3.4 [203, 238]</td>
<td>1.6</td>
<td>1.5</td>
<td>0.9 [234] (1.1)</td>
</tr>
<tr>
<td>Infant mortality (%)</td>
<td>4.0 [225]</td>
<td>0.5 - 5.5 [209, 237]</td>
<td>0.0 – 1.0 [239]</td>
<td>1.5</td>
<td>0.1 [234] (0.0)</td>
</tr>
<tr>
<td>Description</td>
<td>Range</td>
<td>References</td>
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<td>-------------------------------------------------</td>
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<td>---------------------------------------------------------------------------</td>
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<tr>
<td></td>
<td>38.5 – 91.3</td>
<td>[203, 209, 220, 230, 231, 236, 238, 242-244]</td>
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<tr>
<td></td>
<td>20.0 – 79.4</td>
<td>[209, 220, 221, 233, 239, 244-247]</td>
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<td></td>
<td>?</td>
<td>?</td>
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<tr>
<td>NAS requiring treatment or hospitalisation (%)</td>
<td>13.3 – 77.5</td>
<td>[203, 225, 236, 241, 248]</td>
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<td></td>
<td>27 – 90</td>
<td>[203, 209, 210, 226, 232, 236, 249-255]</td>
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<tr>
<td></td>
<td>1.6 – 82</td>
<td>[209, 210, 232, 239, 245, 249-252, 255, 257-259]</td>
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<td></td>
<td>7.5</td>
<td>(0.2)</td>
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<td></td>
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<tr>
<td>Congenital anomalies (%)</td>
<td>2.9 - 26</td>
<td>[186, 223, 224]</td>
<td></td>
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<tr>
<td></td>
<td>0.4 – 15.4</td>
<td>[226, 232, 238, 244, 256, 260, 261]</td>
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<tr>
<td></td>
<td>0.3 – 9.8</td>
<td>[220, 232, 233, 239, 247, 259]</td>
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<td></td>
<td>8.8</td>
<td>(5.8)</td>
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<td></td>
<td></td>
<td>[262]</td>
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<tr>
<td>Birth weight (g)</td>
<td>2393 – 2803</td>
<td>[186-188, 203, 223, 225, 227, 230, 231, 235, 236]</td>
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<td></td>
<td>249-252, 254, 255, 257, 260, 261]</td>
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<tr>
<td></td>
<td>2816 – 3530</td>
<td>[208, 210, 220, 221, 232, 239, 246, 247, 249-252, 255, 257-259, 264,</td>
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<td></td>
<td>265]</td>
<td>3137</td>
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<td></td>
<td>3337</td>
<td>[219] (3378)</td>
<td></td>
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<tr>
<td>Low birth weight (&lt;2500g) (%)</td>
<td>28.6 – 62.5</td>
<td>[223, 229, 231, 235, 241, 266]</td>
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<td></td>
<td>7.7 – 37.5</td>
<td>[210, 216, 229, 231, 244, 261]</td>
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<tr>
<td></td>
<td>6.3 – 12.1</td>
<td>[210, 221, 244]</td>
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<td></td>
<td>11.8</td>
<td>(6.6)</td>
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<td></td>
<td></td>
<td>[219] (4.6)</td>
<td></td>
<td></td>
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<tr>
<td>Infant hospital duration (days)</td>
<td>3.8 – 31.8</td>
<td>[187, 224, 229, 235]</td>
<td></td>
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<td></td>
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<tr>
<td></td>
<td>3.5 – 44</td>
<td>[187, 208, 209, 226, 229, 250, 251, 254, 255, 257, 263]</td>
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<td></td>
<td>5.6 – 21</td>
<td>[208, 209, 221, 250, 255, 257, 258, 264, 265]</td>
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<td></td>
<td>5.5</td>
<td>(3.0)**</td>
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<td></td>
<td></td>
<td>[267] (4.3)</td>
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<tr>
<td>Special care (days)</td>
<td>33.2</td>
<td>[230]</td>
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<tr>
<td></td>
<td>5.9 – 35.5</td>
<td>[230, 235, 261]</td>
<td></td>
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<tr>
<td></td>
<td>4.7 - 19.4</td>
<td>[235]</td>
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<td></td>
<td>2.5</td>
<td>(0.5)</td>
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<tr>
<td>Gestational age at delivery (weeks)</td>
<td>36.5 – 38.4</td>
<td>[186-188, 203, 224, 230, 231, 235]</td>
<td></td>
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<tr>
<td></td>
<td>37.5 – 39.4</td>
<td>[187, 188, 203, 208, 210, 216, 226, 230-232, 242, 250, 252, 254, 255,</td>
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<td></td>
<td>257, 260, 261, 263, 268-270]</td>
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<tr>
<td></td>
<td>37.5 – 39.7</td>
<td>[208, 210, 221, 232, 239, 246, 250, 252, 255, 257-259, 264, 265]</td>
<td></td>
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<tr>
<td></td>
<td>38.0</td>
<td>(38.8)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td>[267] (38.7)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Length at birth (cm)</td>
<td>46.1 - 47.3</td>
<td>[186, 223]</td>
<td></td>
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<tr>
<td></td>
<td>47.1 – 49.6</td>
<td>[208, 210, 220, 249, 254, 255, 257, 260]</td>
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<tr>
<td></td>
<td>46.3 – 52.8</td>
<td>[208, 210, 220, 221, 239, 246, 249, 255, 257, 258, 264]</td>
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<tr>
<td></td>
<td>48.8</td>
<td>(50.0)</td>
<td></td>
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<tr>
<td>Category</td>
<td>Head circumference (cm)</td>
<td>Preterm (&lt;37 weeks) (%)</td>
<td>Apgar 1 min</td>
<td>Apgar 5 mins</td>
<td></td>
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<tr>
<td></td>
<td>33.9</td>
<td>3.8</td>
<td>7.9</td>
<td>8.8</td>
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</tr>
</tbody>
</table>

* Category C: Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible.

** Category B3: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformations or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is uncertain in humans.

*** Median

**** The study by Hulse et al (2004) was excluded in this table as it is likely these patients would have been included in the current study.
7.2. **Clinical implications and recommendations**

7.2.1. Opioid dependent patients

Given the significant reductions in mortality associated with opioid overdose, implant naltrexone should be considered the preferred treatment to oral naltrexone in opioid dependent patients. This conclusion is consistent with other empirical research investigating the efficacy of oral versus implant naltrexone [146].

The study identified a significantly higher rate of mental health morbidity in female patients entering naltrexone treatment compared to those entering methadone or buprenorphine, potentially as a result of increased entry barriers into methadone and buprenorphine treatment programs. Clearly it is important that strategies be in place for patients who present for methadone and buprenorphine treatment who are unable to complete administrative entry obligations, so they are not precluded from treatment entry. Similarly given the high rates of morbidity and mortality associated with illicit opioid use and the disorganized life these patients often lead, delays between first contact and treatment entry will be an impediment to treatment. As such, systems should be implemented to address this.

The induction period was shown to be a particularly high risk period for all three treatment groups. For naltrexone, this period was associated with very high rates of hospital admissions, while for methadone patients high rates of fatal opioid overdose were observed. For services providing any of these three pharmacotherapies, this time period should be targeted to reduce negative health outcomes. This is particularly important for implant naltrexone patients, who unlike methadone and buprenorphine patients do not have daily contact with health professions for pharmacotherapy dispensing. One possibility is the initial use of short term residential treatment to allow stabilisation of patients who are considered at high risk. It is further recommended that patients treated with implant naltrexone be integrated into a mental healthcare service, delivered by medical and other health professionals, and regular counselling is promoted to address the high mental health needs of these patients. For all treatments, consideration should be given to the initial two-week stabilisation of high risk patients, particularly male patients and patients with a recent hospitalisation for an opioid overdose (two years prior to treatment).

As the induction period was associated with such a high rate of morbidity and mortality in all three treatments, care should be taken to reduce number of times patients move on and off
treatment. For naltrexone patients, retreatment between 4 and 6 months post treatment may reduce return to opioid use and limit the morbidity associated with the initial first month of treatment. Similarly, the median time spent on methadone and buprenorphine per treatment episode was relatively short (7.5 and 3.6 months respectively), with patients on average having at least two treatments, but in some cases patients were re-treated more than 10 times with the same pharmacotherapy. Data is needed to determine why methadone and buprenorphine patients move in and out of treatment. Furthermore, initiatives must be developed and implemented to retain patients in treatment until they are ready to move to an opioid free lifestyle.

To target the high rates of ED attendances for non-urgent reasons and accommodate the disorganized life style associated with opioid use disorders, it may be worth considering extending the opening hours of drug and alcohol services, particularly those that can provide GP services. This would likely reduce the pressure on ED services.

7.2.2. Opioid dependent women

The morbidity and mortality in opioid dependent women was substantially different to their male counterparts and varied between the treatments. While women had lower rates of mortality, admissions to hospital and ED far surpassed those of males, particularly in terms of mental health events. Women treated with naltrexone had a significantly lower mortality rate compared with methadone treated women, however rates of both hospital and ED attendances in naltrexone treated women were higher than methadone. As such, and given the difference in female experiences with opioid use disorders compared with male patients (i.e. prostitution, domestic violence, pregnancy) dedicated services that directly target the needs of females are both needed and recommended.

Contraception also needs to be included as an integral part of treatment services for opioid dependent women to target the high rates of pregnancy, particularly in women treated with implant naltrexone. Ideally long term contraceptive options such as Implanon® should be considered and encouraged with minimal cost barriers. The increased risk of pregnancy associated with naltrexone needs to be outlined to women considering this treatment.

The stigma associated with opioid use disorders can be a barrier to patients attending medical services for routine medical care [400] and thus addiction services need to have the capacity to
treat more than just the addiction. This further argues for GP services to be provided within addiction treatment services.

### 7.2.3. Pregnant opioid dependent women

Obstetric and neonatal outcomes for women treated with implant naltrexone were as good, and in many instances better than for methadone and buprenorphine. Thus, patients who are stable on naltrexone treatment should be allowed to remain on treatment rather than transferred onto an alternative pharmacotherapy. For women, who become pregnant while dependent on illicit opioids, implant naltrexone may be a suitable option however more controlled research is required to replicate the result of this study.

Given the high rates of neonatal mortality, congenital abnormalities, and NAS associated with methadone, buprenorphine should be considered in preference to methadone. However, pregnant women who are stable on methadone should be allowed to remain on methadone, as compliance with the new treatment is not guaranteed, with women often opting to return to methadone. In a study by Jones et al. (2006) in which four women were successfully transferred from methadone to buprenorphine during pregnancy, all women made the decision to return to methadone [401].

Taking into account the high rates of young, single women of a low socioeconomic status in the three opioid pharmacotherapies, appropriate and targeted services are required to promote positive outcomes for these mothers and their children. Additionally given the known complications associated with cigarette smoking [402, 403] and the high rates in pregnant women using opioid pharmacotherapies who smoke, treatment service providers should target smoking cessation particularly in stable patients.

### 7.2.4. Children exposed to opioid pharmacotherapies in utero

Differences in the prevalence of cause specific hospital admissions and out-patient mental health events in children exposed to naltrexone, methadone or buprenorphine, required further research, to replicate and support the results, as the numbers were relatively low. Additional research would also help identify the specific diseases that contribute to the increased prevalence, as in this study due to the limited sample size, categories of admissions were grouped into body systems/structures.
Children gestationally exposed to any of the three opioid pharmacotherapies had poorer health outcomes compared to the control group. Additionally, there appears to be an under diagnosis of HCV and potentially other transmissible diseases, with zero children diagnosed with HCV despite a prevalence of approximately 60% in the mothers. In previous studies, children exposed to methadone and buprenorphine have also been reported to have increased incidence of behavioural problems and learning difficulties [404-406]. As such, establishing and maintaining contact with these children from birth may be an effective way of targeting interventions to improve the health and lives of these children. This may include regular HCV screening, health services to target the high incidence of infection and respiratory problems, psychiatric screening, and educational services. The merit associated with these interventions, the associated costs and the potential benefits related to following up these children would need to be assessed by the Department of Health.

7.3. Future research

7.3.1. Opioid dependent patients

While implant naltrexone was shown to reduce mortality compared with oral naltrexone, further research is required to compare the safety of the two preparations in a larger population. However, as the research thus far indicates superior efficacy [146], and good biocompatibility [137, 138], and given both products use the same active ingredient, further safety studies may not be a priority.

While data supported the safety of implant naltrexone as an alternative to either methadone or buprenorphine, a well-designed randomised controlled trial examining efficacy of implant naltrexone compared with methadone and/or buprenorphine is required. Such a study is important, as the health, particularly the mental health, of patients prior to treatment did not appear to be equivalent across the three treatments, in particular in female patients with high rates of hospitalisation for mental illness in the naltrexone implant cohort. Additionally, research is also needed to examine how the use of implant naltrexone influences other aspects of a patient’s life such as quality of life, social productivity, and criminal activity.

7.3.2. Pregnancy and in utero exposure

While thesis study bridges a number of gaps regarding the use of naltrexone during pregnancy, there is still a number of questions about its long term safety, especially in regards some of the findings from non-clinical studies in regards to changes in pain perception, sensitivity to
opioids and developmental milestones [364-366]. The results of the study provide substantial supporting data for a further research into the use of implant naltrexone during pregnancy. Additional prospective studies could additionally examine the use of illicit opioids and other drugs, control for a wide range of maternal and environmental factors and address questions that were unable to be addressed in thesis such the prevalence of NAS (including milder cases not requiring hospitalisation) and rates of termination (as highlighted in Table 32). Studies should also include an extended follow-up of children to refute or confirm the varying rates of hospital admissions associated with different diagnoses such as respiratory, and ear related diseases/disorders, as well as the high incidence of out-patient mental health events in children exposed to buprenorphine.

Longitudinal follow up of this neonatal cohort and other exposed neonates through to adulthood is recommended to ensure that lifetime health events are captured and the full extent of effects of neonatal exposure can be quantified. Follow up may be expanded to include developmental and behavioural outcomes, potentially utilizing data from the department of education, child services, and corrective services.

Naltrexone has also been successfully used in the treatment of alcohol dependence [160, 161]. Given the cautiously optimistic results in this study and the high levels of physical and mental health issues associated with alcohol dependence and binge drinking during pregnancy, the results of this study may also support further research into the use of sustained release naltrexone preparations in the treatment of heavy drinking during pregnancy and its ability to reduce the incidence of Fetal Alcohol Spectrum Disorders.
8. Conclusions

8.1. Morbidity and mortality

The use of implant naltrexone was shown to be a safer alternative to oral naltrexone in terms of morbidity, significantly reducing rates of fatal opioid overdose and all-cause mortality in the first four months following treatment. Accordingly, given this and the previously demonstrated levels of superior efficacy [146], implant naltrexone should be used in preference to oral naltrexone where possible.

Implant naltrexone was generally comparable to both methadone and buprenorphine in terms of morbidity and mortality, indicating that naltrexone is a safe alternative for use in opioid dependent patients, particularly for patients who wish to become abstinent. Patients receiving implant naltrexone treatment should be carefully monitored for the first 28 days, as this period is associated with increased rates of hospitalisation and non-fatal opioid overdose. Data support further investigation into a direct randomised comparison of the three treatments so that both safety and efficacy can be objectively compared. In particular, further research into the use of implant naltrexone in sub-groups, such as a female patients and patient with mental health comorbidity is required.

8.2. Pregnancy and child outcomes

The data highlighted the need for drugs and alcohol services to ensure patients have access to reliable contraception, to reduce the incidence of unwanted pregnancy. This is particularly important for patients entering naltrexone implant treatment, given the high rates of birth.

The presented data evokes cautious optimism about the potential for the use of implant naltrexone in pregnant opioid dependent patients and provides support for a large randomised controlled trial. While identifying some important areas for future research, the data also highlighted some of the serious risks associated with the use of methadone in pregnancy (i.e. neonatal mortality, birth anomalies) that were not associated with buprenorphine or implant naltrexone. Further prospective studies are required to further investigate the safety of naltrexone use during pregnancy.
9. References


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