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

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BACKGROUND

Drug addiction is characterized by bouts of relapse, and this relapse is often provoked by stressful experiences.

Pharmacological interventions to effectively disrupt patterns of stress-induced drug seeking are presently lacking.

This lack of effective interventions is largely attributable to failed translation from preclinical to human research, and from the human laboratory to clinical trials.

Failed translation may in part be due to lack of consideration for sex as a biological variable.

AIMS

1) Report common techniques used to promote stress-induced drug seeking behavior in preclinical models and in the human laboratory.
2) Describe pharmacotherapeutic strategies assayed to prevent stress-induced relapse to cocaine, opioids, methamphetamine, and cannabis in both human and animal models.
3) Address factors in this research that contribute to failed translation, with an emphasis on the potential for biological sex to mediate outcomes.

TECHNIQUES

	Preclinical	Human
Comparable	Foot Shock	Cold Pressor Task
	Yohimbine	Yohimbine
	CRF Infusion	CRH Infusion
	Social Defeat	Trier Social Stress Test
	Stress-Associated Cue	Stress Imagery
Incomparable	Restraint	Maastricht Acute Stress Test
	Forced Swim Test	
	Food Deprivation	Ecological Momentary Assessment

RESULTS

Noradrenergic Targets

Preclinical	Human	Clinical trial
α-2 Agonist	**α-2 Agonist**	**α-2 Agonist**
• Cocaine ✓	• Cocaine ? ♀	• Cannabis ✗
• Opioid ✓	• Cannabis (+/- THC) ?	• Opioid (+/- bup.) ✓
• Cocaine + Opioid ✓	• Opioid (+ naltrex.) ✓	
β Antagonist	**β Antagonist**	**β Antagonist**
• Cocaine ✓	• Opioid ?	• Cocaine ✗
• Opioid ?		

1) Evidence of sex differences
2) α agonists may be efficacious for cocaine, opioids
3) β antagonists show potential for opioids; need clinical trial

Neuroactive Peptide Targets

Preclinical	Human	Clinical trial
Oxytocin	**Oxytocin**	**Oxytocin**
• Cocaine ?	• Cocaine ? ♀	• Cocaine + Opioid ✓
• Meth ✓ ♀	• Cannabis ✓ ♂	• Meth (adjunct to therapy) ✗
• Opioid ✓		• Cannabis (adjunct to therapy) ✓
NPY Antagonist		
• Opioid ?		
NPS Antagonist		
• Cocaine ✓		
NK-1 Antagonist		
• Cocaine ✓		

1) Evidence of sex differences
2) Oxytocin may be efficacious for cocaine/opioid or cannabis dependence
3) Further research of oxytocin warranted

Cannabinoid Targets

Preclinical	Human	Clinical trial
CB1 Antagonist	**CB1 Agonist**	**CB1 Agonist**
• Cocaine ?	• Cannabis ✓	• Cannabis ✗
Cannabidiol	**Cannabidiol**	**THC + CBD**
• Cocaine ✓	• Opioid ✓	• Cannabis ?
FAAH Inhibitor	**THC + CBD**	**FAAH Inhibitor**
• Cocaine ✓	• Cannabis ✗	• Cannabis ✓
• Meth ✗		
MAGL Inhibitor		
• Meth ✓		

1) Lack of research in females
2) Cannabidiol, FAAH inhibitors may be efficacious for cannabis, opioids
3) Need to assess impact of sex

Glutamatergic Targets

Preclinical	Human	Clinical trial
N-acetylcysteine	**N-acetylcysteine**	**N-acetylcysteine**
• Cocaine ✓	• Cocaine ✓	• Cocaine ✗
mGluR2/3 Agonist	**NMDA Agonist**	• Cannabis ?
• Cocaine ✓	• Cocaine ✗	• Meth (+ naltrex.) ✗
mGluR5 Antagonist		
• Cocaine ✓		
NMDA Antagonist		
• Cocaine ✓		

1) No evidence of sex differences
2) Current strategies have failed to translate to humans
3) Further preclinical research into novel approaches recommended

Serotonergic Targets

Preclinical	Human	Clinical trial
5-HT2C Agonist	**SARI**	**SARI**
• Cocaine ✓	• Cannabis ?	• Cannabis ✗
		SSRI
		• Cannabis ✗
		5HT Modulator
		• Cannabis ✗ ♂
		5-HT1A Agonist
		• Cannabis ✗ ♂
		• Opioid ✗

1) Evidence of sex differences
2) Currently approved antidepressant medications ineffective for stress-induced relapse
3) Further research of novel approaches recommended

Dopaminergic Targets

Preclinical	Human	Clinical trial
D1 Antagonist	**D1/5 Antagonist**	**Mixed DA Agonist**
• Opioid ?	• Cocaine ✗	• Cocaine ?
D2 Antagonist	**D1 Agonist**	• Cocaine + Opioid ✓
• Opioid ✗	• Cocaine ?	
D3 Antagonist	**D2 Agonist**	
• Cocaine ✓	• Cocaine ✗	
• Opioid ✗	**D1/D2 Agonist**	
Mixed Antagonist	• Cocaine ✗ ♀	
• Cocaine ✓		
• Opioid ✓		

1) Evidence of sex differences
2) Limited potential for DA antagonists in humans due to side effects

CRF/HPA Axis Targets

Preclinical	Human	Clinical trial
CRF1 Antagonist		**Cortisol Synthesis Inhibitor**
• Cocaine ✓		• Cocaine ✓
• Meth ✓		
• Opioid ✓		
Cortisol Synthesis Inhibitor		
• Cocaine ✓		

1) Minimal research conducted in humans due to failed CRF1 antagonist alcohol trials
2) Lack of research in females
3) Further research with cortisol synthesis inhibitors is warranted

LEGEND

- Preclinical
- Human laboratory
- Clinical trial
- ✓ Largely effective
- ✗ Largely ineffective
- ? Mixed results
- ♀ Better outcomes in females
- ♂ Better outcomes in males

CONCLUSIONS

Noradrenergic, neuroactive peptide, and cannabinoid treatments show promise to attenuate stress-induced relapse; most interventions failed to translate across models.

Evidence of sex differences was observed across nearly all systems with adequate female representation. Yet, sex was often not considered when evaluating treatment efficacy, and most preclinical research remains exclusively in males.

Future research must critically evaluate models used in order to best achieve translational efficacy.

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