Int J Ment Health Addiction (2018) 16:187–198
https://doi.org/10.1007/s11469-017-9856-6

ORIGINAL ARTICLE

# Self-Injuring Behavior and Mental Illness in Opioid-Dependent Patients Treated with Implant Naltrexone, Methadone, and Buprenorphine in Western Australia

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Published online: 20 December 2017


**Abstract** This study 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. Patients treated between 2001 and 2010 were linked with hospital, emergency (ED), outpatient mental health, and mortality records. Rates of health events were compared between the three groups using survival analysis and generalized estimating equations. Rates of suicide and ISH in patients treated with naltrexone were comparable to patients treated with methadone or buprenorphine. Rates of mental health and psychiatric hospital admissions, ED attendances, and outpatient 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 outpatient mental health events compared with naltrexone patients. Naltrexone was associated with high rates of mental health events, however further controlled research is required.

**Keywords** Buprenorphine · Methadone · Mental health · Naltrexone · Opioid · Self-injuring behavior

Endogenous opioids have euphoric properties and have been linked to mood modulation (Lutz and Kieffer 2013; Stanciu et al. 2017). As such, dysfunction and abnormalities in the opioid

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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 (Berrocoso et al. 2009; Goodwin et al. 1993; Schmauss and Emrich 1985; Sher and Stanley 2008).

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 (Roth et al. 1996), (ii) reduced levels of beta-endorphin and met-encephalin in the CSF of NSSI individuals compared with controls (Stanley et al. 2010), and (iii) reports of reduced pain sensitivity (Franklin et al. 2012; McCoy et al. 2010). In suicidal patients, changes to the affinity and distribution of the mu opioid receptor have been observed (Escriba et al. 2004; Gabilondo et al. 1995; Sher and Stanley 2008; Zalsman et al. 2005).

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 (Comings et al. 2000). Consistent with this, the removal of the delta opioid receptor in knockout mice was shown to result in increased levels of anxiety and depression (Filliol et al. 2000). Similarly, examination of serum β-endorphin levels found that high levels may be associated major depression (Goodwin et al. 1993), and more severe anxiety, phobia, and compulsivity in depressed patients (Darko et al. 1992). The kappa opioid receptor has also been associated with emotional response and mood regulation, particularly during stressful situations (Lalanne et al. 2014). With kappa agonist and antagonists having a stimulatory and inhibitory-like effect on depressive symptoms, via modulation of dopamine signaling (Lalanne et al. 2014; Lutz and Kieffer 2013). As such, kappa opioid antagonists such as buprenorphine have been investigated as treatment for major depressive disorders (Maurizio et al. 2016). Additionally, alterations to the opioid system have been observed in patients with schizophrenia (Bernstein et al. 2002) and post-traumatic stress disorder (Hamner and Hitri 1992; Hoffman et al. 1989).

High rates of self-harming behavior and other mental health disorders have been observed in opioid-dependent patients (Grella and Lovinger 2012; Rosen et al. 2008). 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 (Lutz and Kieffer 2013), a shared genetic influence/vulnerability or shared environmental triggers (Cerdá et al. 2010), 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 (Tenore 2008). However, conversely, as noted above, the use of the opioid antagonist naltrexone has shown to reduce NSSI behavior in affected patients (Roth et al. 1996). 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 (Bodkin et al. 1995; Karp et al. 2014; Kosten et al. 1990).

Given the significant role endogenous opioid 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 dependence. In non-dependent controls, the use the short acting opioid antagonist naloxone was shown to dose dependently increase self-ratings of both tension-anxiety and anger-hostility (Grevert and Goldstein 1977; Pickar et al. 1982). However in opioid-dependent patients, preliminary evidence suggest the use of naltrexone is not associated with increase rates of depression (Miotto et al. 1997) or mental health-related hospitalization (Ngo et al. 2007). However, given the significant role endogenous opioid likely play in mood stabilization, the use of methadone a full opioid agonist, or buprenorphine, a partial agonist (mu) and antagonist (kappa) 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 implant naltrexone, methadone, or buprenorphine.

## Methods

### Participants

The study included all opioid-dependent patients treated for the first time with methadone ($n = 3515$), buprenorphine ($n = 3250$), or implant naltrexone ($n = 1461$) 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 published (Kelty and Hulse 2017).

### 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. The protocols used by the WA Data Linkage and the surrounding infrastructure are outlined in Kelman et al. and Holman et al. (Holman et al. 1999; Kelman et al. 2002).

### Analysis

Hospitalizations and fatalities involving intentional self-harm (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 (inpatient) were calculated as a further indicator of the mental health of the three cohorts. Rates of outpatient mental health events were also calculated and expressed ptpy.

Rates of ISH and other mental illnesses was 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 31 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. Analysis was carried out by a suitable qualified biostatistician (EK) using Stata IC/13.

### 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

### Demographics

The study consisted of 5646 opioid dependent patients, of which 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 previously published (Kelty and Hulse 2017).

### 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, eight 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). 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 one 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 with naltrexone compared with both methadone (RR 1.35, CI 1.10–1.67) and buprenorphine (RR 1.28, CI 1.03–1.59).

## Mental Health Presentations

Of the 20,066 hospital admissions observed in the opioid-dependent cohort, 5671 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 (Table 1).

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 2).

Personality disorders were the most common mental health diagnosis associated with hospital admissions, accounting for around a third of all mental health admissions (Table 3), followed by depression, anxiety, schizophrenia, and bipolar. Compared with the naltrexone cohort, there were fewer patients in the methadone cohort with hospital admission with a bipolar diagnosis, and fewer patients in the buprenorphine cohort with a hospital admission with a personality disorder diagnosis.

**Table 1** Rates of mortality and hospital admissions involving self-injuring behavior in patients treated with implant naltrexone, methadone, or buprenorphine

| | Naltrexone | Methadone | Buprenorphine |
|---|---|---|---|
| Fatalities | | | |
| Post-treatment | 1.3 | 1.2 | 0.9 |
| - Induction | 4.3 | 4.0 | 4.1 |
| - On treatment | 2.5 | 0.8 | 0.4* |
| - Off treatment | 0.9 | 1.3 | 1.0 |
| Hospitalization | | | |
| Pre-treatment | 63.0 | 47.5 | 49.8 |
| Post-treatment | 40.9 | 35.1 | 29.3 |
| - Induction | 164.8 | 28.3*** | 64.0* |
| - On treatment | 60.4 | 24.5*** | 18.9*** |
| - Off treatment | 31.5 | 43.8** | 34.1* |

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$

**Table 2** Rates of hospital, ED, and outpatient mental health events in opioid-dependent patients treated with implant naltrexone, compared with methadone and buprenorphine

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

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

*$p < 0.05$; ** $p < 0.01$; ***$p < 0.001$

Of the 28,832 ED attendances, 1490 were assigned a mental health diagnosis (5.2%) equating to 57.7 attendances ptpy. 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 ptpy), followed by methadone (81.3 ptpy) and buprenorphine (70 ptpy). Following the commencement of treatment, rates of ED attendance with a mental health diagnosis in patients treated with implant naltrexone were elevated compared with methadone and buprenorphine, particularly during induction period and while on treatment.

**Table 3** Rates of type specific mental health hospital admissions in opioid-dependent patients treated with implant naltrexone, methadone, or buprenorphine

| | Naltrexone | | Methadone | | Buprenorphine | |
|---|---|---|---|---|---|---|
| | Rate (ptpy) | % of pt | Rate (ptpy) | % of pt | Rate (ptpy) | % of pt |
| Mental health | 169.3 | 18.1 | 112.3*** | 16.9** | 156.2 | 14.3* |
| Anxiety | 11.8 | 3.1 | 18.1** | 3.6 | 44.0*** | 3.3 |
| Bipolar | 24.1 | 2.3 | 4.8*** | 1.2** | 15.9*** | 1.5 |
| Depression | 35.9 | 3.4 | 22.0*** | 2.8 | 33.1 | 3.1 |
| Personality disorder | 52.8 | 6.7 | 41.5** | 6.3 | 41.4* | 4.5* |
| Schitzophrenia | 45.9 | 2.0 | 17.5*** | 2.6 | 12.9*** | 2.1 |

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

Overall, 72,665 outpatient mental health events were recorded (1764.2 ptpy), with a median contact time of 30 min (IQR 15–60 min). Post-treatment rates of outpatient 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 outpatient events in each treatment was not significantly different (naltrexone 29.8%, methadone 33.1%, and buprenorphine 27.2%).

### Gender Differences

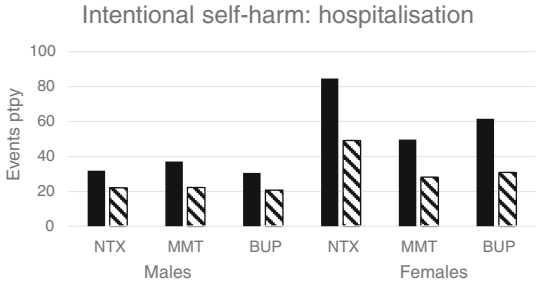
Rates of mental health events in male patients in the three groups were comparable with the exception of high rates of mental health outpatient attendances in naltrexone patients compared with both methadone and buprenorphine patients. In contrast, females in the naltrexone cohort had very high rates of mental health events across all measures compared with methadone and buprenorphine patients, but showed substantial reductions following treatment with the exception of outpatient mental health events which increased following treatment (Fig. 1).

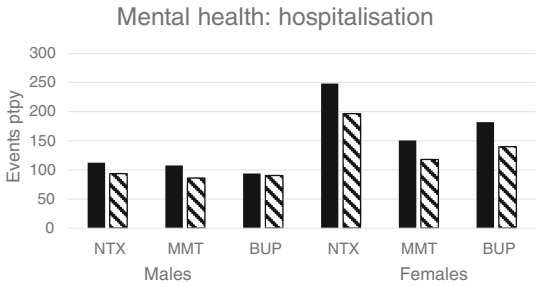
## Discussion

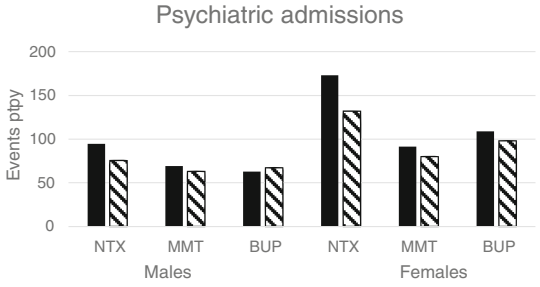
Prior to treatment there were differences in severity and/or prevalence of ISH and other mental illness in patients entering the three treatments. In particular, female patients receiving naltrexone implant treatment had very high rates of mental health events compared with methadone and buprenorphine. 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 stabilization, rates of outpatient mental health events among females treated with implant naltrexone increased, while remaining relatively unchanged in methadone and buprenorphine patients of both sex. Increases in the rates of outpatient 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.

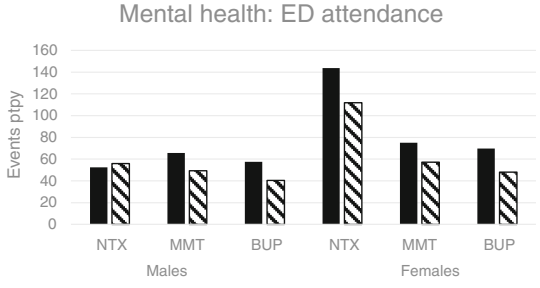
The study raises concerns about the equity and access to service delivery to opioid-dependent patients with mental health comorbidity. Those with the most severe mental health histories, particularly female patient with severe mental illness, are less likely to be afforded the opportunity to enter methadone 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 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.


Intentional self-harm: hospitalisation
Events ptpy
100
80
60
40
20
0
NTX
MMT
BUP
NTX
MMT
BUP
Males
Females


Mental health: hospitalisation
Events ptpy
300
250
200
150
100
50
0
NTX
MMT
BUP
NTX
MMT
BUP
Males
Females


Psychiatric admissions
Events ptpy
200
150
100
50
0
NTX
MMT
BUP
NTX
MMT
BUP
Males
Females


Mental health: ED attendance
Events ptpy
160
140
120
100
80
60
40
20
0
NTX
MMT
BUP
NTX
MMT
BUP
Males
Females

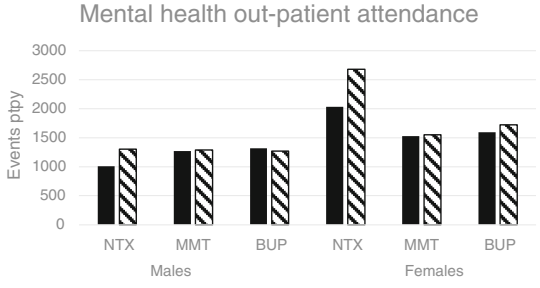

Mental health out-patient attendance
Events ptpy
3000
2500
2000
1500
1000
500
0
NTX
MMT
BUP
NTX
MMT
BUP
Males
Females

**Fig. 1** 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

During induction onto all pharmacotherapies, rates of suicide were high, however in methadone and buprenorphine cohorts this was not associated with high rates of hospitalization for ISH, while in naltrexone patients hospitalization for ISH was 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 patient treated with naltrexone who were using opioid 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 hospitalization 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 hospitalization 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 hospitalization for intentional self-harm were not significantly different. Similarly, hospitalization 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.

## Clinical Implications

While ISH and other mental illness contribute significantly to the burden opioid dependence 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 behavior, there is generally substantial difference in the intention, frequency, and lethality of the behavior. The identification of intentional self-harm and other mental illness relied on correct diagnosis and allocation of ICD-10 codes. In particular, high rates of discrepancies have been observed in fatalities classified as intentional self-harm (83.7%) (Daking and Dodds 2007), while much lower rates of inaccuracy have been observed in hospital admission diagnoses of intentional self-harm (14.7%) (Davie et al. 2008).

The study was a retrospective cohort study, thus patients selected the treatment they deemed most suitable. The lack of randomization 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 outpatient events were not assigned a diagnosis.

The three opiate pharmacotherapies act on different opioid receptors, with different combinations of agonist and antagonist action. Each opioid receptors has been shown to have very different effects on mental health. The inability to isolate the effect of each receptor type on mood is a limitation of this study.

## 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.

**Acknowledgements** The study authors would like to acknowledge the assistance of the WA Data Linkage Branch and the Data Custodians.

**Funding** Funding for this study was provided by the State Health Research Advisory Council via a Research Translation Project Grant.

**Compliance with Ethical Standards**

**Conflict of Interest** Erin Kelty and Gary Hulse have no interests to declare.

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