Methamphetamine Addiction Treatment Challenges

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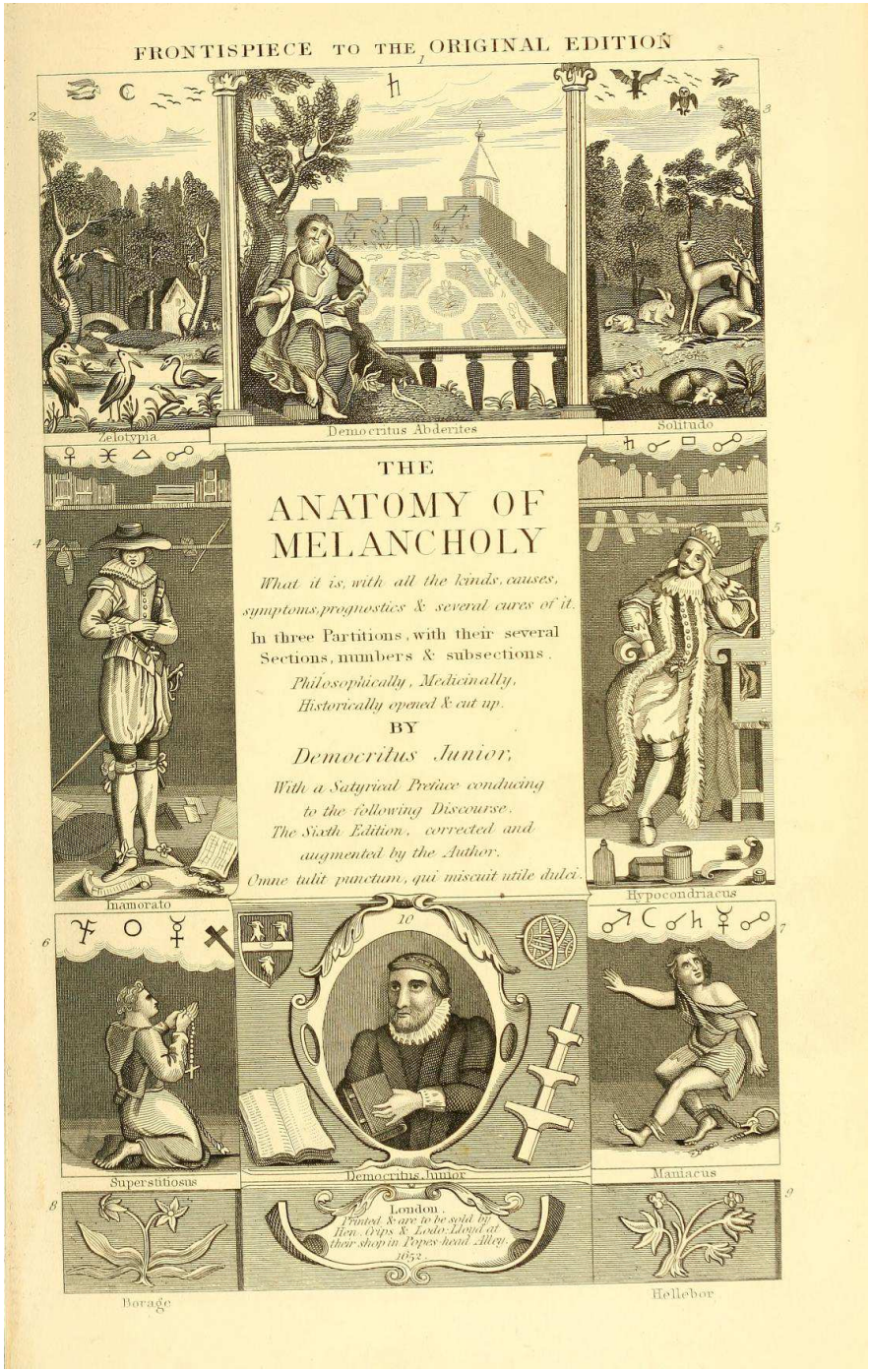


- And as that great captaine Zisca would have a drumme made of his skinne when he was dead, because he thought the very noise of it would put his enimies to flight, I doubt not, but that these following lines, when they shall be recited, or hereafter read, will drive away Melancholy (though I be gone) as much as Zisca's drumme could terrify his foes.

Amphetamine-type Stimulants (ATS)

- Amphetamine-type stimulants (ATS): amphetamine, methamphetamine, and other substances with similar mechanism of action and effects
- Mechanism of action: cause release of monoamine neurotransmitters (dopamine, norepinephrine, and serotonin) into the synapse and block reuptake
- Highly addictive
- Lower doses treat ADHD and narcolepsy; higher doses (with addiction) may lead to vesicular dopamine depletion and neurotoxicity

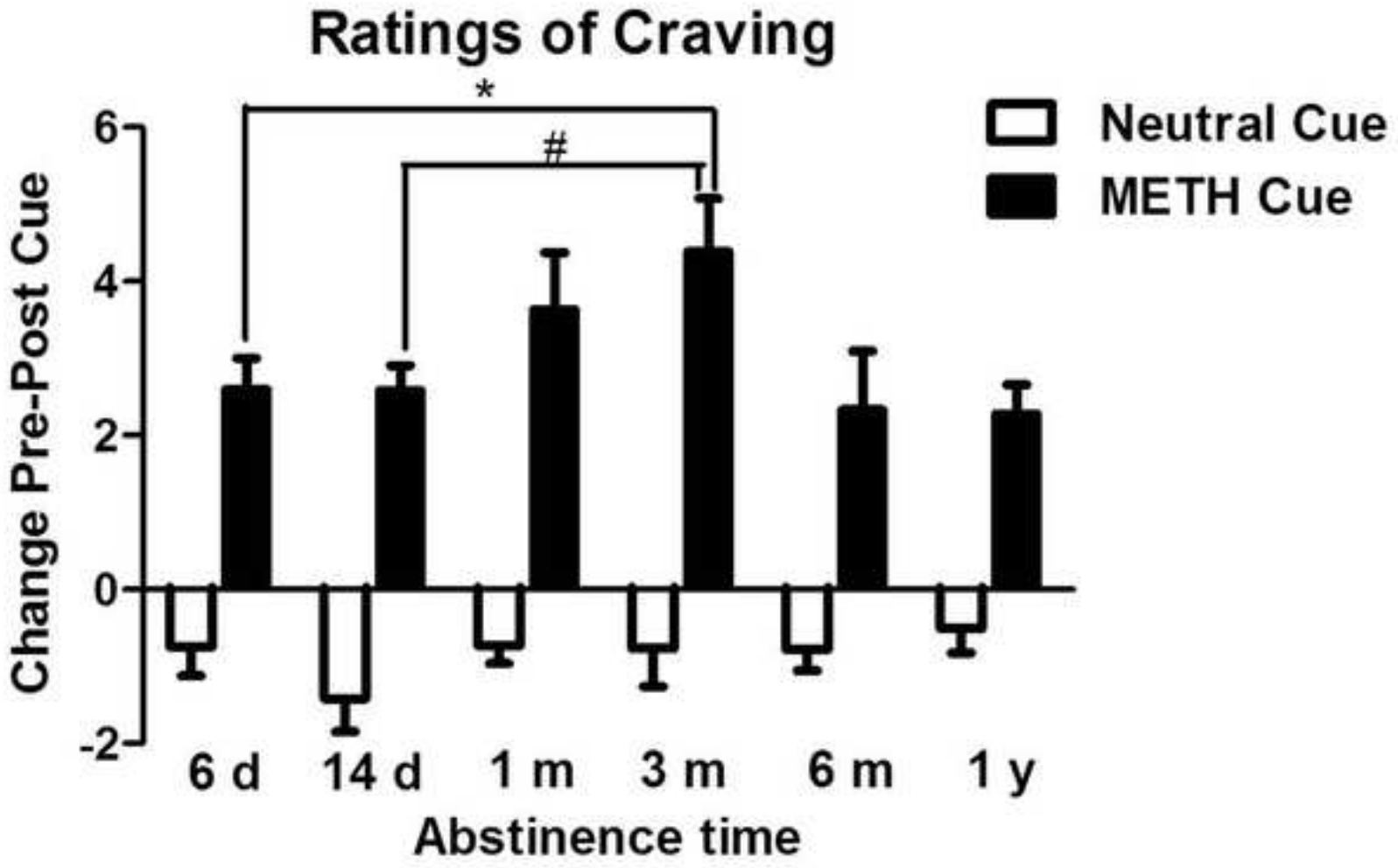
Acute Effects of ATS Use

- Increased energy, arousal, focused attention
- Behavioral activation
- Feelings of euphoria, confidence, well-being
- Hyper-sexuality
- Physiological effects: increase blood pressure and heart rate; relax bronchioles; increase fat metabolism; decrease appetite
- Potential agitation, paranoia, psychosis, hyperthermia
- Effects more intense (and transient) when smoked or injected than when ingested orally

Patterns and Phases of ATS Addiction

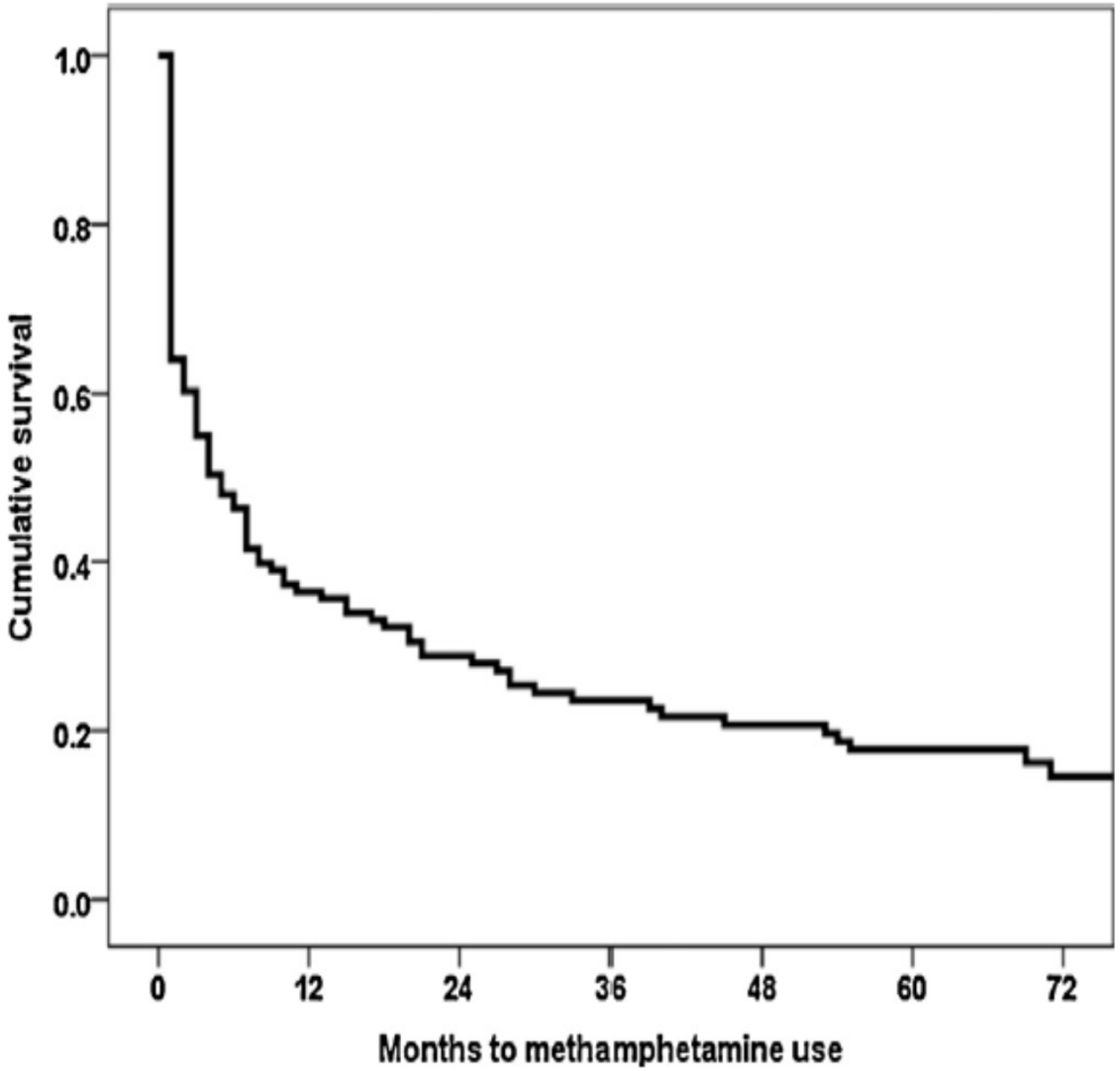
- Transition from casual use to addiction
- Persistent, daily use (often to work long hours and stay awake) or “Binge-and-Crash” pattern
- “Tweaking” (early withdrawal, 4-24 hours after binge): scattered thinking, paranoia, irritability, hyper-vigilance, and hallucinations
- Crash: Severe fatigue, depression, irritability, clouded thinking, aversion to ATS or craving
- Protracted abstinence: mood disturbances, executive function and other cognitive deficits (c/w cortical and striatal gray- and white-matter abnormalities), incubation of craving

Figure 5. Effects of exposure to METH and neutral cues on self-reported craving as a function of length of abstinence.



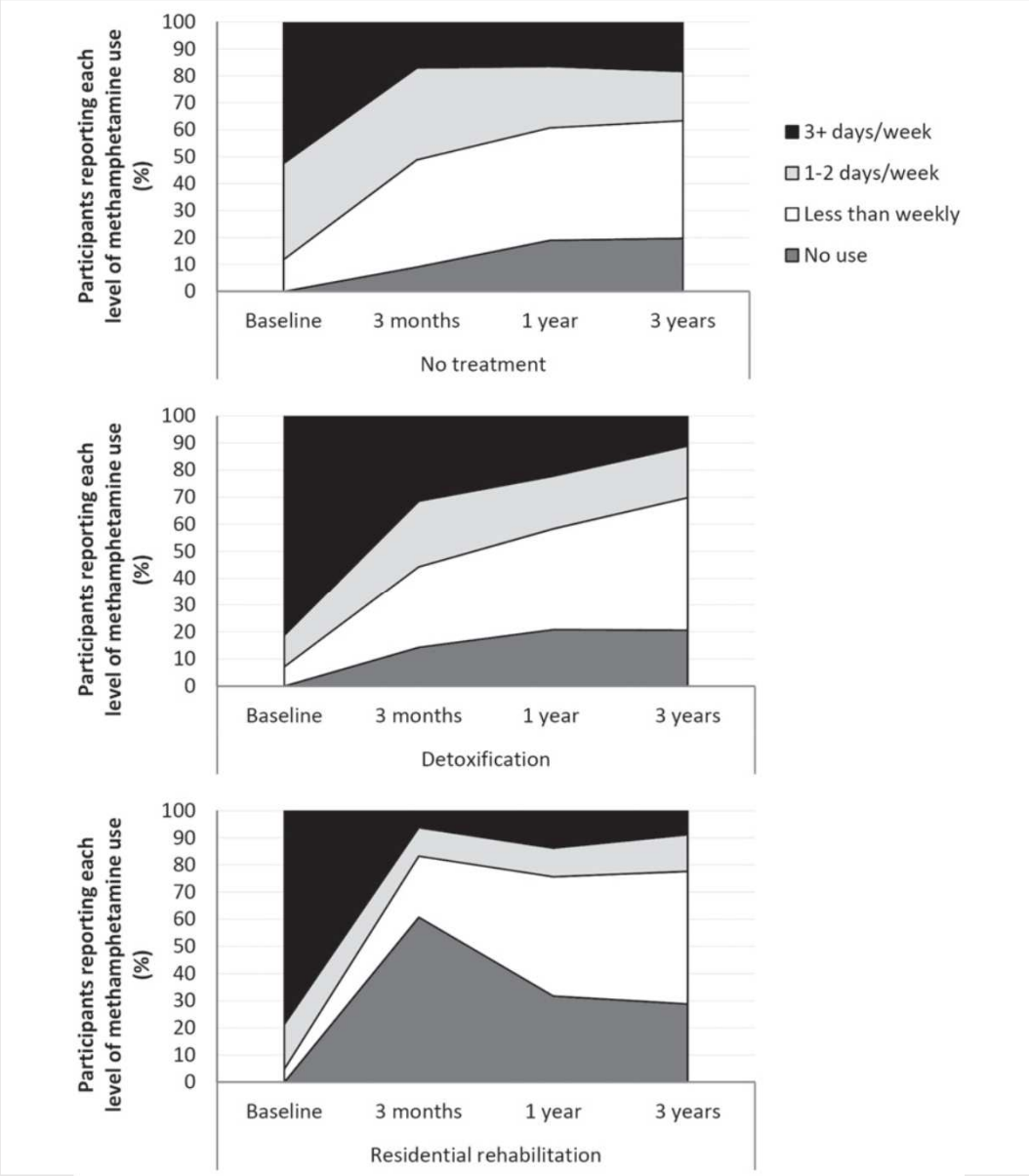
Wang G, Shi J, Chen N, Xu L, Li J, et al. (2013) Effects of Length of Abstinence on Decision-Making and Craving in Methamphetamine Abusers. PLoS ONE 8(7): e68791. doi:10.1371/journal.pone.0068791
http://journals.plos.org/plosone/article?id=info:doi/10.1371/journal.pone.0068791

High Rates of Relapse Following Treatment for ATS Addiction



Impact of Treatment on ATS Use

- Compared 3 cohorts
  - Untreated (n=101)
  - Detox only (n=112)
  - Residential (n=248)
- Continuous abstinence rates highest at 3 months, 1 and 3 years higher post residential tx
  - 33% increase at 3 months compared to detox or no tx
  - Benefits drop at 1 and 3 years



Amphetamine-type Stimulants (ATS): How Big a Problem?

- Estimated 35.7 million nonmedical ATS users (UNODC 2016); 2nd most common drug of abuse
- Estimated 17-18 million ATS dependent (Degenhardt 2014)
- Great regional variability in
  - Prevalence of ATS use
  - Co-occurring ATS and other drug (esp. heroin)
- Highest prevalence and continued increases in use of methamphetamine and co-occurring heroin use in Southeast Asia and Australia

Burden of ATS Varies by Region

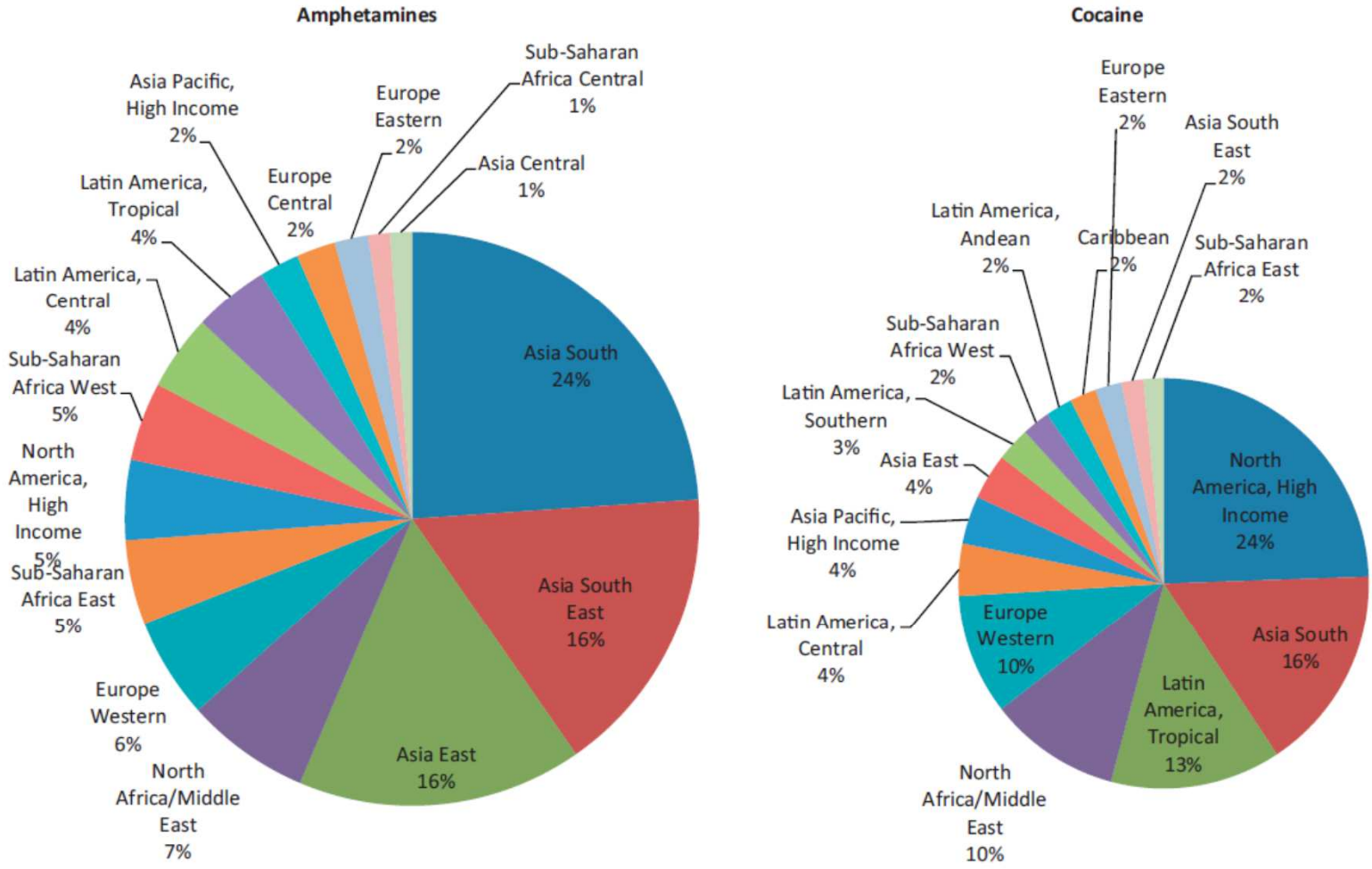
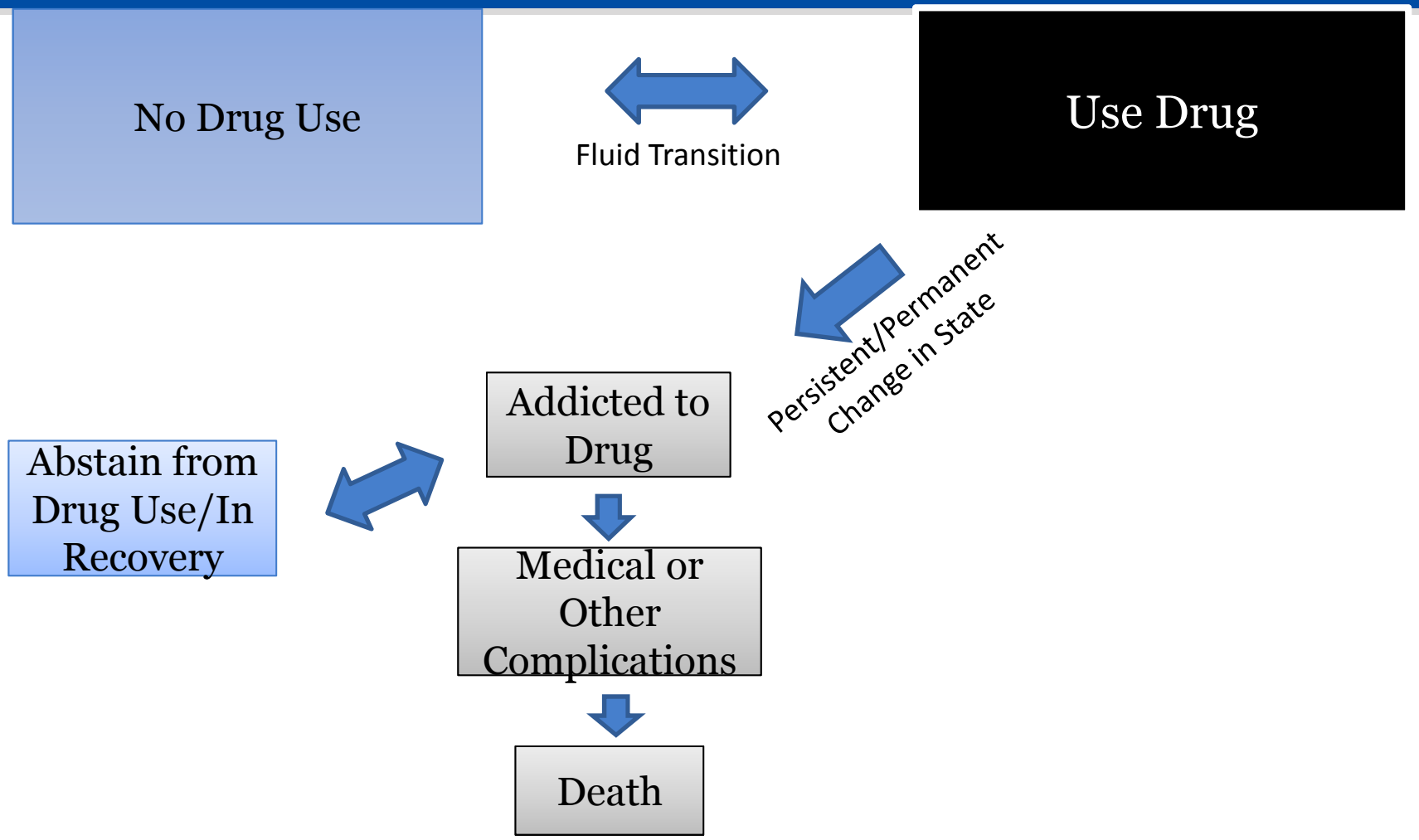


Fig. 2. Distribution of estimated crude DALYs due to amphetamine and cocaine dependence by geographic region, 2010.

What makes addiction so persistent?



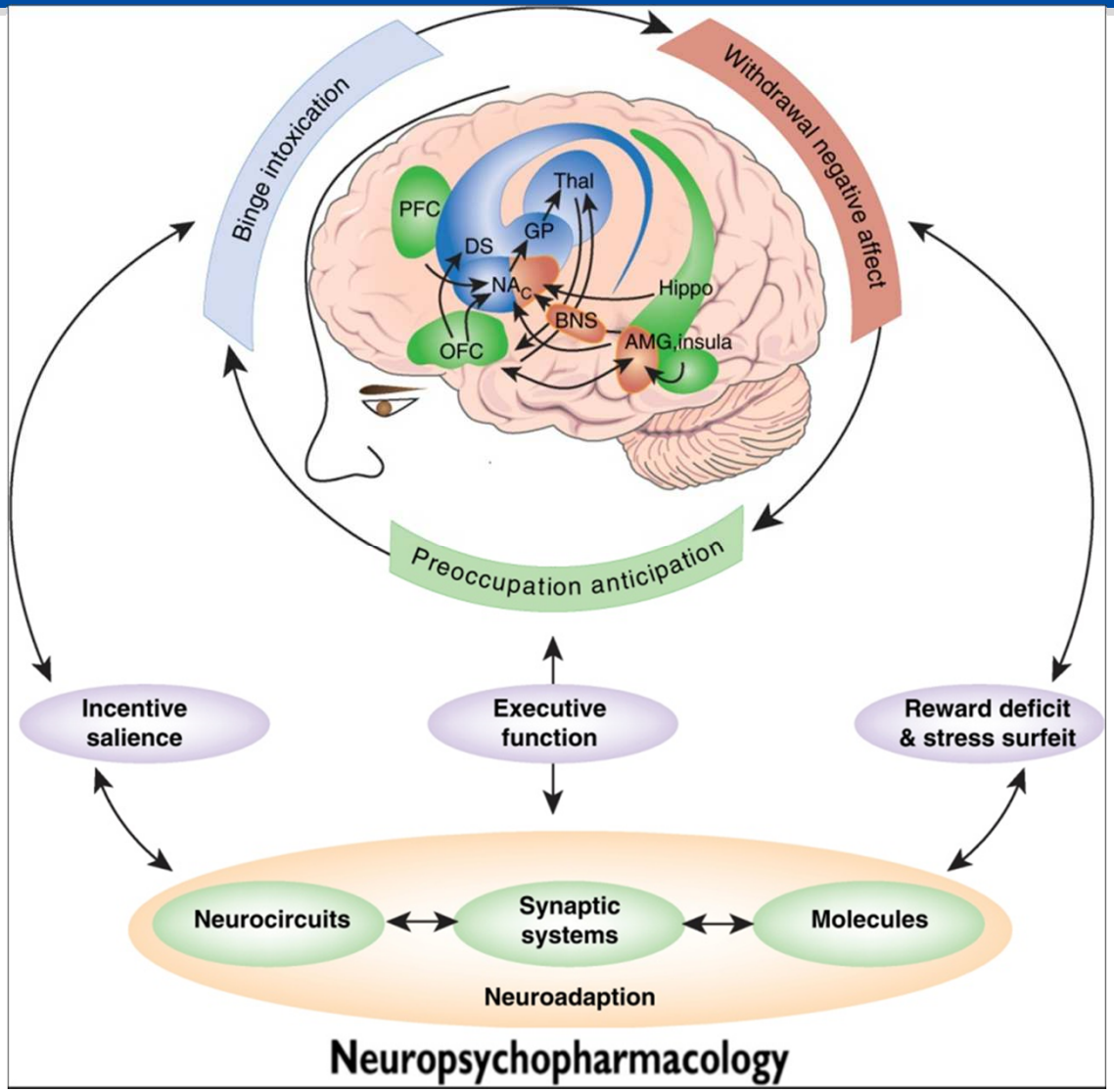
Transition: Not using ⟺ using drug

- Fluid transition: Shift in balance of factors affecting the transition has big impact on whether person uses
  - Social factors affecting transition
    - Drug availability and costs
    - Perceived benefits and risks
    - Peer, family, cultural influences
    - Stress and reward frustration
  - Individual risk factors
    - Adolescence/Young Adult
    - Curious, novelty-seeking, risk-taking or impulsive
    - Psychiatric vulnerability, depression, anxiety

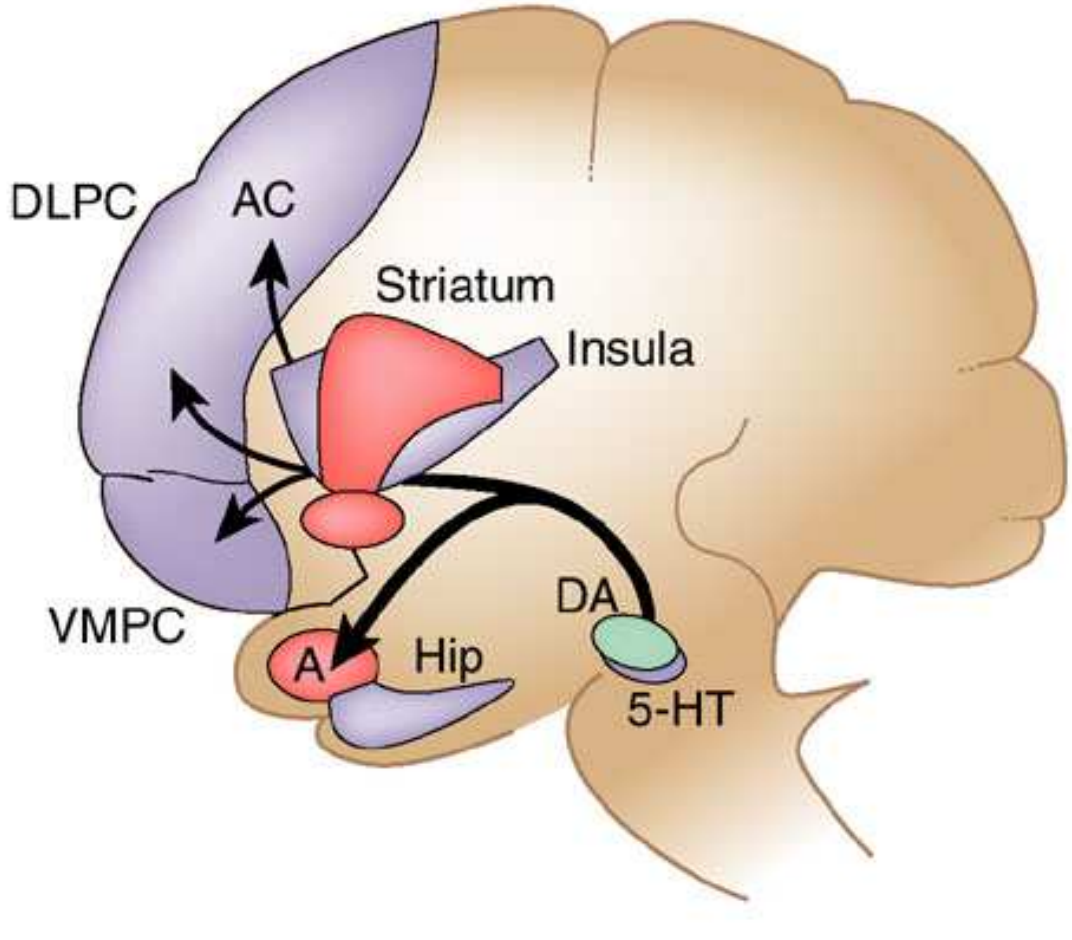
Transition to Addiction

- Genetic vulnerability
- Drug-generated neurobiological changes
  - Develop powerful memory traces of pleasurable drug effects—haunted by memory and desire
  - Decreased function of brain reward system and sensitization of "anti-reward" and stress systems
  - Increased impulsivity/decreased reflective functioning
- Repeated use and drug reward leads to habit formation/automatic behaviors and responses

Neurobiology of addiction schematic

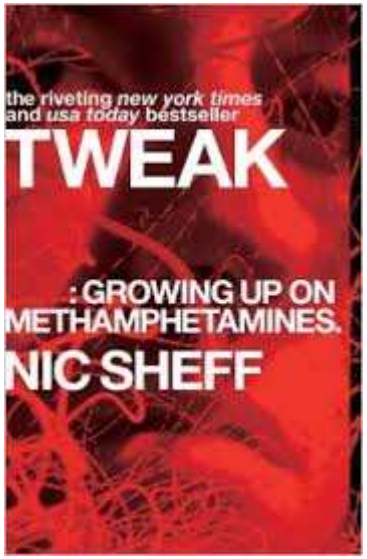


Addiction: Effects on impulsive system and reflective/cortical control system



Implications of transition to addiction

- Transition to addiction difficult to reverse.
- Hallmarks of addiction:
  - Continued use or relapse despite adverse consequences
  - Drug becomes primary/sole reward, increased salience
    - Impaired reward system, decreased responsiveness to normal rewards, loss of motivation for normal rewards
    - Chronic irritability, dysphoria, emotional distress, sleep disturbances
  - Loss of control: desire/impulse compulsion to use stronger and cortical control impaired by drug effects and "dark side of addiction"—impaired stress system



But early that morning, when I took those off-white crushed shards up that blue, cut plastic straws—well, my whole world pretty much changed after that. There was a feeling like—my God, this is what I've been missing my entire life. It completed me. I felt whole for the first time….

I guess I've pretty much spent the last four years chasing that first high. I wanted desperately to feel that wholeness again. It was like, I don't know, like everything else faded out. All my dreams, my hopes, ambitions, relationships—they all fell away as I took more and more crystal….The fact was, I couldn't stop. That sounds like a cop-out, but it's the truth. It's like I'm being held captive by some insatiable monster that will not let me stop. All my values, all my beliefs, everything I care about, they all go away the moment I get high. There is a sort of insanity that takes over…. The more I used, the more I did things I was ashamed of, and the more I had to use so I never had to face that.

- [After multiple rehab programs, Nic stops using for 18 months, working at a rehab program, until he relapses following a break-up.] Honestly, I was as surprised by my own actions as anyone else. The morning of my relapse, I had no idea I was actually going to do it…. I pull back the plunger, watch the blood rush up into the mixture, and then slam it all home. I cough….My eyes water—my head pounding like maybe I'll pass out, my breathing going so fast. "Goddamn, goddamn," I say, the lights dimming out and really, I mean, there's no feeling like it. The high is perfection….It is a different world…heightened, exciting. I light a cigarette and my fingers move spasmodically and I start talking, talking, talking. The waves of the drug keep sweeping through me and my palms turn sweaty and I grit my teeth….I feel like it's all happening…I can get any job I want….Nothing, I mean nothing, can stop me….

Going for the Gold

Clinical and treatment implications of transition to addiction

- Transition to addiction difficult to reverse.
- Hallmarks of addiction:
  - Continued use or relapse despite adverse consequences
  - Drug becomes primary/sole reward, increased salience
    - Impaired reward system, decreased responsiveness to normal rewards, loss of motivation for normal rewards
    - Chronic irritability, dysphoria, emotional distress, disrupted sleep
  - Loss of control:
    - Intense desire/impulse or compulsion to use
    - Cortical impulse control impaired by drug effects, stress, dysphoria, craving

Potential medication targets

- Treat overdose, withdrawal, or psychosis
- Block or attenuate drug reward
- Block or reduce craving
- Restore "normal" brain functioning—
  - e.g., ameliorate drug-related mood deficits, improve cognitive functioning, or enhance learning of new memories
- Improve impulse control
- Treat underlying psychiatric disorders

Medications Studied for ATS Addiction

- Naltrexone—rationale: block opioid-modulation of ATS response and reduce opioid-mediated craving*
- Dopamine or serotonin antagonists (risperidone, haloperidol, aripiprazole)—rationale: block dopamine response to ATS
  - Doses tested associated with increased ATS use
- Agonist treatment (dexamphetamine, methylphenidate)—rationale: substitute sustained release oral agent medication to induce tolerance/reduce "high" from ATS abuse and prevent "withdrawal"
  - Psychostimulants improve cocaine outcomes in some studies; high drop-out and difficult to verify abstinence if used to treat ATS
- Dopamine/noradrenaline-enhancing medications (buproprion)
- Serotonergic or noradrenergic modulators (fluoxetine, sertraline, imipramine, ondansetron, mirtazapine*, atomoxetine*)
- GABA modulators (baclofen, gabapentin, topimirate)
- * Some preclinical and clinical trials supporting potential efficacy

Comprehensive Reviews of Studies of Medication Treatments for ATS Dependence

"After 20 years of efforts worldwide to develop a broadly effective medication for dependence on methamphetamine or amphetamine-type stimulants, no candidate has emerged." Brensilver et. al., Drug and Alcohol Review 2013.

"The search for an effective medication continues, and until one is found, the mainstay of treatment remains behavioral interventions." Phillips et. al., Neuropharmacology 2014 review.

Drug and Alcohol REVIEW

APSAD

Drug and Alcohol Review (September 2013), 32, 449–460
DOI: 10.1111/dar.12048

COMPREHENSIVE REVIEW

Pharmacotherapy of amphetamine-type stimulant dependence: An update

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Abstract

Issues. *Methamphetamine- or amphetamine-type stimulants are the second most frequently used illicit drug worldwide, second only to cannabis. Behavioural treatments are efficacious, but their impact is limited underscoring the need for other treatment options, notably, pharmacotherapy.* ***Approach.*** *A review of randomised controlled trials of pharmacotherapies for methamphetamine- or amphetamine-type stimulants was performed using PubMed and Google Scholar databases. Evidence for efficacy of medications is reported.* ***Key Findings.*** *Clinical trials have yielded no broadly effective pharmacotherapy. Promising signals have been observed for methylphenidate, naltrexone, bupropion and mirtazapine in subgroups of patients in reducing stimulant use (e.g. patients with less severe dependence at baseline and men who have sex with men), though none has produced an unambiguous, replicable signal of efficacy.* ***Implications.*** *Problems in Phase II trials, including high dropout rates, missing data and a lack of agreement on outcomes, complicate efforts to find a broadly effective pharmacotherapy for amphetamine-type stimulant disorders. Efforts to address these problems include calls for better validation of pharmacological target exposure, receptor binding and functional modulation. As well, there is a need for agreement in using findings from preclinical and early phases of the medication development process for selecting better pharmacotherapy candidates.* ***Conclusion.*** *After over 20 years of efforts worldwide to develop a broadly effective medication for dependence on methamphetamine- or amphetamine-type stimulants, no candidate has emerged. This highlights the need for new compounds, consistent and stringent research methods, better integration between preclinical and clinical stages of medication development, and improved collaboration between government, industry and researchers.* [Brensilver M, Heinzerling KG, Shoptaw S. Pharmacotherapy of amphetamine-type stimulant dependence: An update. *Drug Alcohol Rev* 2013;32:449–460]

A growing methamphetamine dependence therapeutic graveyard

Commentary on RCT of buproprion for treating ATS dependence (Carson D & Taylor E, Addiction 2014)

Notes difficulties detecting medication effects with typically high drop-out rates, poor protocol adherence, small sample size, narrow range of doses evaluated, heterogeneity of participants/miss effects on subgroups (no biomarkers for predicting response),

Overly strict primary outcome measure (abstinence) may miss some therapeutic effects

?overly selective drug targets

Addiction
COMMENTARY

Commentary on Heinzerling *et al.* (2014): A growing methamphetamine dependence therapeutics graveyard

Methamphetamine remains one of the most widely used illicit substances in the world. This highly addictive psychostimulant has multiple sites of action in the brain, acting as a potent indirect agonist of dopamine, noradrenaline, and serotonin [1]. In addition to its intense euphoric effects, the acute hyperdopaminergic action of methamphetamine often results in heightened risk-taking behavior, severe aggression, and psychotic symptoms. Chronic methamphetamine abuse results in neurotoxic effects leading to psychological problems, including depression, anxiety, social isolation, psychosis, and neurocognitive deficits [2]. Despite an urgent need, there are currently no widely accepted psychological or pharmacological treatments for methamphetamine dependence, and certainly no medications approved by major regulatory bodies [3].

In recent years, several indirect dopamine agonists and partial agonists (e.g. aripiprazole, *d*-amphetamine, methylphenidate, and modafinil), opioid antagonists (e.g. naltrexone), and serotonin/norepinephrine re-uptake inhibitors (e.g. ondansetron and mirtazapine) have advanced to early-stage clinical trials [4]. Despite positive pre-clinical findings, most of these clinical studies have failed to provide any convincing results. At best, they show effectiveness in treating only specific subgroups of patients and highlight the necessity to collect thorough phenotypic information during screening in order to determine the patient groups most likely to respond to pharmacotherapeutic intervention. Furthermore, of the small number of drugs that have shown promise in treating methamphetamine dependence, many maintain significant abuse potential. Perhaps unsurprisingly, these drugs (e.g. *d*-amphetamine and methylphenidate) are members of the amphetamine-type stimulant family and act on similar, if not identical, neural pathways to methamphetamine itself [3]. Thus, the identification of effective therapeutics with low abuse potential is of critical importance.

In this issue, Heinzerling *et al.* [5] outline results from a double-blind, randomized, placebo-controlled 12-week treatment trial of bupropion for methamphetamine-dependent patients with less than daily use. This study aimed to replicate findings from two previously published clinical trials that showed efficacy of bupropion in treating a subgroup of patients with lower frequency of methamphetamine use at baseline [6,7]. Bupropion is a popular antidepressant agent with additional approval for aiding smoking cessation; it inhibits the re-uptake of dopamine and noradrenaline, increases dopamine in the synaptic cleft by blocking presynaptic dopamine transporter activity, and also targets noradrenaline transporters and nicotinic receptors. Importantly, although bupropion shares some of the pharmacodynamic properties of methamphetamine, it is far less potent and maintains substantially lower abuse potential than amphetamine-type stimulants [8]. It has been proposed that bupropion may treat withdrawal symptoms and cognitive deficits associated with methamphetamine dependence by increasing depleted cytoplasmic monoamine (e.g. dopamine and noradrenaline) concentrations [9].

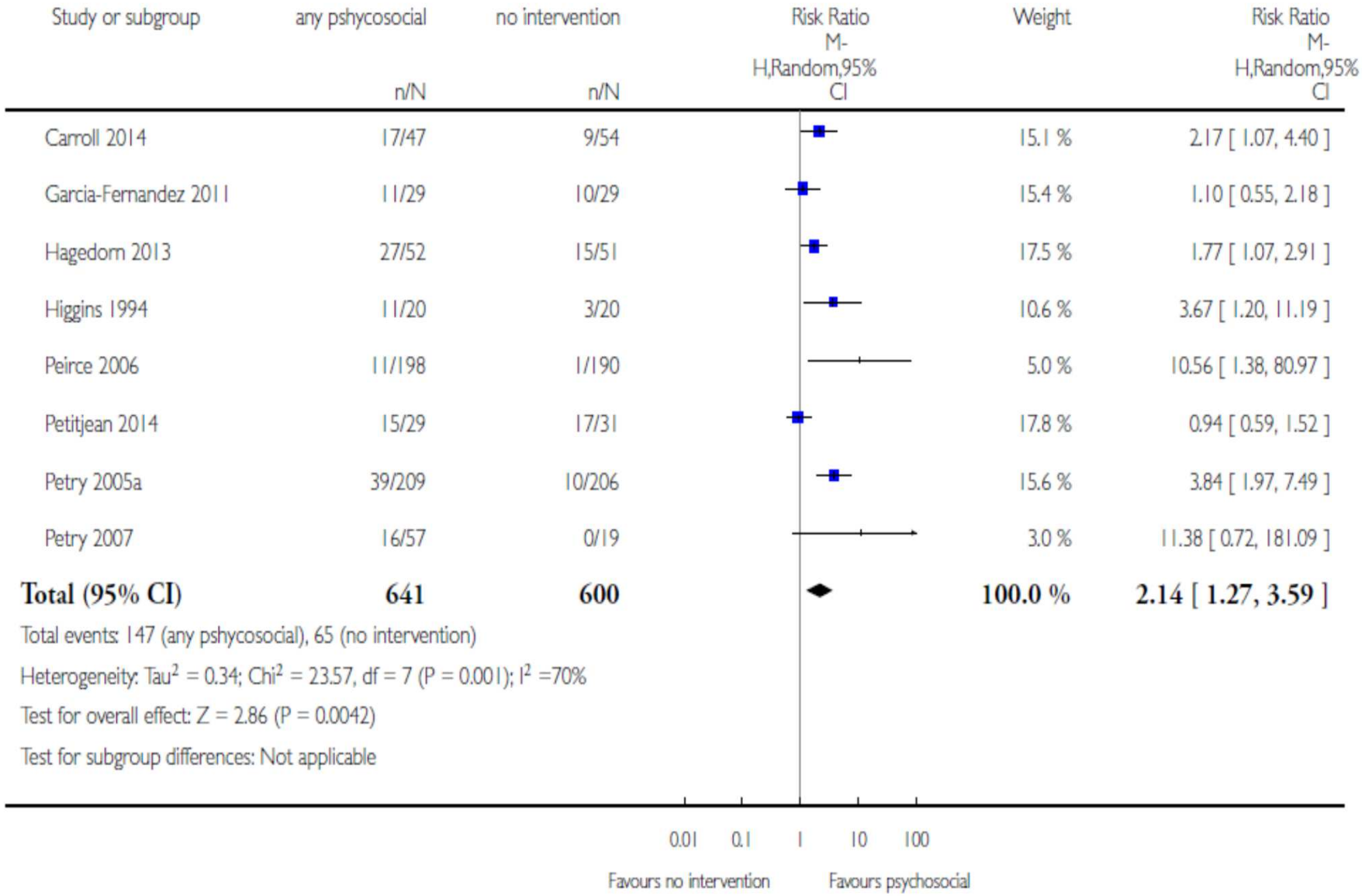
Unfortunately, Heinzerling *et al.*'s study provided no evidence for an effect of bupropion in treating methamphetamine dependence as measured by end-of-treatment abstinence. It is disappointing to consider that these findings may result in bupropion being added to the growing methamphetamine-dependence therapeutics graveyard alongside once-promising drugs such as aripiprazole, topiramate, and baclofen. However, Heinzerling *et al.*'s study provides opportunities for understanding some of the obstacles faced by scientists when designing clinical treatment trials for this patient population, and raises questions about how best to proceed with drug development in this field. The recruitment of methamphetamine users into tightly controlled clinical treatment trials presents many difficulties, including high rates of infectious disease, significant cognitive impairment, co-occurring psychiatric disorders, and polysubstance abuse among patients [10]. These challenges are evident in the sizeable exclusion rate in Heinzerling *et al.*'s study; that is, of the 294 participants screened only 84 were randomized to a treatment group. An additional challenge in the assessment of novel therapeutics is the selection of effective outcome measures. Heinzerling *et al.* used end-of-treatment abstinence—defined as having no drug metabolites in urine at weeks 11 and 12, as well as having missed no more than one urine screen per week throughout the study—as their primary outcome measure. Unsurprisingly, a significant amount of data was discounted due to a large number of participants (56%) not showing up consistently for urine sampling and the majority of patients being classified as medication non-adherent (68%). It is clear from this research that any possible benefits from bupropion would be impossible to determine with confidence due to the extreme difficulties in maintaining patient compliance to what is essentially a very straightforward clinical trial protocol.

There is no denying that methamphetamine users represent one of the most difficult-to-treat patient groups in all fields of medicine. We propose that the majority of drugs tested in early clinical studies, including

Efficacy of Psychosocial Treatments for Psychostimulant Misuse

- 2016 Cochrane meta-analysis of 52 clinical trials: **Psychosocial treatments (CBT, CRA, CM):**
  - **Reduced drop-out rate** (risk ratio (RR): 0.83, 95% confidence interval (CI) 0.76 to −0.91, 24 studies, 3393 participants; moderate quality evidence)
  - **Increased continuous abstinence at end of treatment** (RR: 2.14, 95% CI 1.27 to −3.59, 8 studies, 1241 participants, low quality)
  - **Did not increase continuous abstinence at longest follow-up** (RR: 2.12, 95% CI 0.77 to −5.86, 4 studies, 324 participants, low quality)
  - **Increased longest period of abstinence** (standardised mean difference: 0.48, 95% CI 0.34 to 0.63, 10 studies, 4 participants, high quality).
- Limitations: Most studies conducted in U.S. Most evaluated treatments for cocaine not ATS use. Most evaluated experimental psychosocial intervention as an add-on to treatment-as-usual; consequently, results may underestimate effects of psychosocial interventions

Psychosocial Treatments Improve Continuous Abstinence (end of treatment)



Behavioral or Psychosocial Treatments for ATS Addiction

- Many different treatments evaluated:
  - Cognitive Behavioral Therapy (CBT), Community Reinforcement Approach (CRA), Contingency Management, Behavioral Drug Counseling (using short-term behavioral contracts to activate patients and engage them in non-drug-related reinforcing behaviors), Twelve-Step Facilitation (TSF), Mindfulness-Based Relapse Prevention, Matrix Model
- Key factors affecting treatment outcome: Therapist characteristics, working alliance, treatment fidelity
- Key tasks and components:
  - Engage and retain patient in treatment
  - Educate patient about addiction and recovery
  - Foster optimism and engagement in non-drug-related, rewarding activities and relationships
  - Teach and rehearse relapse prevention and habit control strategies

Treatment Fidelity and Practice Matter

Compared weekly drug counseling alone (treatment as usual, TAU) and TAU with computer-based CBT

CBT: (i) understanding and changing patterns of substance use, (ii) coping with craving, (iii) refusing offers of drugs and alcohol, (iv) problem-solving skills, (v) identifying and changing thoughts about drugs and alcohol and (vi) improving decision-making skills.

CBT led to significantly greater quality of coping responses to high risk situations (end of treatment and 3-month follow-up) and

Quality of coping responses associated with drug use outcomes for those receiving CBT

CBT's effect on drug use outcomes partially due to improvement of quality of coping responses

Addiction

RESEARCH REPORT

doi:10.1111/j.1360-0443.2010.03076.x

Quality versus quantity: acquisition of coping skills following computerized cognitive–behavioral therapy for substance use disorders

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ABSTRACT

Aims To evaluate the changes over time in quality and quantity of coping skills acquired following cognitive behav-ioral therapy (CBT), and examine potential mediating effects on substance use outcomes. **Design** A randomized controlled trial (RCT) evaluating the effectiveness of a computerized version of CBT (CBT4CBT) as an adjunct to standard out-patient treatment over an 8-week period. **Setting** Data were collected from individuals seeking treat-ment for substance dependence in an out-patient community setting. **Participants** Fifty-two substance abusing individuals (50% African American), with an average age of 42 years, and a majority reporting cocaine as their primary drug of choice. **Measurements** Participants' responses to behavioral role-plays of situations associated with high risk for drug and alcohol use were audio-taped and rated independently to assess their coping responses. **Find-ings** There were statistically significant increases in mean ratings of the quality of participants' coping responses for those assigned to CBT4CBT compared to treatment as usual, and these differences remained significant 3 months after treatment completion. Moreover, quality of coping responses mediated the effect of treatment on participants' duration of abstinence during the follow-up period. **Conclusions** These findings suggest that assignment to the computerized CBT program improved participants' coping skills, as measured by independent ratings of a role-playing task. It is also the first study to test and support quality of coping skills acquired as a mediator of the effect of CBT for substance use.

Keywords CBT, computer-assisted therapy, coping skills, mediator, substance use.

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Submitted 17 November 2009; initial review completed 22 February 2010; final version accepted 30 April 2010

Providing High Fidelity Behavioral Treatments

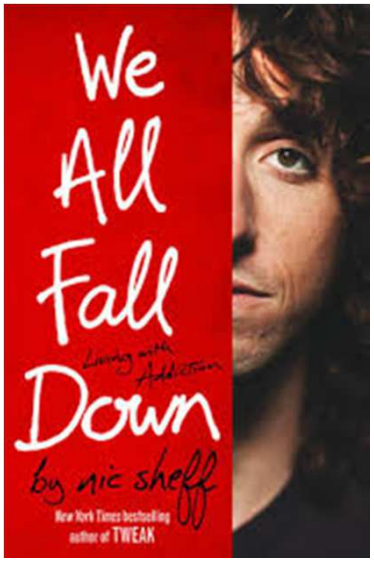
- Learning to provide the new treatment is hard work, just like recovery!
- It involves learning and consolidating new habits and not falling back into old ones
  - Stress of clinical encounter can lead therapist to revert to old habits
- It takes time and practice to consolidate learning and new practices (in addition to lectures, seminars or workshops)

High Fidelity Behavioral Contracting & Contingency Management

- Behavioral contracts: short-term, achievable goals
  - Return for counseling and treatment
  - Take small, persistent steps to engage in non-drug-related, rewarding social, family, recreational, or work activities
- Goal achievement is reinforcing and improves self-esteem/efficacy
- Contingency management:
  - Efficacy depends on consistency, salience, immediacy of reinforcement
  - Positive reinforcement works better than punishment
  - Learning occurs over time
  - Mobilize family to provide tangible and non-tangible rewards (e.g., special meals or enjoyable family activities)

Practical Clinical Considerations

- Behavioral and psychosocial treatments improve outcomes
- Relapse common even after long abstinence
  - Long-term treatment, recovery support services critical
  - Recovery Management Check-ups to reengage in treatment
  - Bad habits easy to fall into. Good habits harder and take longer to develop and strengthen, often with slips back before new, healthy habits consolidate
- Treat co-occurring psychiatric disorders—amphetamine-induced psychosis, bipolar disorder, depression



Nic Sheff's meth run continued for more than two years, until he entered another rehab program and subsequently wrote his highly acclaimed first memoir, *Tweaked*. While drawing huge crowds on his book tour, Nic relapsed again.

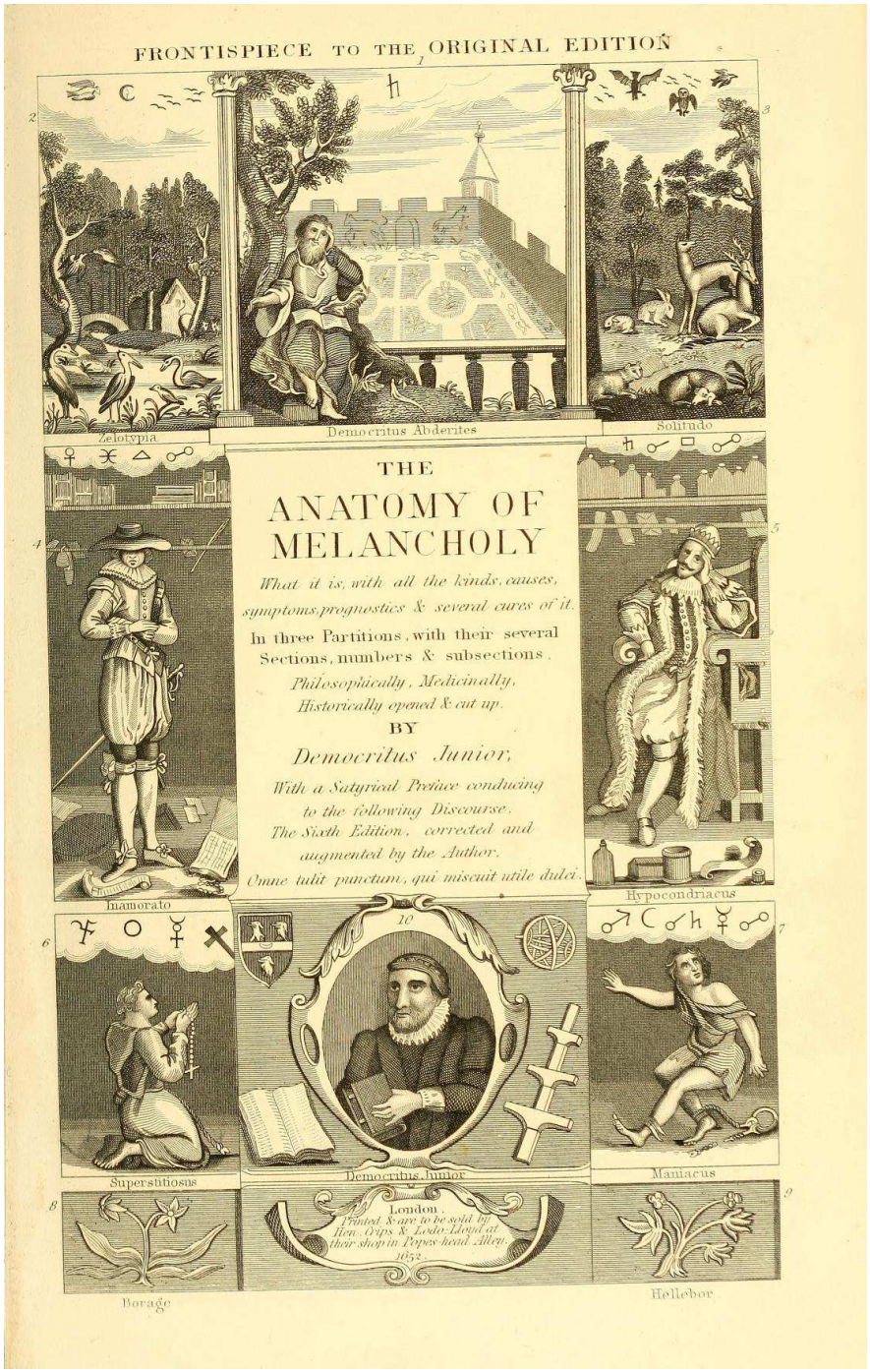
"But I didn't relapse as bad as I had before. And I definitely didn't enjoy it anywhere near as much as I used to. There was nothing fun and carefree about getting high. I knew the damage I was causing. It was impossible to keep lying to myself about it. And I honestly couldn't get into my relapse. I was taking pills every day and I knew I couldn't stop on my own, but there was really nothing enjoyable about it at all. Plus, I could see so clearly where it was going to lead. I could see myself spiraling down. So I did something that would have seemed pretty much impossible ever before. I called my dad…. I was expecting him to be all angry and pissed off and blaming…. But what he said to me was, "Nic, I'm so sorry. I'm so sorry that you have to go through this. And I'm sorry this is so hard for you."

- “I couldn’t believe it. Hell, I started totally crying. ‘Cause it was true, you know, and he understood. I didn’t want to be an addict. This wasn’t something I was doing ‘cause it was a ton of fun and I was just flipping the whole world off all the time, being like, “Fuck you, I’m having a good time and I don’t care about anything else.” It wasn’t like that at all. The truth was, I was in a whole lot of pain and so I’d reach out to drugs to try’n make myself feel better, and then I’d end up being enslaved by the drugs—starting the cycle all over again. Because once I started, that was it: the addiction would take hold. My dad understood that. He’d stopped blaming me. And, in a way, well, I guess that allowed me to stop blaming myself.” (Nic Sheff, The Fix, 8/5/11)

The Goal of Treatment?

Switch from tunnel vision goal of getting/using drug

To this: Engaging in life's other pleasures



- Melancholy: “a common infirmity of body and soul…such a one…hath as much need of spiritual as a corporal cure” and “require a whole physician. A divine in this compound mixed malady can do little alone, a physician in some kinds of melancholy much less, both make an absolute cure.”
- Heeding the drumbeat of methamphetamine or put to flight by the noise/memory of Zisca’s drum: Our role as physicians/therapists is to stick by our patients, maintain optimism, provide guidance, offer promising therapies (psychosocial or medication), and work to develop better treatments.