Biomedical Chemistry Update on Pharmacotherapy for Alcohol Use Disorder

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Abstract:

Alcohol Use Disorder (AUD) is highly undertreated despite its increasing prevalence and societal costs. As such circumstances have transpired, pharmacotherapy for AUD has become essential clinical treatment with the goal of achieving either: (1) Harm Reduction i.e. reducing alcohol intake or (2) Abstinence i.e. achieving complete cessation. Three U.S. F.D.A. cleared medications are currently available to treat AUD. Naltrexone is a mu-opioid receptor antagonist which interferes with reward effects blocking the impact of increased β-endorphin during drinking leading to reduced alcohol 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 alcohol-associated cues where mu-opioid receptor densities correlate with cravings for alcohol. Acamprosate is a N-methyl D-aspartate (NMDA) receptor antagonist which modulates glutamate, the most common excitatory neurotransmitter in brain, and the NMDA receptor has high alcohol sensitivity. Acamprosate also modulates gamma-aminobutyric acid (GABA), the primary inhibitory neurotransmitter in brain. As a result, this agent stabilizes neurotransmission by restoring balance between these excitatory and inhibitory systems. Disulfiram inhibits acetaldehyde dehydrogenase. Its irreversible binding to this enzyme inhibits the metabolism of acetaldehyde to acetate which leads to increases in plasma acetaldehyde levels. If alcohol is consumed, the accumulated acetaldehyde causes a highly unpleasant and potentially life-threatening reaction. Along with such approved medications, there are other promising non-approved pharmacotherapies for AUD including: Topiramate (glutamate receptor antagonist, GABA agonist and dopamine release inhibitor), Gabapentin (GABA agonist activity) and Baclofen (stereoselective GABA-B agonist). Taken as a whole, these medications form a substantive foundation for evidence-based AUD pharmacotherapy which is indeed established as the standard of care.