**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: 5Oral: 10-15 | 2.5-4 h | Hepatic via hydrolysis | Normeperidine | Bolus: 25-100 mg q 2-3 hInfusion: 15-35 mg/hOral: 50-150 mg q3-4 h | Seizures | -Accumulation normeperidine in renal failure causes seizures |
| Methadone(IV/Oral) | IV: 10-20Oral:30-60  | 8-59 h | Hepatic via N-demethylation (CYP3A4 and 2B6 substrate) | None | IV:2.5-10 mg q8-12hPT: 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 mgInfusion:1-2 mg/hPT: 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/kgInfusion: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: 1-3SL: 30 | IV: 164 minSL:2.5+0.85 min | -Hepatic and small intestine demethylation and dealkylation-Renal elimination | None | Bolus: 0.5 mcg/kgInfusion:0.5 mcg/kg/hSL: 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:2-5PT: 15 | 20-50 h | Hepatic via hydoxylation (CYP 3A4/5 Substrate) | Temazepam | Bolus: 0.03-0.1 mg/kg ever 0.5-6 hPT: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: 5-20PT: 15-60  | 10-20 h | Hepatic via glucuronidation | None | Bolus: 0.02-0.06 mg/kg q 2-6 hInfusion: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:3-5PT: 10-20  | 3-12 h | Hepatic via hydroxylation (CYP3A4/5 substrate) | α1-hydroxymida-zolam | Bolus: 0.01-0.05 mg/kgInfusion: 0.02-0.1 mg/kg/h | -Delirium-Hypotension-Respiratory Depression | -Use caution in renal and hepatic dysfunction-Many drug interactions |
| Olanzapine | IM: 15PT: 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/dayPT: 5-20 mg qday | -Anticholinergic -EPS-NMS-Neuromuscular Weakness |  |
| Phenobarbital | IV: 5PO: 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:15PT: 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/kgInfusion: 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/kgInfusion: 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/kgInfusion: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/kgInfusion: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/kgInfusion: 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.