

Promising Pharmacological Treatment of Stimulant Use Disorder: Time for Translation to Clinical Practice

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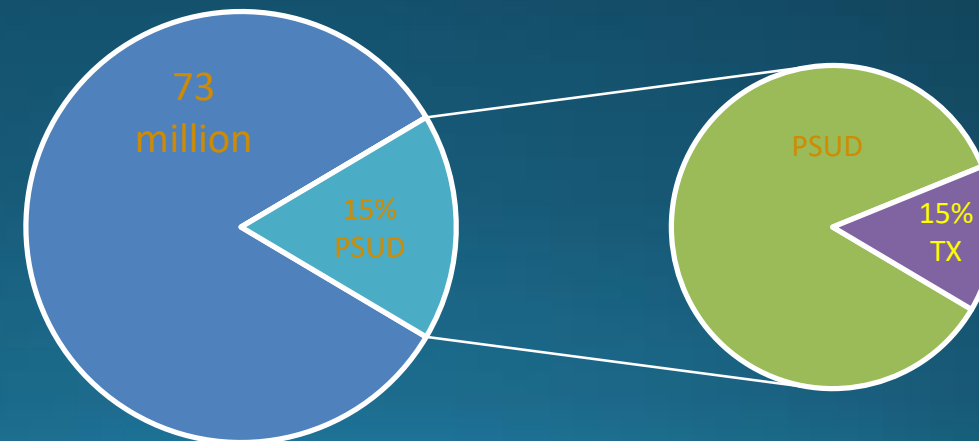
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Psychostimulant Use Disorder (PSUD)

- Worldwide, 73 million people used illicit (psycho)stimulants: twice as many as those who used opioids
- Some will develop a PSUD, which causes significant health and psychosocial problems
- Only small portion of people with PSUD have access to or receive treatment (large regional disparities)

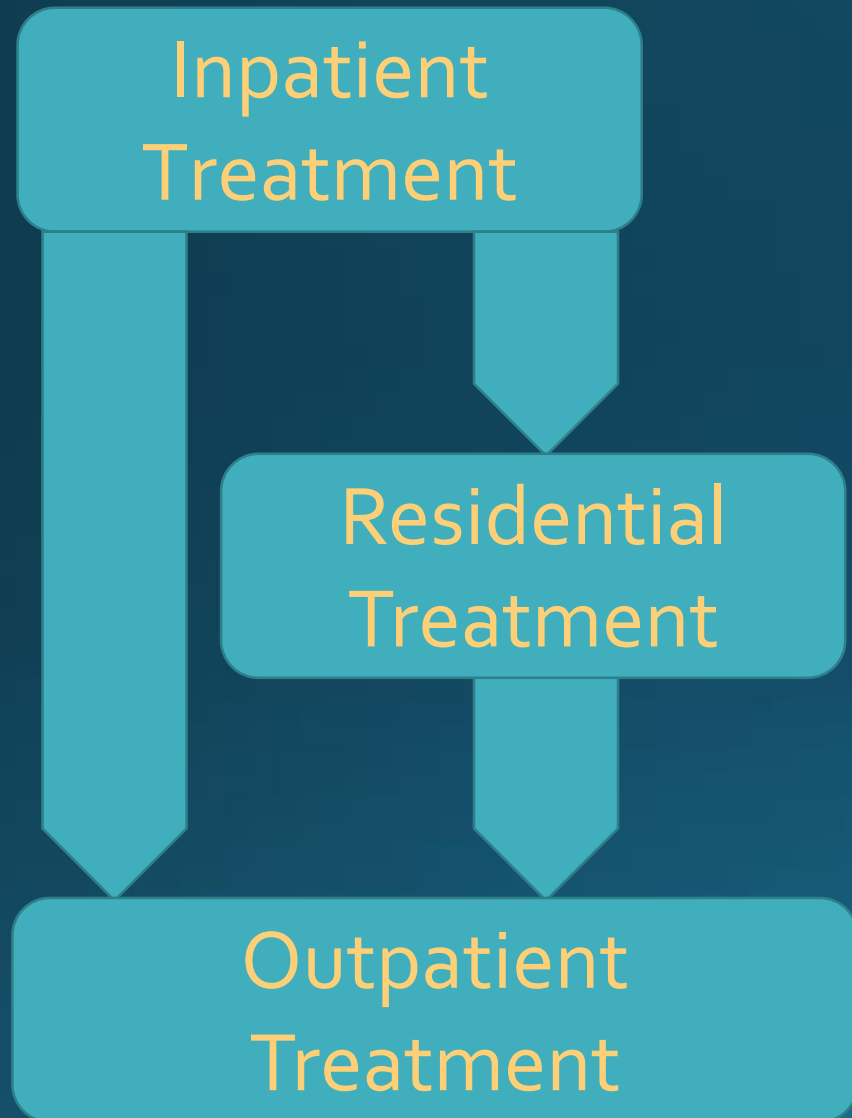
Illicit Stimulant Users



PSUD: Treatment

- Almost all patients who are in treatment receive only psychosocial interventions
 - In contrast to treatment of opioid use disorder where medications are a standard of care
- Psychosocial interventions (e.g., CBT)
 - limited effectiveness (for frequent users and cognitively impaired individ.)
 - poor treatment engagement
 - expensive to deliver

Current treatment framework for PSUD

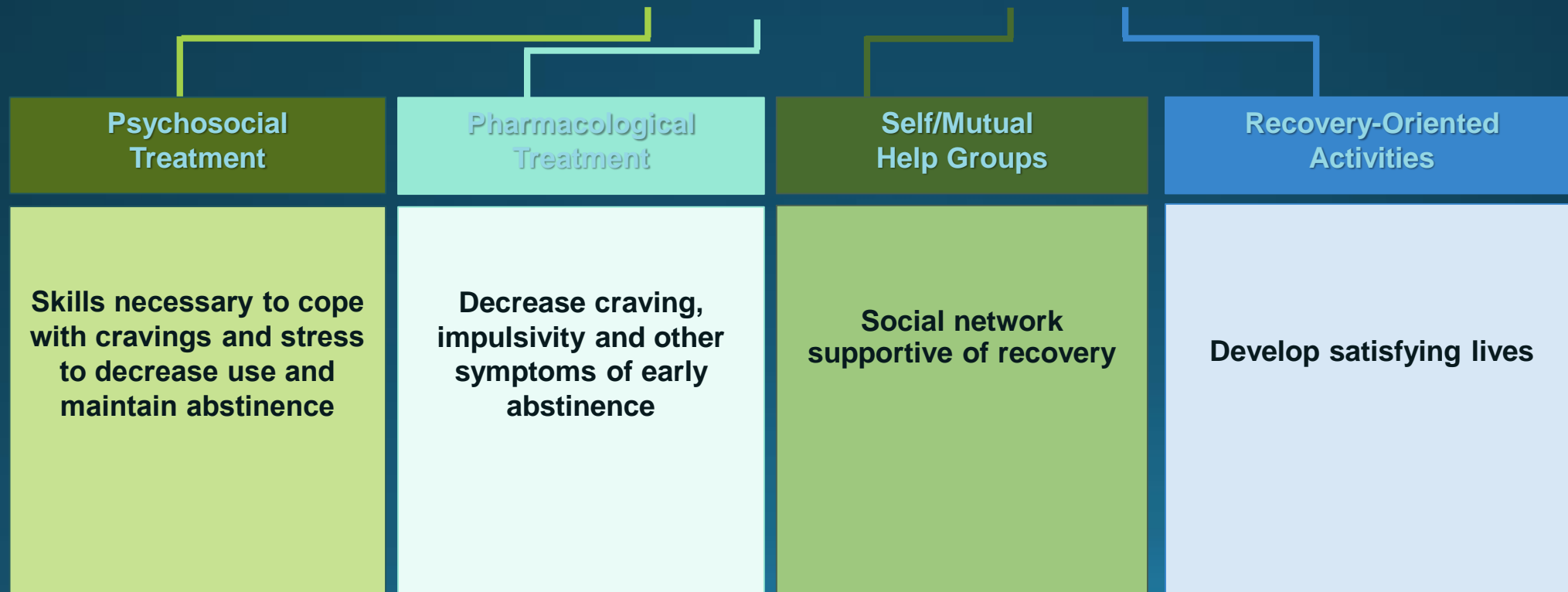


- Medical/psychiatric stabilization - “detox”
 - Short-term medication use
 - No effect on drug use, high relapse rates
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- Drug rehab or TC model
 - Only psychosocial interventions, high cost
 - Large decrease of use, but high relapse rates
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- Psychosocial-only, “abstinence-based”
 - Low cost
 - Small reductions of use

Addiction: Medical Framework

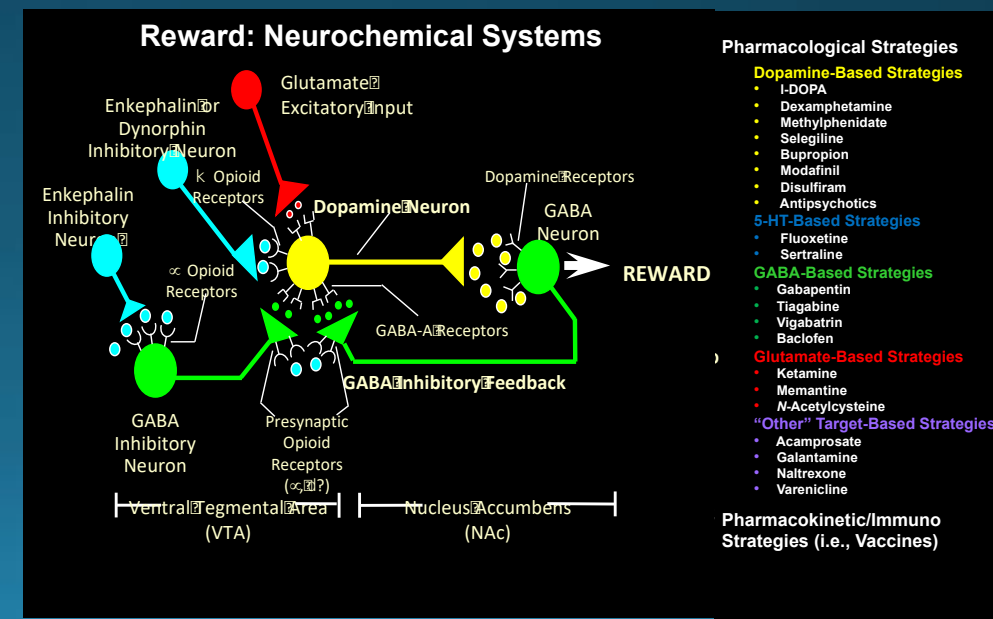
- Addiction is an acquired bio-behavioral brain disorder
 - It is more likely to develop in people with a genetic predisposition
 - In vulnerable individuals, taking drugs changes the brain
 - There is an abnormal functioning of brain circuits involved in processing of motivation, memory, reward, and decision making
 - Abnormal functioning is responsible for symptoms
 - Disturbances of mood, cognition, and decision-making
 - Abnormal reactivity to stress and environmental cues
 - Overwhelming craving and difficulty with controlling behavior
 - Impaired insight and the impaired ability to care for self
 - Once developed, addiction has a chronic and relapsing course
 - Abnormal brain responses persist for many months/years

Addiction: Treatment Components



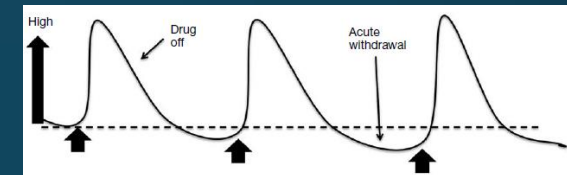
PSUD: Pharmacological Treatments

- Substantial research effort went to finding medications that could improve outcomes of treatment for PSUD
- At present time there is no widely accepted medication to play this role **but** there are several candidate medications that were found effective when tested in quality controlled clinical trials
- The most effective approach to date is **agonist-based treatment**

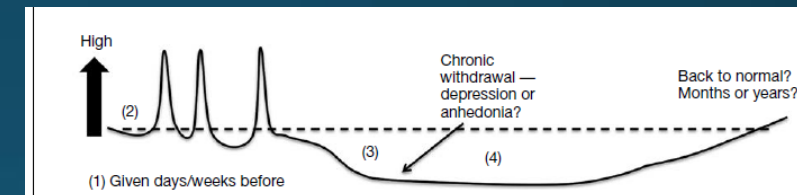


Agonist Approach: Rationale

- Both cocaine and ATSs acutely increase brain levels of dopamine, serotonin, and noradrenaline producing euphoria and other physical effects



- However, chronic users (PSUD) have reduced functioning of DA system



- These changes may be responsible for the continuing use and relapse
 - Low energy, low mood/anhedonia, \downarrow cognition/decision making, \uparrow impulsivity
- Correcting those abnormalities can reduce symptoms and help reduce use
 - Agonist-type medication increase DA/NA activity in the brain (pfc)

Agonist Approach: Rationale (2)

- Several agonist medications are used for treatment of other disorders
 - Methylphenidate (Ritalin, Concerta), Amphetamines (Adderall), modafinil
 - High comorbidity and overlapping neurobiology between PSUD and ADHD
- Supervised/medical use of a drug-like substance can stabilize and keep patients in treatment and access other services and medical interventions
- Offering medications may motivate patients for additional treatment
- Patients accept agonist, positive subjective effects promote medication adherence
- Stimulant medication may improve cognitive functioning and improve outcome of psychosocial interventions

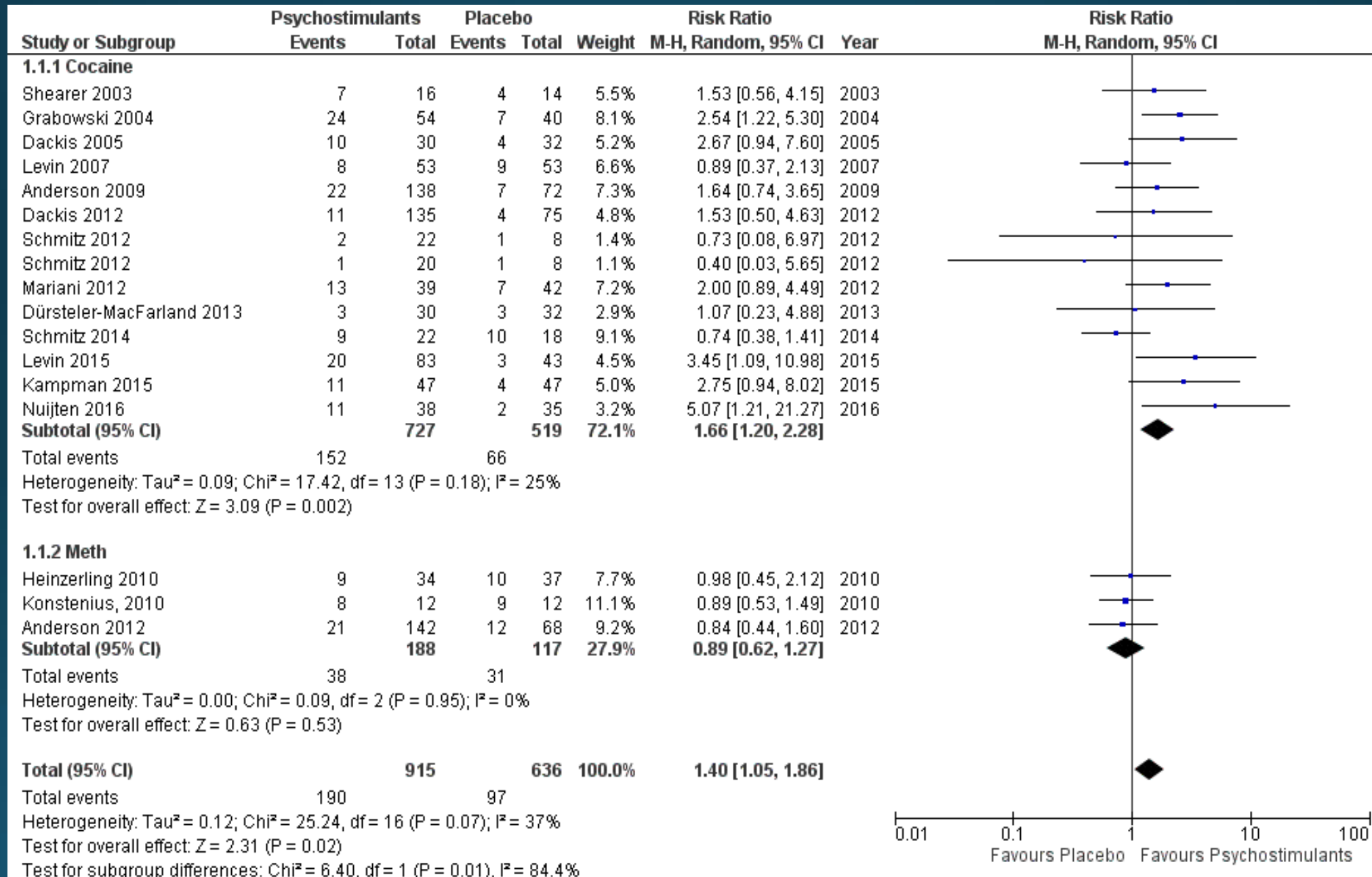
Agonist: assuring treatment safety

- Most potent agonists are classified as controlled substances because of the potential for abuse and diversion
 - Treatment must include plan to minimize this risk
 - Similar concerns exist with opioid agonists
- XR preparations have slow onset of action and slower rate of elimination providing stable blood level
 - Less likely to be abused and better adherence
- There is potential for adverse cardiovascular effects and the need to screen out individuals with cardiovascular disease

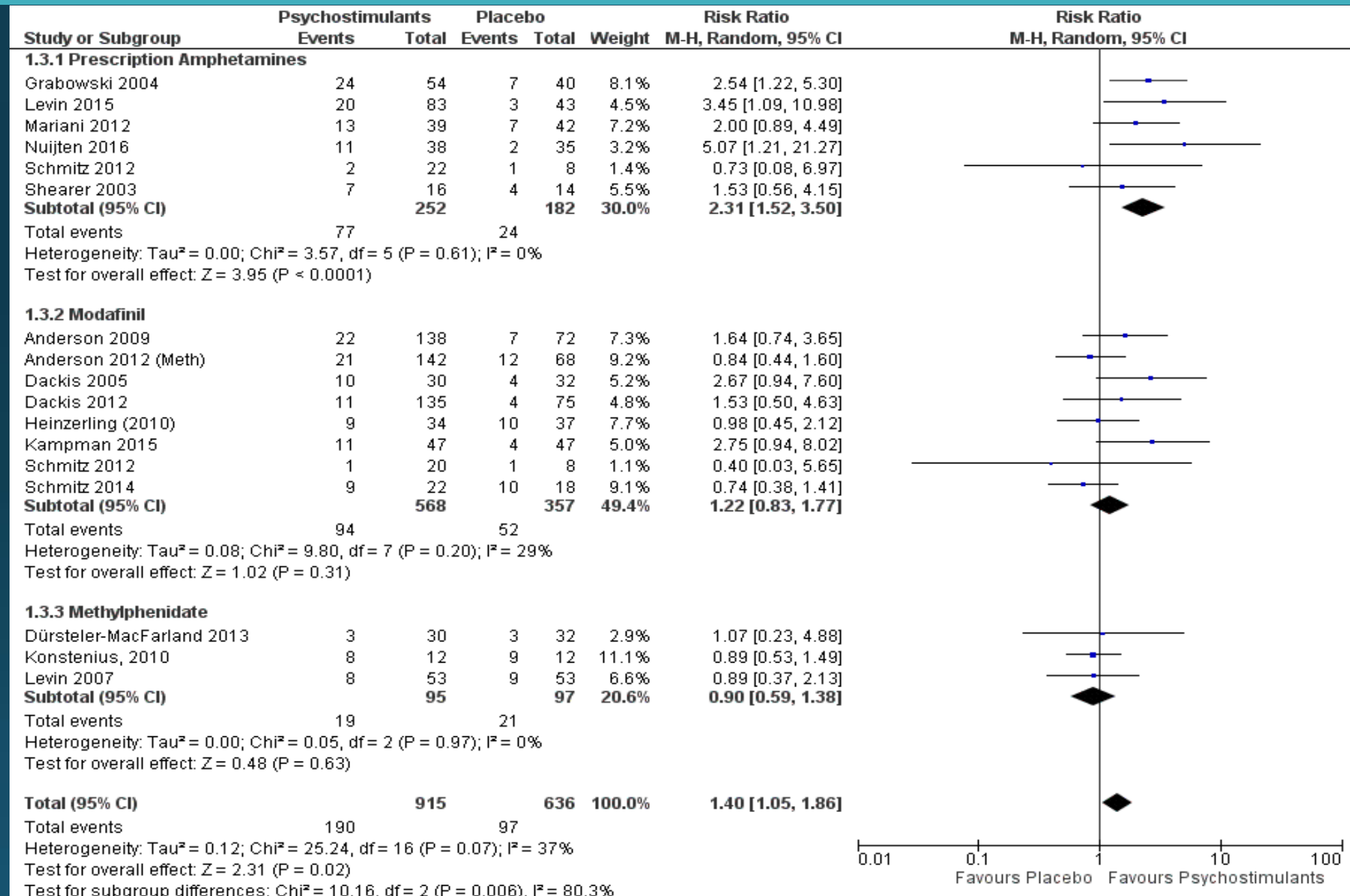
Agonist Strategy: Meta-analysis 2019 *(Tardelli et al., 2019)*

- Systematic review and a meta-analysis of RCT that used agonists for the treatment of Cocaine or Amphetamine-type PSUD
- Medications: scheduled prescription stimulants: **modafinil**, **methylphenidate**, or an **amphetamine-type medication** (dexamphetamine, mixed amphetamine salts and lisdexamphetamine)
- Outcome Measure: **sustained abstinence** from the drug (2-3 wks)
 - Sustained abstinence, particularly at the end of treatment, is an outcome strongly related to cocaine use during follow-up *(Carroll et al., 2014)*

Sustained Abstinence: Cocaine vs. Amphetamine Use Disorder (Tardelli et al., 2019)



Sustained Abstinence: Effect of medication (Tardelli et al., 2019)

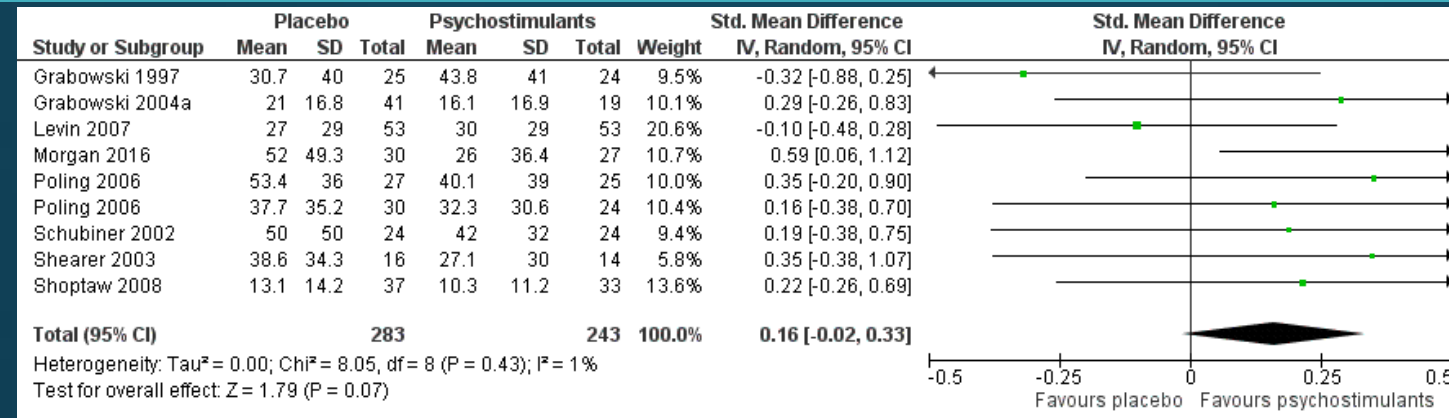


Agonist Strategy: Meta-Analysis 2019

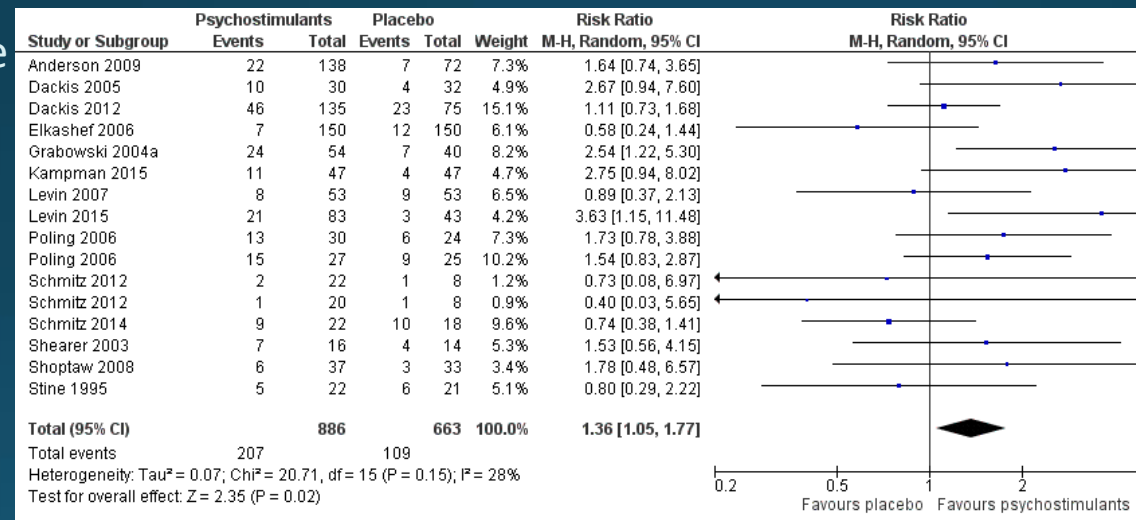
- *We found that:*
 - *Prescription psychostimulants were effective in promoting sustained abstinence in the treatment of PSUD, particularly Cocaine Use Disorder (low-quality evidence)*
 - *Prescription amphetamines were particularly efficacious on promoting sustained abstinence on patients with Cocaine Use Disorder (high-quality evidence)*

Agonist Strategy for Cocaine UD: Cochrane 2016

Cocaine use



Sustained Abstinence



- ... evidence that a higher proportion of participants achieved sustained cocaine abstinence with psychostimulants than with placebo (low quality evidence, small benefit)
- In consonance with the efficacy of substitute treatment for heroin use and for nicotine dependence, the findings of this review suggest that psychostimulants are a promising treatment for cocaine dependence

Implementing medical model to treat patients with PSUD

- **Attract** patients into treatment and keep them engaged
 - Outreach work: offering food, shelter, and welcoming environment
 - Inpatient/residential services if stabilization is needed
- **Offer treatment**
 - **Medications** to help reduce craving and impulsivity, improve mood and cognition to decrease drug use/prevent relapse
 - Supportive, friendly, and accepting therapeutic environment
 - Therapy to change pathological behaviors and retain patients in treatment
 - Connect with peer-support networks and recovery-oriented services
- **Diagnose and treat** co-occurring conditions
 - Other Substance Use Disorders (alcohol, opioids)
 - Psychiatric problems (depression, anxiety, PTSD, psychosis)
 - Medical problems (e.g., infections, dental, reproductive services)
- **Collect evidence** to test health and economic benefits of this model