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Medication Treatment of Opioid Use Disorder

Short title: Medication treatment of opioid use disorder

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Abstract

Opioid Use Disorder (OUD) is a chronic, relapsing condition, often associated with legal, interpersonal and employment problems. Medications demonstrated to be effective for OUD are methadone (a full opioid agonist), buprenorphine (a partial agonist) and naltrexone (an opioid antagonist). Methadone and buprenorphine act by suppressing opioid withdrawal symptoms, and by attenuating the effects of other opioids. Naltrexone blocks the effects of opioid agonists. Oral methadone has the strongest evidence for effectiveness. Longer duration of treatment allows restoration of social connections and is associated with better outcomes. Treatments for OUD may be limited by poor adherence to treatment recommendations, and high rates of relapse and increased risk of overdose after leaving treatment. Treatment with methadone and buprenorphine has the additional risk of diversion and misuse of medication. New depot and implant formulations of buprenorphine and naltrexone have been developed to address issues of safety and problems of poor treatment adherence. For people with OUD who do not respond to these treatments, there is accumulating evidence for supervised injectable opioid treatment (prescribing pharmaceutical heroin). Another medication mode of minimizing risk of overdose is take-home naloxone (THN). Naloxone is an opioid antagonist used to reverse opioid overdose, and THN programs aim to prevent fatal overdose. All medication-assisted treatment is limited by lack of access, and stigma. In seeking to stem the rising toll from OUD, expanding access to approved treatment such as methadone, for which there remains the best evidence of efficacy, may be the most useful approach.

Introduction - Medication Assisted Treatment

Three medications are currently registered in the US (and many other jurisdictions) for use in Medication Assisted Treatment (MAT) of opioid use disorder (OUD). Most experience has been with methadone, which remains the gold standard against which other medications have been compared. Methadone is a full opioid agonist, producing dose-dependent analgesia, sedation. and risk of respiratory depression in overdose. It has a long but variable half-life, usually around 22 hours, but ranging 13-50 hours (1). Buprenorphine is categorised as a partial agonist at the mu-opioid receptor; it has a high affinity for the mu-opioid receptor; low doses produce typical opioid effects, but increasing doses prolong rather than increase opioid agonist effects (2). Naltrexone is a mu-opioid receptor antagonist, blocking the effects of opioids (and precipitating withdrawal if administered to a person currently dependent on opioids). It has been used clinically as an aid to sustaining abstinence, blocking the pleasurable effects of opioids and reducing the risk of relapse after impulsive use of opioids.

Follow-up studies of people seeking treatment demonstrate that the course of OUD tends to be a chronic, relapsing one, particularly for people with poor social supports or mental health issues (3). Treatment of OUD does not fit an acute care paradigm, with the objective of cure, but is better conceptualised as the management of a chronic condition (4). Longer episodes of continuous treatment are associated with later, and a lower likelihood, of returning to treatment – a measure of relapse (5). The duration of methadone treatment has been demonstrated to be a linear, non-threshold predictor of outcome (6); longer episodes of treatment are associated with better outcomes.

Slowly tapering doses of methadone or buprenorphine have been used in medically managed withdrawal from opioids (“detoxification”). However, short-term abstinence is not predictive of long-term remission (7). Given the consistent evidence of the importance of treatment duration, the

likelihood of relapse with treatment discontinuation, and increased risk of overdose after detoxification (8), offering medically managed withdrawal alone increases risks with uncertain benefit. A flexible approach to patients who request detoxification is to initiate MAT with the option of continuing or reducing slowly to abstinence, depending on patient's progress (9).

The objectives of long-term management include reduced risk of death and disease, improvement in mental health and outlook, and restoration of social role impaired through such issues as unemployment, disrupted family relations, and involvement with criminal justice system (4). These objectives are most likely to be achieved if patients stop or markedly reduce their use of illicit opioids (10, 11). Most research on effectiveness of MAT has been undertaken with methadone. In suppressing the use of illicit opioids, methadone treatment is more effective than short-term treatment or no treatment (12). Methadone treatment attracts and retains in treatment more people with OUD than drug-free approaches (12,13). The suppression of illicit opioid use which follows entry to treatment results in a reduced risk of fatal overdose for as long as people remain in treatment (14,15). Reduction in crime (16,17), and subjective improvement in quality of life (18) also occur through reduced use of illicit opioids during methadone treatment.

Premature dropping out of treatment is common, and people often cycle in and out of short episodes of MAT (19,20). In part, poor response to MAT is due to variations in treatment delivery, which often deviates from what has been demonstrated to be effective (21, 22). In particular, use of subtherapeutic doses of methadone and buprenorphine have compromised treatment effectiveness (23). The importance of adequate doses reflects the pharmacological mechanism of action of methadone and buprenorphine - suppressing opioid withdrawal, attenuating the effects of injected opioids, and protecting against overdose (23).

A single daily dose of 30mg methadone is sufficient to block the emergence of opioid withdrawal for at least 24 hours in most people with OUD (24). However, at this daily dose, many patients persist in injecting street opioids. Higher doses of methadone induce opioid tolerance, reducing the rewarding effect of injected opioids. A pooled review of randomised controlled trials reported that high dose (60-100mg/day methadone) was more effective in producing abstinence from non-prescribed opioids as detected by urine testing than was middle (40-60mg) doses or low dose (<40mg) (25).

Buprenorphine at dose >8mg/day has been reported to suppress opioid withdrawal for 24 hours in opioid-dependent subjects (26). However, to suppress use of illicit opioids during treatment, higher doses of buprenorphine are more effective. Buprenorphine binds to opioid receptors, producing prompt blockade of other opioids. Positron Emission Tomography (PET) scanning indicates that buprenorphine 2mg produced 41% inhibition of carfentanil binding, 16mg produced 80% inhibition, and 32mg produced 84% inhibition (27). Consistent with these laboratory findings, a meta-analysis of published trials concluded that buprenorphine doses >16mg/day were more effective than doses <16mg at retaining subjects in treatment (28).

An oral dose of 50mg naltrexone produces mu opioid receptor blockade lasting 24 to 36 hours. It is difficult to induct people onto naltrexone due to the need for a period of abstinence before initiating antagonist treatment; and once in treatment, there is a high rate of early discontinuation (29, 30). Methadone and buprenorphine produce “drug liking” responses in people with OUD, and people who miss doses experience opioid withdrawal. These responses contribute to holding people in treatment. Naltrexone produces no positive opioid effects, and this may contribute to erratic compliance, early drop-out and resulting increased risk of fatal overdose (31).

Safety of MAT

Respiratory depression and overdose

Methadone produces respiratory depression if administered to non-tolerant individuals. Methadone treatment involves inducing a higher level of tolerance than occurs during use of illicit drugs, and if the dose is raised too rapidly, respiratory depression, potentially fatal, results. During induction, the blood level achieved by a stable dose progressively increases over the first week, due to tissue binding and to methadone's long half-life. A dose which was tolerated on day 1 may produce fatal respiratory depression in non-tolerant patients on day 2 or 3. Clinical guidelines recommend methadone doses need to start low and be slowly increased to avoid fatalities in the first month of treatment (15). Increasing doses of buprenorphine produce little or no increase in opioid effects. This "ceiling effect" reduces the risk of respiratory depression in the event of overdose. Induction onto buprenorphine is associated with a significantly lower risk of overdose than induction onto methadone (15).

While adhering to MAT, patients are at reduced risk of overdose; however, there is a significantly increased risk of fatal overdose in the month after leaving any form of treatment for OUD (5,15, 31). Benzodiazepine use is common among people with OUD, and concurrent use of benzodiazepines and methadone is associated with an increased risk of fatal overdose and emergency room (ER) presentations (32, 33).

QT Interval prolongation

Methadone prolongs the QTc interval, and high-dose methadone has been associated with the ventricular tachycardia "torsades de pointes" (34). This is rare complication, and there is little

consensus on the implications for treatment programs (35). Buprenorphine appears to have minimal impact on the QTc (36).

Diversion

As prescribing of methadone or buprenorphine increases in a jurisdiction, there is an increase in overdose deaths from these drugs amongst people not in treatment (37). Some degree of diversion is inevitable when prescribing agonist medication (38), and much of the diverted mediation goes to people with OUD who are not in treatment. Measures to minimize diversion include ensuring good access to treatment, and administering doses under direct observation, restricting unsupervised doses to people who meet criteria of stability (38). There have not been reports of problems associated with diversion and misuse of naltrexone.

In some countries (e.g. UK, Australia), methadone and buprenorphine are administered under direct observation. In these jurisdictions, both medications can be prescribed in primary care and dispensed (with observation) by community pharmacists. In the US and France, methadone is only available via clinic-based programs and administered mainly under direct observation, but buprenorphine can be prescribed by trained doctors, with medication not directly observed. This model of treatment is made possible because buprenorphine diversion is associated with significantly less risk of fatal overdose than is diverted methadone (39). Office-based treatment improves access, reduces stigma and requires less costly infrastructure.

The provision of buprenorphine without supervised administration potentially risks diversion. An extreme example is that buprenorphine diverted from France created a black market in Georgia, where injected buprenorphine became the primary drug of abuse (40). A combination of

buprenorphine and naloxone has been marketed to minimize intravenous misuse. The rationale is that taken orally or sublingually, the naloxone has only low bioavailability whereas, if the medication is crushed and injected, naloxone attenuates the opioid agonist effect, and precipitates withdrawal in people dependent on opioids. There is conflicting evidence as to the effectiveness of the combination in deterring intravenous misuse; the added naloxone appears to reduce, but does not abolish, intravenous misuse (41).

Comparing effectiveness of medications used in MAT

Large-scale observational studies (15) and pooled analysis of randomised trials (12) concur that retention in buprenorphine is inferior to retention in methadone. The impact of differences in retention has been demonstrated in a large trial which randomised participants to methadone or sublingual buprenorphine-naloxone (BNx) at flexible doses (42). At 24 weeks, 74% remained on methadone, and 46% on BNx, a clinically and statistically significant difference. Doses higher than 16mg BNx and >60mg of methadone were associated with fewer opioid-positive urine tests. Non-prescribed opioid use was significantly lower among BNx than methadone participants during the first 9 weeks, but not thereafter. This reflects the pharmacological differences between the full agonist and partial agonist - methadone suppresses the response to illicit opioid use in a dose-dependent and time-dependent fashion, through the progressive development of tolerance (43), whereas buprenorphine promptly occupies mu receptors and produces a degree of receptor blockade. However, the benefits of early suppression of illicit opioid use were offset by poor retention. Even with the highest BNx dose level of 30–32mg, the retention rate was less than the rate in the methadone group, and approximately 30% of the participants continued illicit opioid use. Significantly more BNx participants left the trial because they no longer wished to participate in their assigned treatment (25.6% vs. 12.4%, $p < .001$).

A qualitative study of a subset of participants in this trial (44) reported that for some, withdrawal symptoms or negative reactions continued beyond the induction period, despite dosage adjustments. Some participants reached a dose of 32 mg but continued to feel sick. These results are consistent with findings from a double-blind, double-dummy comparison of methadone and buprenorphine (45), in which respondents on buprenorphine reported significantly more withdrawal symptoms, and less positive opioid effects from their medication, than did subjects receiving methadone.

A follow-up study to the trial comparing BNx and methadone was conducted a mean of 4.5 years post-randomization; 73% of participants were interviewed and asked to provide a urine sample (46). Opioid use at follow-up was significantly higher among participants originally randomized to BNx, mainly due to less participation in treatment. At follow-up, mortality was not different between the two randomized conditions. However, clinical trials may be underpowered to detect differences in mortality. A large data-linkage study from Australia (15) investigated mortality, and overdose mortality, in 32,033 people who had commenced methadone or buprenorphine. It confirmed a significantly higher death rate during induction onto methadone compared to buprenorphine, no difference during treatment, but in the month after leaving treatment, drug-related mortality was significantly lower for the methadone cohort (adjusted drug-related mortality rate ratio 0·50, 0·29–0·86).

New formulations: Long-acting buprenorphine and naltrexone formulations

Enhancing retention in treatments for OUD, especially with naltrexone and buprenorphine, is key to improving long-term outcomes. One approach to improving adherence has been development of sustained-release preparations. Two depot injections of buprenorphine, and one buprenorphine implant, have been tested in clinical trials. One trial of depot buprenorphine compared it to

sublingual BNx, and reported the depot was not inferior (47). The second trial, using a different depot, reported it was superior to placebo (48). One trial of buprenorphine implants has been reported, demonstrating non-inferiority to sublingual BNx (49). Based on these studies, it is not possible to conclude that any of these depot preparations is superior in efficacy to the others, nor that depot preparations are superior to sublingual buprenorphine. In all trials of depot buprenorphine, more than half of urine samples were opioid positive in the active treatment groups, in part due to high drop-out rates.

A sustained-release injectable formulation of naltrexone, designed to block opioid effects for 1 month, was tested in an open-label trial. Opioid-dependent individuals were randomised to either sustained release naltrexone or sublingual BNx (50). There were more dropouts during induction in the naltrexone group (72%, compared to 94% in BNx). On an intention-to-treat analysis, relapse at 24 weeks was 65% for naltrexone, and 57% for buprenorphine; this difference was attributable to induction failures. Among participants successfully inducted, 24-week relapse events were similar across study groups. Opioid-negative urine samples ($p<0{\cdot}0001$) and opioid-abstinent days ($p<0{\cdot}0001$) favoured BNx compared with the depot among the intention-to-treat population, but were similar across study groups among the per-protocol population. A smaller Norwegian trial (51) reported similar results, although on the retained-in-treatment comparison naltrexone was superior to BNx in suppressing heroin use.

Overall, depot preparations of buprenorphine tested to date have not performed better than sublingual BNx. Retention in depot naltrexone was better than usually observed in studies using oral naltrexone, but not superior to sublingual BNx. As with all forms of treatment for OUD, the naltrexone depot probably does not avoid the risk of overdose after it ceases to deliver a therapeutic blood level, as there have been case reports of fatalities following naltrexone depot (52).

Comparing MAT with non-medical approaches to OUD

Despite the limitations of MAT, it has distinct advantages over other approaches to treatment of OUD. An observational study from the US (53) looked at participation in MAT using Medicaid data on people aged 22 or less with a diagnosis of OUD. The end point was retention in treatment as shown by no Medicaid claims within 60 days. Early introduction of any medication was associated with better retention than drug-free approaches; median retention was 123 days in buprenorphine, 150 days in naltrexone, 324 days in methadone, and 67 days among youths who received only behavioral health services. Medication assisted treatments were each independently associated with lower attrition from treatment compared with receipt of behavioral health services alone. This study has limitations, being non-randomised, and with an end-point that did not clearly identify how subjects were doing. However, it has the advantage of being a real-world study. Receipt of medication helped hold young people with OUD in treatment. Naltrexone and buprenorphine were similarly effective in retaining people, although not as effective as methadone.

MAT in Pregnancy

OUD during pregnancy is associated with many adverse outcomes, including an increased risk of stillbirth, prematurity, intrauterine growth retardation, and prolonged hospital stay post-delivery (54). Management of the pregnant woman with OUD is optimised by use of a coordinated, specialist team including social services, addiction medicine, obstetrics and neonatology (55). When used in conjunction with comprehensive care, methadone and buprenorphine have been demonstrated to improve treatment outcomes in pregnant women with OUD (56). The objective of medication management is to provide a stable intrauterine milieu, minimizing episodes of opioid intoxication and opioid withdrawal. Outcomes when methadone was continued throughout pregnancy were superior to those observed in women managed with methadone withdrawal during pregnancy (56).

Babies exposed to methadone in utero are at high risk of neonatal abstinence syndrome (NAS), characterised by irritability and autonomic dysfunction. Recent data demonstrates that buprenorphine is a safe alternative to methadone in pregnancy, and is associated with significantly lower severity of NAS (57).

Whereas use of methadone and buprenorphine in pregnancy is now accepted, there is less experience with naltrexone in managing OUD in pregnancy. Opioid withdrawal during pregnancy is associated with increased risk of miscarriage and of fetal distress, making it risky to initiate naltrexone during pregnancy (58).

Heroin assisted treatment

In the mid-1990s, confronted with a heroin epidemic, Swiss clinicians introduced a highly structured treatment, involving the injecting of pharmaceutical heroin up to 3 times daily under direct observation (59). A subsequent series of randomised trials provided the evidence for this treatment. Pooled analysis of trials showed that more than half of apparently 'un-treatable' or poorly-responding patients substantially disengage from use of street heroin within 6 months, with reductions in criminal involvement, and improvement in health and well-being (60). From these findings has emerged a new treatment modality, now available in Canada and some European countries – Heroin Assisted Treatment (HAT). Injected hydromorphone has also been trialled, and appears to be of similar efficacy as injected heroin (61).

HAT is a treatment for individuals with injecting OUD who have failed to derive benefit from other treatments. It involves supervised injection of pharmaceutical heroin up to 3 times daily, with concurrent oral methadone (or other long-acting opioid) available to minimize withdrawal in the

inter-dosing intervals. The rationale for prescribing pharmaceutical heroin is to enable some individuals with the most entrenched addiction to stop use of illicit opioids, breaking the link with associated health risks and criminal activities. HAT patients often have histories of poor therapeutic relationships in previous treatments; trials demonstrate that with skilled staff to provide support and supervision, HAT can hold previously treatment-resistant subjects in structured treatment (62).

The major adverse events associated with HAT are respiratory depression and seizures, both of which tend to occur within minutes after injection. Pooled analysis from trials indicates that there was a significantly higher risk of serious adverse events linked to medication in the HAT groups compared to methadone groups, but no deaths attributable to prescribed medication, as overdoses were managed by supervising staff (60).

RCTs are short-term studies, and give little indication about long-term outcomes. Much remains to be learned about the place of HAT in a treatment system. The cost is several times more than with buprenorphine or methadone maintenance (although not as expensive as long-term residential rehabilitation or prison); however, cost-benefit analyses have reported that HAT is cost-effective since other treatments deliver such poor results for these patients (63).

Naloxone

Naloxone is an opioid antagonist; intravenous or intramuscular naloxone promptly reverses opioid effects, and is routinely used to reverse opioid overdose. Pre-provision of a Take-Home Naloxone (THN) kit to injecting drug users, plus training the recipients in emergency management of the overdose situation, is an intervention being introduced in many countries. The objective is to reduce opioid overdose fatalities. The rationale is that most overdoses occur in the presence of others, with observers often taking actions (not always well-informed) to reverse overdose. Target populations have shown high levels of willingness to engage actively with emergency resuscitation.

THN projects report real-world emergency use of about 10% of naloxone distributed. Two recent, independently conducted Bradford-Hill public health analyses (64, 65) both concluded, on the basis of published evidence from a range of sources, that THN reduces the risk of fatal overdose.

The development of new concentrated naloxone nasal sprays (three different products now in use globally) should increase the acceptability of wider THN. The unit dose used in ER and ambulance setting is 0.4mg, often administered intramuscularly, with repeat dosing as necessary. All THN kits include more than one dose (typically twin-pack). The new naloxone nasal sprays deliver doses ranging from 1-4mg per spray with approximately 50% bioavailability (66).

There remains much to be learned about use of THN. Differing local drug problems (such as fentanyl availability in North America) may mean that higher doses of naloxone are required. Higher doses of naloxone can precipitate withdrawal in dependent users, and so a dose-titration approach, starting with lower doses, is proposed by other countries (67). THN depends on competence by lay responders, and there are also differences in the importance attached to training. Some advocates concentrate on attention to respiratory depression and the provision of assisted breathing whilst others present much fuller training including cardiopulmonary resuscitation. THN schemes generally stress the importance of early ambulance call alongside assisted breathing.

Cost often obstructs THN provision. In some countries, take-home naloxone kits are provided at no cost to the individual recipient, whereas other countries require the individual to meet the subsidised or full-price cost. Naloxone itself is cheap, with naloxone ampoules costing a dollar, whereas newer formulations can cost hundreds of dollars.

Which medication for which patient?

There is consistent evidence for the greater pharmacological effectiveness of methadone in retaining people in structured treatment. The distinct advantages of buprenorphine and naltrexone is that they do not require daily attendance for supervised administration, making them valuable options for individuals who can benefit from less structured treatment. There is currently no evidence to predict which patient will do best with which medication. The main guide is patient preference. A flexible approach to treatment is optimal, adjusting medication and treatment conditions according to response. “Stepped care”, in which people commence treatment on buprenorphine can transfer promptly to methadone if not responding, has been demonstrated to be as effective as initiating treatment with methadone (68). A French study confirmed that individuals not responding to buprenorphine, who were transferred to methadone, had significantly improved outcomes (16). In people not responding to methadone, transfer to HAT can result in improved outcomes (60).

Responding to the North American Opioid Epidemic

North America is in the grip of an “opioid crisis”. Escalating opioid overdose deaths are attributable to overlapping epidemics – a longer-phase epidemic of prescription opioid use with associated deaths, a more recent epidemic of illicit heroin use and mortality, and most recently a sharp-onset epidemic of use of illicitly-manufactured fentanyl. Age-standardised mortality rates for fentanyl, fentanyl analogues, and tramadol were 0.3 per 100,000 in 1999, 1.0 in 2013, 1.8 in 2014, 3.1 in 2015, and 6.2 in 2016. In contrast, mortality rates for heroin increased from 0.7 in 1999, to 1.0 in 2010, to 4.9 in 2016; and from methadone, ranged from 0.3 in 1999 to 1.8 in 2006, and 1.0 in 2016 (69).

OUD underlies the growing opioid overdose crisis in North America. Opioid overdose deaths could be reduced by ensuring people with OUD have access to treatment that is affordable, and of adequate quality such that patients remain and have a greater likelihood of good outcomes (70). In the current North American opioid epidemic, there is a lack of treatment spaces. For two decades US authorities have sought to expand treatment, particularly buprenorphine treatment. However, in

2012, a decade after treatment expansion began, it was estimated that the maximal potential availability of methadone or buprenorphine treatment was about 60% of the number of individuals with OUD (71); and actual availability fell well short of potential. About half of DATA-waived physicians actually prescribed buprenorphine; of these prescribers, the majority did not prescribe to their maximum patient limit. A further recent response has been the much wider provision of take-home naloxone so that, when overdose occurs, fatal outcome can be avoided, and the FDA is now considering whether emergency naloxone packs should be co-prescribed with some or all opioid prescriptions (72).

Conclusion

Methadone has the best evidence for effectiveness; buprenorphine and naltrexone also have evidence of effectiveness and provide distinct different benefits and are important treatment options. Evidence of whether the new, sustained-release formulations of buprenorphine and naltrexone bring distinct advantage is not yet available. Some people with injecting OUD and a poor response to conventional treatments can benefit from the more intensive treatment of HAT. Provision of naloxone to people not currently in treatment may be one measure to reduce the overdose toll.

Expanding access to methadone treatment, through allowing methadone prescribing in primary care and dispensing in pharmacies, has been proposed as the most useful approach to expanding access to effective treatment in the US, where currently methadone treatment is more highly restricted than in many other countries (73). Based on the greater pharmacological efficacy of methadone in holding people in treatment, this seems a timely recommendation.

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Disclosure

James Bell in the last 5 years has been a paid consultant for Martindale Pharma, and for Indivior. He has received funding support to attend conferences from Indivior.

John Strang is a researcher and clinician who, through his university, has worked with various pharmaceutical companies to identify new or improved treatments and his employer (King's College London) has received grants, travel costs and/or consultancy payments; this has included consultations with, past 3 years, Martindale, Indivior, Mundipharma, Camurus, Molteni Farma and the university and clinical services have received supplies of study medications for trials from companies including Camurus and also iGen. His employer (King's College London) has also registered intellectual property on a novel buccal naloxone formulation, naming JS and colleagues, and he was earlier named in a patent registration by a pharmaceutical company regarding concentrated nasal naloxone spray.

References

1. Inturrisi C (2005) Pharmacology of methadone and its isomers Minerva Anestesiologica 71; 7-8: 435-437

2. Walsh SL, Eissenberg T (2003) The clinical pharmacology of buprenorphine: extrapolating from the laboratory to the clinic. Drug and Alcohol Dependence 70, S13–S27.

3. Hser, Y., Hoffman, V., Grella, C., Anglin, M.D., 2001. A 33-year follow-up of narcotic addicts. Arch. Gen. Psychiatry 58, 503–508

4. McLellan AT, McKay JR, Forman R, Cacciola J, & Kemp J (2005) Reconsidering the evaluation of addiction treatment: from retrospective follow-up to concurrent recovery monitoring *Addiction,* 100; 447–458

5. Bell J, Trinh L, Butler B, Randall D, Rubin G (2009) Comparing retention in treatment and mortality in people after initial entry to methadone and buprenorphine treatment Addiction 104; 1193-1200

6. Zhang Z, Friedmann PD, Gerstein DR (2003) Does retention matter? Treatment duration and improvement in drug use Addiction, 98; 673-684

7. Moos RH (2007) Theory-based processes that promote the remission of substance use disorders. Clin Psychol Rev 27(5); 537-51

8. Wines JD, Saitz R, Hortone NJ, Lloyd-Travaglini C, Samet JH (2007) Overdose after detoxification: A prospective study Drug and Alcohol Dependence 89; 161–169

9. Lintzeris N, Bell J, Bammer G, Jolly D, & Rushworth L (2002) A randomised, controlled trial of buprenorphine in the management of short-term ambulatory heroin withdrawal. Addiction, 97; 1395-1404

10. Dennis ML, Scott CK, Funk R, Foss MA. The duration and correlates of addiction and treatment careers. Journal of Substance Abuse Treatment. 2005;28 Suppl 1:S51-62

11. Gossop M, Marsden J, Stewart D, Treacy S (2001) Outcomes after methadone maintenance and methadone reduction treatments: two-year follow-up results from the National Treatment Outcome Research Study Drug & Alcohol Dependence 62(3); 255-64

12. Mattick RP, Breen C, Kimber J, Davoli M. (2014) Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database of Systematic Reviews 2014, Issue 2. Art. No.: CD002207. DOI: 10.1002/14651858.CD002207.pub4.

13. Teesson M, Mills K, Ross J, Darke S, Williamson A & Havard A (2007) The impact of treatment on 3 years' outcome for heroin dependence: findings from the Australian Treatment Outcome Study (ATOS) Addiction 103; 80-88

14. Clausen T, Anchersen K, & Waal H (2008) Mortality prior to, during and after opioid maintenance treatment (OMT); a national, prospective cross-registry study. Drug and Alcohol Dependence 94; 151-57

15. Kimber J, Larney S, Hickman M, Randall D, Degenhardt L (2015) Mortality risk of opioid substitution therapy with methadone versus buprenorphine: a retrospective cohort study Lancet Psychiatry 2: 901–08

16. Carrieria P, Vilotitcha A, Nordmann S, Lions C, Michel L, Mora M, et al (2017) Decrease in self-reported offences and incarceration rates during methadone treatment: A comparison between patients switching from buprenorphine to methadone and maintenance treatment incident users (ANRS-Methaville trial) International Journal of Drug Policy 39; 86-91

17. Russolillo A, Moniruzzaman, McCandless L, Patterson M, Somers JM (2018) Associations between methadone maintenance treatment and crime: a 17-year longitudinal cohort study of Canadian provincial offenders. Addiction 113; 4: 656-667 https://doi.org/10.1111/add.14059

18. De Maeyer J, Vanderplasschen W, Camfield L, Vanheule S, Sabbe B, Broekaert E (2011) A good quality of life under the influence of methadone: A qualitative study among opiate-dependent individuals International Journal of Nursing Studies 48 (2011) 1244-1257

19. Bell J, Burrell T, Indig D, & Gilmour S (2006) Cycling in and out of treatment; participation in methadone treatment in NSW, 1990-2002. *Drug and Alcohol Dependence* 81; 55-61

20. Zhang L, Zou X, Zhang D, Li X, Zhao P, et al. (2015) Investigation of Repeat Client Drop-Out and Re-Enrolment Cycles in Fourteen Methadone Maintenance Treatment Clinics in Guangdong, China. PLOS ONE 10(10): e0139942. https://doi.org/10.1371/journal.pone.0139942

21. Barnett PG, Trafton JA, Humphreys K (2010) The cost of concordance with opiate substitution treatment guidelines. Journal of Substance Abuse Treatment 39: 141-9

22. D'Aunno T & Vaughan TE (1992) Variation in methadone treatment practices: results from a national study. Journal of the American Medical Association, 267(2)**,** 253-258

23. Bell J (2012) Maintenance Pharmacological Treatment of Opiate Dependence British Journal of Clinical Pharmacology DOI: 10.1111/bcp.12051

24. Walsh SL, Strain EC (2006) Pharmacology of methadone. In Strain EC and Stitzer M eds *The treatment of opioid dependence,* John Hopkins University Press, Baltimore pp59-76

25. Faggiano F, Vigna-Taglianti F, Versino E, Lemma P. (2003) Methadone maintenance at different dosages for opioid dependence. Cochrane Database of Systematic Reviews Issue 3. Art. No.: CD002208. DOI: 10.1002/14651858.CD002208

26. Kuhlman JJ, Levine B, Johnson RE, Fudala PJ, Cone EJ (1998) Relationship of plasma buprenorphine and norbuprenorphine to withdrawal symptoms during dose induction, maintenance and withdrawal from sublingual buprenorphine Addiction 93; 4: 549-559

27. Greenwald MK, Johanson C, Moody DE, Woods JH, Kilbourn MR, Koeppe RA, Schuster CR & Zubieta J (2003) Effects of Buprenorphine Maintenance Dose on mu-Opioid Receptor Availability, Plasma Concentrations, and Antagonist Blockade in Heroin-Dependent Volunteers Neuropsychopharmacology 28, 2000–2009

28. Fareed A, Vayalapalli S , Casarella J & Drexler K (2012) Effect of Buprenorphine Dose on Treatment Outcome, Journal of Addictive Diseases, 31:1, 8-18

29. Morgan JR, Schackman BR, Leff JA, Linas BP (2018) Injectable naltrexone, oral naltrexone, and buprenorphine utilization and discontinuation among individuals treated for opioid use disorder in a United States commercially insured population JSAT 85, Pages 90–96

30. Tucker T, Ritter AJ (2000) Naltrexone in the treatment of heroin dependence: a literature review. Drug Alcohol Review 19; 1: 73-82

31. Degenhardt L, Larney S, Kimber J, Farrell M, Hall W (2015) Excess mortality among opioid-using patients treated with oral naltrexone in Australia Drug and Alcohol Review 34; 90-96 https://doi.org/10.1111/dar.12205

32. Sun EC, Dixit A, Humphreys K, Darnall BD, Baker LC, Mackey S (2017) Association between concurrent use of prescription opioids and benzodiazepines and overdose: retrospective analysis BMJ 356:j760 http://dx.doi.org/10.1136/bmj.j760

33. McCowan C, Kidd B, Fahey T (2009) Factors associated with mortality in Scottish patients receiving methadone in primary care: retrospective cohort study BMJ 2009;338:b2225 doi:10.1136/bmj.b2225

34. Krantz MJ, Lewkowiez L, Hays H, Woodroffe MA, Robertson AD, Mehler PS (2002) Torsade de Pointes Associated with Very-High-Dose Methadone Annals of Internal Medicine 137; 501-504

35. Treece JM, Al Madani M, El Khoury G, Khraisha O, Martin JE, Baumrucker SJ, etal (2018) Comprehensive review on methadone-induced QT prolongation and torsades. J Pharmacol Pharmacother 9:66-75

36. Wedam EF, Bigelow GE, Johnson RE, Nuzzo PA, Haigney MCP (2007) QT-Interval Effects of Methadone, Levomethadyl, and Buprenorphine in a Randomized Trial Arch Intern Med 167(22):2469-2475

37. Strang J, Hall W, Hickman M, Bird SM (2010) Impact of supervision of methadone consumption on deaths related to methadone overdose (1993-2008): analyses using OD4 index in England and Scotland BMJ 341:c4851 doi:10.1136/bmj.c4851

38. Bell J (2010) The global diversion of pharmaceutical drugs. Opiate treatment and the diversion of pharmaceutical opiates: a clinician's perspective. Addiction 105(9):1531-7

39. Bell J, Butler B, Lawrance A, Batey R, Salmelainen P (2009) Comparing overdose mortality associated with methadone and buprenorphine treatment Drug and Alcohol Dependence 104; 1-2:73-77

40. Cleaver H (2007) Georgian drug misusers switch to Western heroin substitute. BMJ 334(7598):821

41. Degenhardt, L., Larance, B., Bell, J., Winstock, A., Lintzeris, N., Ali, R., Scheuer, N., & Mattick, R. (2009). Injection of OST in Australia following the introduction of a mixed partial agonist-antagonist opioid medication Med J Aust 191 (3): 161-165

42. Hser Y-I, Saxon AJ, Huang D, Hasson A, Thomas C, Hillhouse M, Jacobs P, Teruya C, McLaughlin P, Wiest K, Cohen A, and Ling W (2014) Treatment Retention among Patients Randomized to Buprenorphine/Naloxone Compared to Methadone in A Multi-site Trial *Addiction* 109(1): 79–87. doi:10.1111/add.12333.

43. Volavka J, Verebely K, Resnick R, & Mule S. (1978) Methadone dose, plasma level, and cross-tolerance to heroin in man. The Journal of Nervous and Mental Disease, 166; 104-109

44. Teruya C, Schwartz RP, Mitchell SG, Hasson AL, Thomas C, Buoncristiani SH, et al. (2014) Patient perspectives on buprenorphine/naloxone: a qualitative study of retention during the starting treatment with agonist replacement therapies (START) study. J Psychoactive Drugs. 46(5):412–26.

45. Mattick RP, Ali R, White J, O'Brien S, Wolk S, Danz C (2003) Buprenorphine versus methadone maintenance therapy: a randomized double-blind trial with 405 opioid-dependent patients Addiction 98; 441-452

46. Hser Y-I, Evans E, Huang D, Weiss R, Saxon A, Carroll KM, et al. (2016) Long-term Outcomes after Randomization to Buprenorphine/Naloxone versus Methadone in A Multi-site Trial. Addiction 111(4):695–705

47. Lofwall MR, Walsh SL, Nunes EV, Bailey GL, Sigmon SC, Kampman KM, et al (2018) Weekly and Monthly Subcutaneous Buprenorphine Depot Formulations vs Daily Sublingual Buprenorphine With Naloxone for Treatment of Opioid Use Disorder A Randomized Clinical Trial JAMA Internal Medicine 178(6);764-773. doi:10.1001/jamainternmed.2018.1052

48. Haight BR, Learned SM, Laffont CM, Fudala PJ, Zhao Y, Garofalo AS, et al (2019) Efficacy and safety of a monthly buprenorphine depot injection for opioid use disorder: a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial Lancet; 393: 778–90

49. Rosenthal R, Ling W, Casadonte P, Vocci F, Bailey GL, Kampman K, et al (2013) Buprenorphine Implants for Treatment of Opioid Dependence: Randomized Comparison to Placebo and Sublingual Buprenorphine/Naloxone Addiction. 108(12): 2141–2149.

50. Lee JD, Nunes EV, Novo P, Bachrach K, Bailey GL, Bhatt S, et al (2018) Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicentre, open-label, randomised controlled trial Lancet 391(10118); 309–318. doi:10.1016/S0140-6736(17)32812-X

51. Tanum L, Solli KK, Latif ZE, Benth JS, Opheim A, Sharma-Haase K, et al. Effectiveness of Injectable Extended-Release Naltrexone vs Daily Buprenorphine-Naloxone for Opioid Dependence: A Randomized Clinical Noninferiority Trial. JAMA Psychiatry. 2017;74(12):1197–1205

52. Saucier R, Wolfe D, Dasgupta N (2018) Review of Case Narratives from Fatal Overdoses Associated with Injectable Naltrexone for Opioid Dependence Drug Safety 41; 10: 981–988

53. Hadland SE, Bagley SM, Rodean J, Silverstein M, Levy S, Larochelle MR, et al (2018) Receipt of Timely Addiction Treatment and Association of Early Medication Treatment With Retention in Care Among Youths With Opioid Use Disorder JAMA Pediatr. 172(11):1029-1037. doi:10.1001/jamapediatrics.2018.2143

54. Kennare R, Heard A, Chan A (2005) Substance use during pregnancy: risk factors and obstetric and perinatal outcomes in South Australia. Aust N Z J Obstet Gynaecol 45; 220-5.

55. Alto WA, O'Connor AB (2011) Management of women treated with buprenorphine during pregnancy American Journal of Obstetrics and Gynaecology 205 (4); 302-308

56. Jones HE, O'Grady KE, Malfi D, Tuten M (2008). Methadone maintenance vs. methadone taper during pregnancy: maternal and neonatal outcomes. Am J Addict 17; 372-386

57. Jones HE, Kaltenbach K, Heil SH, Stine SM, Coyle MG, Arria AM, O'Grady KE, Selby P, Martin PR, Fischer G (2010) Neonatal Abstinence Syndrome after Methadone or Buprenorphine Exposure N Engl J Med 2010; 363:2320-2331

58. Jones HE, Chisolm MS, Jansson LM, Terplan M (2013) Naltrexone in the treatment of opioid-dependent pregnant women: the case for a considered and measured approach to research. Addiction 108; 233-47

59. Rehm J, Gschwend P, Steffen T, Gutzwiller F, Dobler-Mikola A, Uchtenhagen A (2001) Feasibility, safety, and efficacy of injectable heroin prescription for refractory opioid addicts: a follow-up study. Lancet 358: 1417–23

60. Strang J, Groshkova T, Uchtenhagen A, van den brink W, Haasen C, Schecter M, et al (2015) Heroin on trial; systematic review and meta-analysis of randomised trials of diamorphine prescribing as treatment for refractory heroin addiction. British Journal of Psychiatry 207(1); 5-14.

61. Oviedo-Joekes E, Guh D, Brissette S, Marsh DC, Nosyk B, Krausz M, et al. Double-blind injectable hydromorphone versus diacetylmorphine for the treatment of opioid dependence: a pilot study. Journal of Substance Abuse Treatment. 2010;38(4):408-11

62. Bell J, Belackova V, Lintzeris N (2018) Supervised Injectable Opioid Treatment for the Management of Opioid Dependence Drugs (2018) 78:1339–1352 https://doi.org/10.1007/s40265-018-0962-y

63. Strang J, Groshkova T, Metrebian N (2012) Recent evidence and current practices of supervised injectable heroin treatment in Europe and beyond. EMCDDA Monograph, Luxembourg: Publications Office of the European Union

64. McDonald R, Strang J (2016) Are take-home naloxone programmes effective? Systematic review utilizing application of the Bradford Hill criteria. Addiction, 111,1177–1187

65. Olsen A, McDonald D, Lenton S, Dietze P (2014) Evidence for take-home naloxone programs: a Bradford Hill analysis. Drug Alcohol Rev, 33; 49–50

66. McDonald R, Lorch U, Woodward J, Bosse B, Johnson H, Mundin G, Smith K, Strang J (2017). Pharmacokinetics of concentrated naloxone nasal spray for opioid overdose reversal: Phase-I healthy volunteer study. *Addiction*, 113: 484-493. doi: 10.1111/add.13849

67. Neale J, Strang J. (2015). Naloxone--does over-antagonism matter? Evidence of iatrogenic harm after emergency treatment of heroin/opioid overdose. Addiction. doi: 10.1111/add.13027

68. Kakko J, Gronbladh L, Svanborg KD, von Wachenfeldt J, Ruck C, Rawlings B, et al (2007) A stepped care strategy using buprenorphine and methadone versus conventional methadone maintenance in heroin dependence: a randomized controlled trial American Journal of Psychiatry. 164(5):797-803

69. Hedegaard H, Warner M, Miniño AM (2107) Drug overdose deaths in the United States, 1999–2016. NCHS Data Brief, no 294. Hyattsville, MD: National Center for Health Statistics

70. Barnett PG, Trafton JA, Humphreys K (2010) The cost of concordance with opiate substitution treatment guidelines. Journal of Substance Abuse Treatment 39: 141-9

71. Wakeman SE, Barnett ML (2018) Primary Care and the Opioid-Overdose Crisis — Buprenorphine Myths and Realities N Engl J Med 2018; 379:1-4 DOI: 10.1056/NEJMp1802741

72. Food and Drug Administration (2019) FDA approves first generic naloxone nasal spray to treat opioid overdose FDA News Release, April 19th, at https://www.fda.gov/news-events/press-announcements/fda-approves-first-generic-naloxone-nasal-spray-treat-opioid-overdose

73. Samet JH, Botticelli M, Bharel M (2018) Methadone in Primary Care — One Small Step for Congress, One Giant Leap for Addiction Treatment NEJM 379; 1; 7-8