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Rapid induction onto sublingual buprenorphine after opioid overdose and successful linkage to treatment for opioid use disorder

Over 70,000 Americans died from drug overdose in 2017, a number unthinkable in 1997 when this number stood at less that 17,000. In 2016 alone, over 1.6 million years of life were lost due to overdose driving an overall decrease in US life expectancy [1,2]. Yearly over 500,000 overdosed patients present to the ED, nearly double the number of visits for ST elevation MI [3-5]. Untreated, the one year standardized mortality ratio exceeds 100 after discharge from an ED visit for non-fatal opioid overdose. That staggering mortality can be reduced by 38–59% if patients treated are treated with medications, such as buprenorphine or methadone, for opioid use disorder (MOUD) [4-7]. Buprenorphine's high-affinity, opioid agonist blockade, and ceiling effect on respiratory depression suggest opioid overdose followed by naloxone reversal and administration of buprenorphine (ODNaloxoneBup) should be safe and effective [6,7]. Our initial experience supports this.

Due caution given the many unknowns around ODNaloxoneBup suggest it should only be considered in an otherwise healthy patient with no suspected co-ingestions and no recent methadone use with a normal level of consciousness, normal mental status, and the ability to provide informed consent. Administration of buprenorphine to patients intoxicated with alcohol, benzodiazepines or other sedative can result in respiratory depression. Patients with acute illness or severe chronic illness such as infection, heart failure, liver failure, respiratory failure or acute renal failure can experience unpredictable sedation and respiratory depression. Patients with altered mental status are not able to provide a reliable history or adequately consider the risks and benefits to provide informed consent. Patients taking methadone should be supported to continue methadone treatment; overdose is not an indication to switch to buprenorphine and may disrupt care (Fig. 1).

There are two major adverse events possible with ODNaloxoneBup: 1) additive sedation with respiratory depression and 2) precipitated withdrawal. While neither of these has been reported at this time, any ED should be prepared and willing to adequately manage these potential complications. Reversal of buprenorphine is accomplished with high-dose naloxone (2-3 mg IV push followed by 4 mg/h infusion) [8,9]. Precipitated withdrawal is treated with an empirically titrated multimodal approach that may include: benzodiazepines, alpha-2 agonists (clonidine or dexmedetomidine), high affinity full agonist opioids (hydromorphone), ketamine, and dopamine antagonists (*e.g.* metoclopramide or haldoperidol) [10].

Here we briefly describe three examples of how ODNaloxoneBup can be accomplished in the ED without the occurrence of serious adverse effects. In all cases, the history and clinical response to naloxone suggested that there was no additional sedative, such as alcohol or benzodiazepine, present. Later toxicologic analysis confirmed this. The first two cases (Patient A and B) are two heroin-using men who presented directly to our ED. Per patient report, at the doorstep to the ED, the two men split a previously street-obtained "orange pill with a white center" that they believed to be Suboxone™. They self-administered the pill fragments sublingually. Both men became unresponsive after presenting to ED triage; they remember walking into the ED but have no recollection of events until several hours later after naloxone reversal. After discussion of risks and benefits buprenorphine was administered. Laboratory testing confirmed the tablet contained fentanyl (see Figs. 2 and 3). The third case (Patient C), is a 42-year-old male heroin user who was found unresponsive on the street. Paramedics administered 2 mg intranasal naloxone and with immediate return to normal mental status and respiratory rate. In the ED the patient reported anxiety and discomfort with a Clinical Opioid Withdrawal Scale score of 4. After discussion of risks and benefits, buprenorphine was administered (see Fig. 2). At presentation all patients clinically displayed opioid overdose without signs or report of sedative use. At discharge all patients were comfortable and had received a 24-h-dose of sublingual buprenorphine. All patients attended their follow up appointment with our Bridge Clinic.

Once naloxone has reversed opioid overdose (regardless of whether withdrawal signs/symptoms have been precipitated), initiation of buprenorphine should yield a relative increase in mu-opioid receptor (MOR) agonism and be experienced as stabilization or withdrawal relief. *In vitro (+NaCl)*, naloxone exhibits 5-fold higher MOR affinity than morphine and comparable MOR affinity as sufentanil and, under these same physiological conditions, buprenorphine exhibits 6-fold higher MOR affinity than naloxone [11]. Following naloxone displacement and reversal of opioid overdose, buprenorphine is therefore expected to displace naloxone from available MORs (and residual naloxone effect should wash out rapidly due to its pharmacokinetics; see Fig. 3). Once bound to MORs, buprenorphine's high-affinity, longer-acting MOR occupancy should effectively prevent return of full agonist toxicity (provide opioid blockade) [4] even if relatively high concentrations of full agonist remain in the circulation [7,12-14]. The positive treatment responses observed in these cases suggest the possibility that as naloxone was metabolized (Patients A and C) and/or displaced from MORs (Patient B), a mixed state of buprenorphine partial agonism and opioid agonism occurred, thereby avoiding an abrupt transition from full to partial agonism that would have been experienced as precipitated withdrawal.

Our experience suggests that patients can be rapidly and successfully inducted onto buprenorphine immediately after naloxone reversal for non-fatal opioid (fentanyl or heroin) overdose during the course of a single ED visit. There were no serious adverse events and all three patients were discharged home in good condition. All three remained engaged in buprenorphine treatment 7 days after ED discharge. Current data and experience are limited, yet it appears that when the risk of death after discharge from the ED after OD without MOUD is known and significant, the risk of a serious adverse event from a small dose of sublingual buprenorphine in a patient who has already undergone full reversal from naloxone is likely small. Consent is a challenging situation in ODNaloxoneBup. In the cases described, all patients where alert and in mild to moderate distress only. Our clinical opinion is that these

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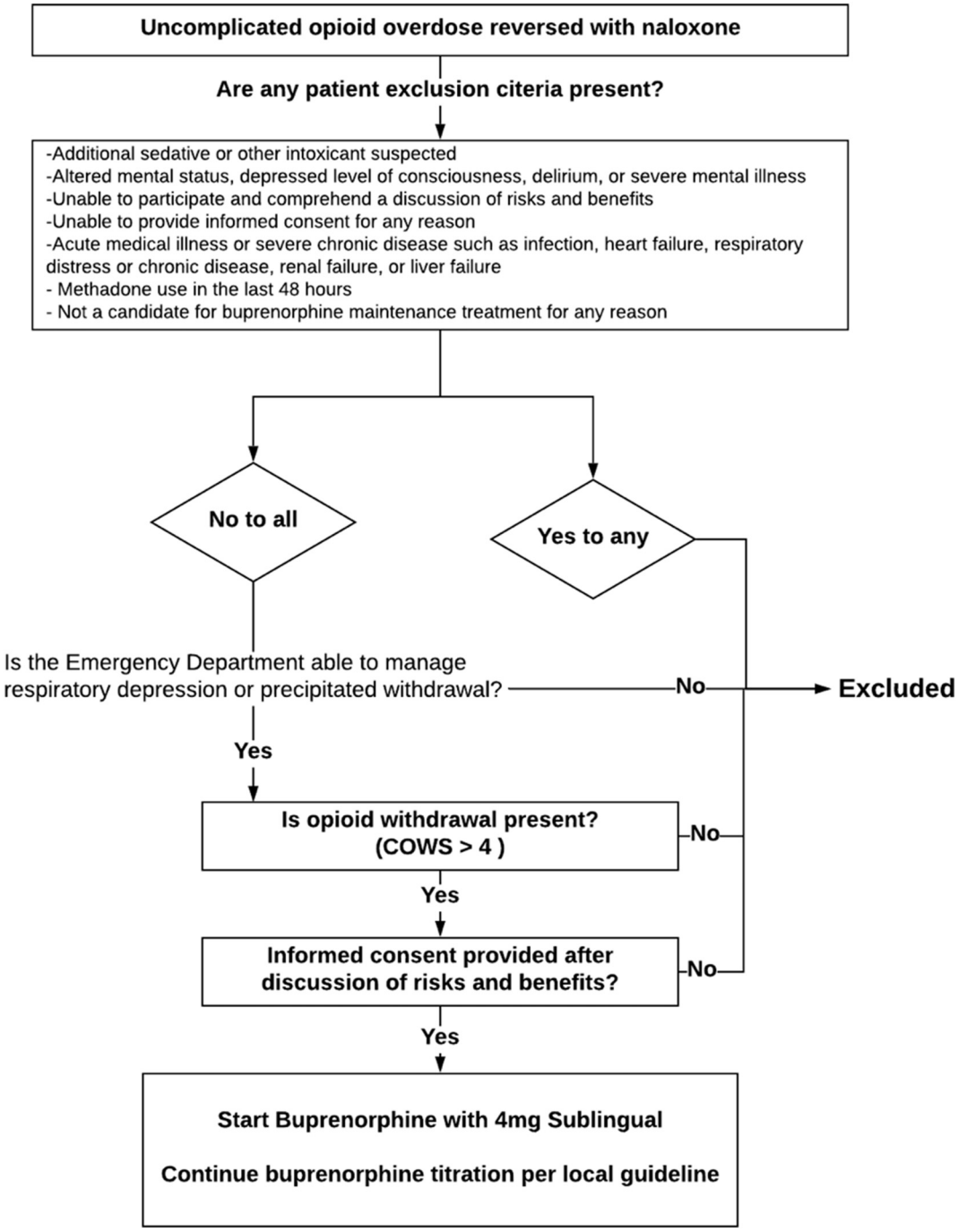

Fig. 1. Suggested guideline for the administration of buprenorphine after reversal of opioid overdose with naloxone.

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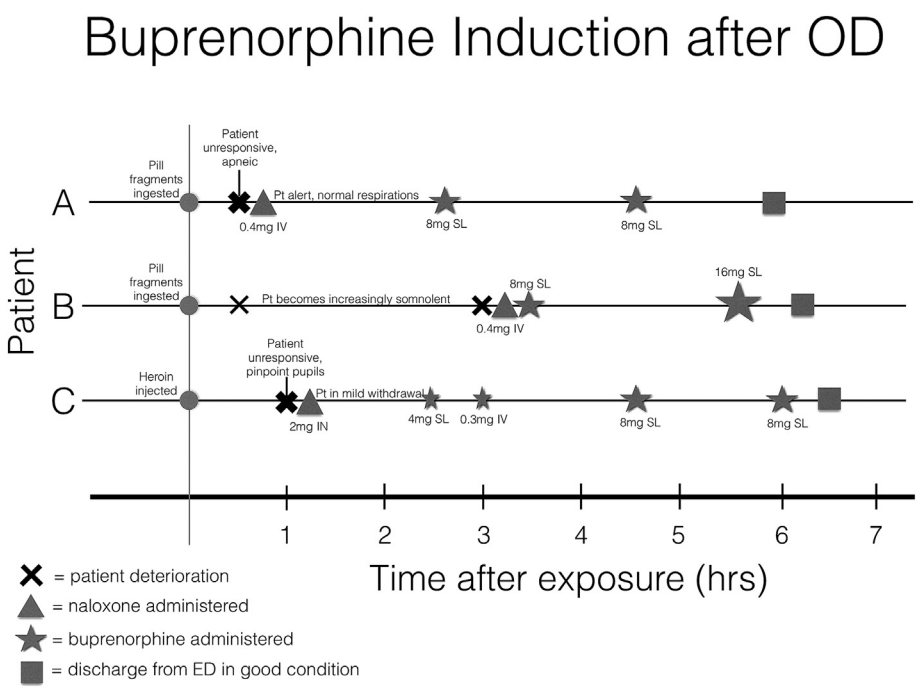

Fig. 2. Timeline of buprenorphine administration after reversal of opioid overdose with naloxone.

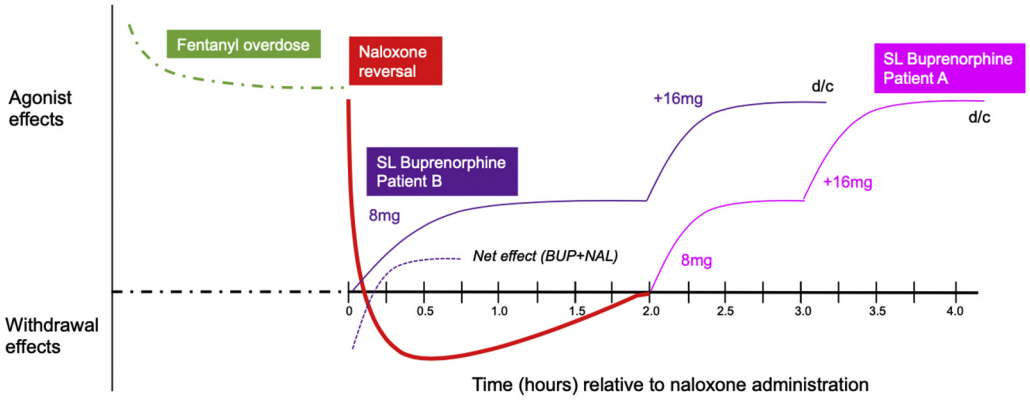

Fig. 3. Hypothesized opioid agonist/withdrawal outcome of ED-based naloxone reversal and buprenorphine administration for patients A and B following fentanyl overdose.

patients were able to comprehend the risks and benefits of ODNaloxoneBup explained to them. In an agitated patient this may not be possible. Our hope is that further study clarifies the many remaining questions and possibilities raised by our preliminary observations.

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