DART
DRUG ABUSE RESEARCH TRAINING

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Pharmacological Interventions for Stress-Induced Relapse: Efficacy Across Sex and Species

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Drug addiction is characterized by bouts of relapse, and this relapse is often provoked by stressful experiences. While this sequence of events is well-described, there remains a lack of pharmacological interventions that can effectively disrupt this pattern. This can partially be attributed to a failure to translate positive findings from preclinical research through the human laboratory and to clinical trials. A critical component of this failed translation is inattention to sex as a biological variable, particularly prior to clinical trial enrollment. Here, we focus on pharmacotherapeutic targets assayed in the prevention stress-induced relapse-like behavior in both human and animal models, emphasizing the influence of biological sex on outcomes. The majority of targets that showed efficacy in rodents failed to do so in human models. Approaches that demonstrate at least some evidence of translational success include noradrenergic treatments (namely α2 agonists, e.g. clonidine, lofexidine), neuroactive peptides (oxytocin), and cannabinoids (cannabidiol, FAAH inhibitors). Sex differences were observed for nearly all approaches that assessed an adequate sample of females, including those that were translationally successful. However, many articles still failed to consider sex as a covariate when conducting analyses of pharmacotherapeutic efficacy. This review underlines a clear need to critically evaluate preclinical and human laboratory models of stress-induced drug seeking for factors that contribute to failed translationally efficacy, and posits biological sex as foremost among these. Further, we encourage additional research effort into those pharmacotherapeutic targets capable of reducing stress-induced drug seeking in both men and women.