



## The State of Opioid Medication Assisted Treatment (MAT)

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### Editorial

Despite efforts to increase availability of medication assisted treatment at the federal level, drug overdoses, particularly those of the opioid category, remain the leading cause of death in Americans younger than 50 years of age [1]. Most of these involve synthetic opioids with a 540% increase in related deaths in the past 3 years [2].

Treatment with MAT reduces risk of mortality by 2.4 times [3]. Recent studies are emerging examining the various available MAT formulations, induction protocols and treatment outcomes as well as the controversial impact of cannabis use on remission. I will attempt to point out several important messages for clinicians to be aware:

#### Some synthetic opioids are able to overcome the Buprenorphine (BUP)-mediated opioid receptor blockade

Fentanyl and other synthetic versions of this class are fast acting and much more potent than morphine. Several of these have been synthesized-Sufentanil, Alfentanil, Lofentanil, Ramifentanil and Carfentanil. Current trends show an increasing amount of street heroin is being cut with these and users may not be aware. A pharmacological study examined the inhibition constants of these from the opioid receptor based on their  $K_i$  values, which are inversely proportional to the receptor binding affinity [4]. According to this data, which includes all but Carfentanil, some synthetic opioids such as Sufentanil could overcome the BUP mediated blockade at the mu receptor. Naltrexone, not included here, has a  $K_i$  value of ~1.3 as reported in literature [5]. Since some of the synthetic opioids have lower  $K_i$  values, these may be able to displace it in individuals who are on Naltrexone MAT.

#### Naloxone is effective at reversing opioid related overdoses however long term survival rates following are low

In a review of >12,000 emergency Naloxone doses given during a 2 year period, 93% of individuals receiving it survived the overdose [6]. Unfortunately, a great number of those do not survive at 1 year follow up-only 84% were still alive. When synthetics are involved in the overdose, multiple doses are required for reversal and sometimes even this may be ineffective. This stresses the importance that overdose survivors are high risk and should be offered MAT prior to ED discharge [7].

#### Emerging studies are reporting comparable outcomes between extended release injectable Naltrexone (XR NTX) and Buprenorphine-naloxone (BUP-NX)

A 2017 12-week study by Tatum demonstrated XR NTX is not inferior to BUP-NX [8]. Both groups experienced comparable treatment retention, opioid negative screens and days abstinent.

Reduced cravings and improved life satisfaction were reported by the in XR NTX group.

A second study by Lee demonstrated XR NTX is comparable to BUP-NX at 24 weeks as marked by comparable numbers of relapse events, opioid negative screens and days abstinent [9]. Cravings were less endorsed by the XR NTX group.

Some of the criticism studies such as these receive is related to not taking into consideration the lengthy washout period required for XR NTX induction. This washout period represents a vulnerable time, placing many at risk for relapse to use. Enrolment for the XR NTX groups typically begins with individuals already inducted on the medication.

#### In facilitating XR NTX induction several protocols are emerging which decrease length of time required for detoxification and retain more in treatment during induction

MAT induction follows detox from opioids. Antagonist induction is limited by the 7-10 days washout period mentioned above, with significant impact on relapse. Recent work has examined the overall withdrawal limit of tolerability from opioids ranking symptomatology into tolerable and intolerable categories. Use of very low dose NTX starting 2-3 days after last heroin dose, along with supportive medications, was deemed to not produce intolerable withdrawal but also to accelerate detoxification time. Sullivan used this protocol comprising of one dose BUP-NX the day following last opioid use followed by incremental daily NTX doses of 1, 3, 13, 25 mg respectively with ultimately IM XR NTX given on day 8. A lower dropout rate compared to standard BUP-NX taper was reported [10].

#### Individuals who have used opioids through IV route require higher BUP dosing than non-IV users for craving control

Pharmacodynamic evidence shows a least 70% mu receptor occupancy is required to achieve both suppression of subjective effects of a standard mu receptor agonist (such as hydromorphone) as well as withdrawal symptoms [11]. This can be achieved with a ~2-3 ng/mL plasma concentration of BUP. Those with histories of high dose of opioid use and through IV routes however require close to 90% receptor occupancy. This corresponds to a ~5-6 ng/mL plasma concentration [12]. To achieve this, individuals may need upwards of 32 mg daily dose, much higher than the Drug Enforcement Agency (DEA) recommendation.

### **An extended release version of BUP ('Sublocade') was recently approved by the FDA and will soon be available for clinical use**

Some of the challenges with the standard daily BUP-NX dosing are the lack of patient adherence to dosing schedule, diversion, abuse and misuse. A staggering 33% of individuals entering treatment programs report use of diverted BUP the month prior [13]. Addressing adherence is imperative. When daily dosing compliance drops below 80%, there is a 10 times likelihood of relapse [14].

To address these, an implantable form ('Probuphine') was previously developed. The lengthy clinical stability time on the oral form required prior to implantation, limited amount of daily dose delivered and the limited number of implantations as well as provider procedural training has hindered much of the clinical applicability. Recently, a new formulation was developed with promise to deliver doses orally-equivalent to upwards of 32 mg daily for the duration of 1 month. Although the data is not yet published in literature, the FDA reviewed and approved it.

### **Individuals who use marijuana are at increased risk of developing an opioid use disorder**

Despite some literature and media advertisement supporting the use of cannabis for claims of pain management benefit and reduction of opioid use, the strongest level of evidence points to an increase in opioid use when cannabis is implicated. Both prescription and non-prescription opioid use is much higher in a medical-cannabis using population. A study examining ties between two "waves" from 2001-2002 and 2004-2005 found that cannabis use endorsed during the first wave was associated with prevalent opioid use as well as initiation of opioid use during the second wave [15].

### **Declaration of Conflict of Interest**

None to report

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