**Supplemental Table 4: Properties of potential second, third and fourth-line analgesics, sedatives and neuromuscular blockers (66, 67)**

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| **Medication** | **Time to onset (mins)** | **Half-Life** | **Primary**  **metabolic**  **pathway** | **Active**  **Metabolite** | **Dosing** | **Adverse Effects** | **Other Notable Characteristics** |
| **Analgesics** | | | | | | | |
| Fentanyl transdermal  patch | 5-15 | 20-27 h | Hepatic via N-dealkylation (CYP 3A4/5 substrate) | None | 12-300 mcg applied q72h | -Serotonin syndrome  -Local irritation | -Takes 24-72h to take effect  -May stay in system for several h after removal  -Dose should be determined through PT or IV opioids prior to administration |
| Hydromorphone (oral) | 15-30 | 2-3 h | Hepatic via glucuronidation | None | 2-4 mg q4-6 h |  | -Safe to use in patients with renal dysfunction |
| Ketamine  (IV) | 0.5 | 2.5 h | Hepatic via N-dealkalation | Norketamine | 0.5 mg/kg IV push followed by 1-2 mcg/kg/min infusion | -Delirium  -Hallucinations  -Hypertension  -Hypotension  -Increased secretions | -Should be used an adjunct to opioids |
| Meperidine  (IV/Oral) | IV: 5  Oral: 10-15 | 2.5-4 h | Hepatic via hydrolysis | Normeperidine | Bolus: 25-100 mg q 2-3 h  Infusion: 15-35 mg/h  Oral: 50-150 mg q3-4 h | Seizures | -Accumulation normeperidine in renal failure causes seizures |
| Methadone  (IV/Oral) | IV: 10-20  Oral:  30-60 | 8-59 h | Hepatic via N-demethylation (CYP3A4 and 2B6 substrate) | None | IV:2.5-10 mg q8-12h  PT: 10-40 mg q8-12h | -QT prolongation  -Serotonin syndrome | -Use caution with hepatic and renal dysfunction |
| Morphine | IV: 5-10  Oral: 30 | 3-4 h | Hepatic via glucuronidation | 6-morphine glucuronide | Bolus: 1-10 mg  Infusion:1-2 mg/h  PT: 10-30 mg q4h | -Hypotension secondary to histamine release  -Cholecystitis | -Use caution with liver or renal dysfunction |
| Oxycodone  (Oral) | 10-15 | 3.2-4 h | Hepatic (CYP3A4 substrate) | Oxymorphone | 5-20 mg q4-6h |  | Easily crushed and administered via PT |
| Remifentanil | 1-3 | 3-10 min | Hydrolysis by plasma and tissue esterases | None | Loading Dose: 1.5 mcg/kg  Infusion:0.15-15 mcg/kg/h | Hyperammonemia | -High incidence of opioid associated tachyphylaxis  -High incidence of opioid associated hyperalgesia  -Accumulation in obese patients, use IBW to dose  -Chest wall rigidity  -Expensive |
| Sufentanil | IV: 1-3  SL: 30 | IV: 164 min  SL:2.5+0.85 min | -Hepatic and small intestine demethylation and dealkylation  -Renal elimination | None | Bolus: 0.5 mcg/kg  Infusion:0.5 mcg/kg/h  SL: 30 mcg q1h prn (no more than 12 doses per day) | -Headache  -Pruritis | -Expensive  -Use caution with renal and liver dysfunction |
| **Sedatives** | | | | | | | |
| Alprazolam | <60 | 6.3-26.9 h | Hepatic (CYP 3A4 substrate) | 4-hydroxy-alprazolam,  α-hydroxy-alprazolam | PT: 0.5 to 2 mg tid | Delirium | -Very short acting, may need more frequent dosing |
| Chloral hydrate | 15-30 | 8-12 h | Hepatic via alcohol dehydrogenase | Trichloro-ethanol | 1000 mg PT q6h | -Delirium  -Hypotension | -May not be available in the United States |
| Clonazepam | 20-40 | 17 to 60 min | Hepatic via glucuronide and sulfate conjugation, (CYP 3A4 substrate) | None | PT: 0.25-1 mg bid | Delirium |  |
| Clonidine | 30-60 | 12-16 h | Hepatic | None | PT: 0.1-0.3 q6-8h | -Headache  -Dizziness  -Hypotension |  |
| Diazepam | IV:2-5  PT: 15 | 20-50 h | Hepatic via hydoxylation (CYP 3A4/5 Substrate) | Temazepam | Bolus:  0.03-0.1 mg/kg ever 0.5-6 h  PT:2-10 mg q3-6h | -Hypotension  -Phlebitis  -Delirium |  |
| Guanfacine | 60-240 | 10-30 h | Hepatic (CYP 3A4 substrate) | None | PT: 0.5-2 mg qday | -Hypotension  -Headache  -Dizziness  -Abdominal pain |  |
| Haloperidol | IV: 3-20  PT: 120 | IV:14-26 h | Hepatic via CYP 3A4 and 2D6 | None | IV or PT: 2-10 mg q6h | -Anticholinergic  -EPS  -NMS  -QT prolongation |  |
| Lorazepam | IV: 5-20  PT: 15-60 | 10-20 h | Hepatic via glucuronidation | None | Bolus: 0.02-0.06 mg/kg q 2-6 h  Infusion:  0.01-0.1 mg/kg/h (<10 mg/h)  PT: 0.5-2 mg q4-6h | -Delirium  -Propylene Glycol Toxicity with IV | -Use caution with renal dysfunction |
| Midazolam | IV:3-5  PT: 10-20 | 3-12 h | Hepatic via hydroxylation (CYP3A4/5 substrate) | α1-hydroxymida-zolam | Bolus: 0.01-0.05 mg/kg  Infusion: 0.02-0.1 mg/kg/h | -Delirium  -Hypotension  -Respiratory Depression | -Use caution in renal and hepatic dysfunction  -Many drug interactions |
| Olanzapine | IM: 15  PT: 30 | 21-54 h | Hepatic via glucuronidation (CYP1A2 substrate) | None | IM: 5 to 10 mg, may repeat 2 and 4 h after initial dose, max 30 mg/day  PT: 5-20 mg qday | -Anticholinergic  -EPS  -NMS  -Neuromuscular Weakness |  |
| Phenobarbital | IV: 5  PO: 60 | 79 h | Hepatic via CYP 2C9, 2C19, 2E1 and N-glucosidation | None | IV/PO: 10-40 mg tid (max 400 mg/day) | -Bradycardia  -Hypotension  -Agranulocytosis  -Thrombocytopenia | -Many drug interactions  -IV is expensive |
| Quetiapine | PT:20-40 | 6 h | Hepatic via CYP 3A4 | N-desalkyl -quetiapine | PT: 50-200 mg bid | -Anticholinergic  -NMS  -Orthostatic Hypotension |  |
| Valproic Acid | IV:15  PT: immediately | 9-19 h | Hepatic via glucuronide conjugation and mitochondrial beta-oxidation (substrate of CYP 2A6, 2B6, 2C19, 2C9, 2E1) | None | IV or PT:  500-1250 mg bid | -Headache  -Hyperammonemia  -Thrombocytopenia  -Pancreatitis | -Use caution with hepatic dysfunction  -Many drug interactions |
| **Neuromuscular Blockers** | | | | | | | |
| Atracurium | 2-3 | 20 min | Hoffman elimination | Laudanosine | Bolus: 0.4-0.5 mg/kg  Infusion: 4 to 20 mcg/kg/min | Prolonged weakness | Safe to use in hepatic and renal dysfunction |
| Cisatracurium | 2-3 | 22-29 min | Hoffman elimination | None | Bolus: 0.1-0.2 mg/kg  Infusion: 1-3 mcg/kg/min | Prolonged weakness | Safe to use in hepatic and renal dysfunction |
| Pancuronium | 3-5 | 89-161 min | -Hepatic  -Renal Elimination | 3-hydroxy pancuronium | Bolus:0.06-0.1 mg/kg  Infusion:1-2 mcg/kg/min | Tachycardia | -Use caution in renal and hepatic dysfunction  -Very long duration of action |
| Rocuronium | 1-2 | 1.4-2.4 h | -Hepatic  -Renal elimination | 17-desacetyl rocuronium | Bolus: 0.6-1 mg/kg  Infusion:8-12 mcg/kg/min | -Tachycardia  -Prolonged weakness | Use continuous infusion with caution in hepatic or renal dysfunction |
| Vecuronium | 2.5-3 | 65-75 min | -Hepatic  -Renal elimination | 3-desacetyl vecuronium | Bolus: 0.08-0.1 mg/kg  Infusion: 0.8 to 1.7 mcg/kg/min | -Prolonged weakness | Use continuous infusion with caution in hepatic or renal dysfunction |

BID twice daily; CYP cytochrome; EPS extrapyramidal symptoms; h hours; IBW ideal body weight; IM intramuscular; IR immediate release; IV intravenous; kg kilograms; mcg micrograms; min minutes; NMS neuroleptic symptoms; PRN ‘as needed’; PT per enteral tube; Q every; SL sublingual.