Biomedical Chemistry Update on Pharmacotherapy for Opioid Use Disorder

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Abstract:
Opioid Use Disorder (OUD) is highly undertreated despite its major prevalence and the ongoing crisis of opioid overdose and death. Pharmacotherapy is an essential tool to reduce opioid misuse and prevent fatal overdose. Such intervention has the primary goals of harm reduction, i.e. reducing opioid intake and medication-assisted therapy (MAT), i.e. sustained medication maintenance. Three U.S. FDA cleared medications are currently available for the treatment of OUD. (1) Naltrexone is a mu-opioid receptor antagonist which interferes with reward effects, blocking the impact of increased β-endorphin during opioid use leading to reduced opioid cravings. Such effects modulate the mesolimbic dopamine system in the ventral tegmental area (VTA) as well as projections to the nucleus accumbens (NA). The NA is the most commonly activated brain region linked with opioid-associated cues where mu-opioid receptor densities correlate with cravings for opioids. Naltrexone extended release (ER) is a long-acting intramuscular depot injection containing a poly-lactic based polymer. Hydrolytic degradation of the polymer capsule slowly releases Naltrexone overtime into systemic circulation, bypassing first-pass metabolism allowing for a sustained therapeutic dose of opioid receptor antagonism at longer durations without daily oral dosing. (2) Methadone is a mu-opioid receptor agonist and N-methyl D-aspartate (NMDA) receptor antagonist. As a mu-opioid agonist, Methadone mimics endorphin effects at a smaller amplitude and with longer duration, leading to withdrawal suppression without reward effects. As an NMDA receptor antagonist, Methadone modulates glutamate, the most common excitatory neurotransmitter in the brain which has high opioid sensitivity. This agent regulates NMDA excitatory changes due to chronic opioid overuse, which slows opioid tolerance, central sensitization, and pain modulation. Thus, opioid withdrawal and tolerance effects are attenuated. (3) Buprenorphine is a high affinity mu-opioid receptor partial agonist, kappa-opioid receptor antagonist, and nociceptin receptor agonist. As a high affinity partial mu-receptor agonist, Buprenorphine suppresses withdrawal without the reward effect, while competitively blocking full activation, leading to reduction of risk for toxicity and fatal overdose. As a kappa-opioid receptor antagonist, Buprenorphine antagonizes receptors spread throughout the central nervous system (CNS), reducing the risk of dysphoria, hyperalgesia, and tolerance effects. As a nociceptin Gi-protein coupled receptor agonist, Buprenorphine downregulates CNS pain processing and mesolimbic dopamine systems, targeting intractable pain and reducing the risk of addiction. With the addition of the complete opioid antagonist Naloxone to Buprenorphine, the oral combination decreases cravings and euphoria, and prevents misuse. Taken as a whole, these medications form a substantive foundation for evidence-based OUD pharmacotherapy which is established as the standard of care.