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The Role of Guanfacine as a Therapeutic Agent to Address Stress-related Pathophysiology in Cocaine Dependent Individuals

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Abstract

The pathophysiology of cocaine addiction is linked to changes within neural systems and brain regions that are critical mediators of stress system sensitivity as well as behavioral processes associated with the regulation of adaptive goal-directed behavior. This is characterized by the up-regulation of core adrenergic and corticotrophin releasing factor (CRF) mechanisms which subserve negative affect and anxiety and impinge upon intracellular pathways in the prefrontal cortex underlying cognitive regulation of stress and negative emotional state. Not only are these mechanisms essential to the severity of cocaine withdrawal symptoms, and hence the trajectory of clinical outcome, but they may also be particularly pertinent to the demography of cocaine dependence. The ability of guanfacine to target overlapping stress, reward and anxiety pathophysiology suggests that it may be a useful agent for attenuating the stress and cue-induced craving state in women especially, but also in men. This is supported by recent research findings from our own laboratory. Additionally, the ability of guanfacine to improve regulatory mechanisms that are key to exerting cognitive and emotional control over drug seeking behavior also suggest that guanfacine may be an effective medication for reducing craving and relapse vulnerability in many drugs of abuse. As cocaine dependent individuals are typically polydrug abusers, and women may be at a greater disadvantage for compulsive drug use than men, it is plausible that medications which target catecholaminergic fronto-striatal inhibitory circuits and simultaneously reduce stress system arousal may provide added benefits for attenuating cocaine dependence.

Introduction

While cocaine dependence is one of the most preventable health care problems in the US, no effective FDA-approved medication currently exist which addresses the high rates of craving and cocaine relapse (Kang et al., 1991; M. S. O'Brien & Anthony, 2005; R. Sinha, 2001). This may be due in part, to many tested medications showing high abuse potential and focusing predominantly on targeting reward attenuation (Amato et al., 2011; Sofuoglu, 2010; Vocci & Ling, 2005). On the basis of prior findings, we propose that affect and behavioral regulation in the face of both internal and external stressors may also represent a

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process integral to the acquisition, maintenance, and outcome of dependence for multiple drugs of abuse in both men and women (Albein-Urios et al., 2012; Carelli & West, 2013; H. C. Fox, Hong, et al., 2009; Koob & Volkow, 2010). As such, these processes may provide effective targets for medications development. This is important in terms of the demography of cocaine use. First, cocaine dependent individuals typically abuse multiple drugs, including nicotine and alcohol (Patkar et al., 2006; Wiseman & McMillan, 1998). Moreover, cigarette smoking is more prevalent in cocaine abusers than alcohol and marijuana (Budney, Higgins, Hughes, & Bickel, 1993; Sees & Clark, 1991) and may serve to increase craving (Epstein, Marrone, Heishman, Schmittner, & Preston, 2010; Reid, Mickalian, Delucchi, Hall, & Berger, 1998) and relapse vulnerability (Dackis & O'Brien, 2001; McKay, Alterman, Mulvaney, & Koppenhaver, 1999). Second, recent changes in gender socialization and gender roles as well as recent gains within the labor force (Bullers, 2012) mean that the traditional gender gap in both licit and street drug consumption has become much smaller (Degenhardt et al., 2008). For example, increases in the prevalence of single, divorced women either living alone or cohabiting as well as a greater number of women in non-traditional occupations have been associated with gender convergence in substance use (McPherson, Casswell, & Pledger, 2004). Moreover, a number of sex-specific risk factors (e.g. stress and sex steroid hormones) set women at a disadvantage for compulsive drug use (Becker & Hu, 2008; Fattore, Altea, & Fratta, 2008) and the negative consequences of drug use in females often appear accelerated or “telescoped” (Back, Brady, Jackson, Salstrom, & Zinzow, 2005). As such, the development of an FDA approved medication that targets this vulnerability in women as well as men who abuse multiple drugs alongside cocaine, is imperative.

On this basis, we present data on the non-stimulant alpha-2 adrenergic agonist Guanfacine HCL, with regard to its role as a viable agent for a) attenuating many of the sex-specific, anxiety and stress-related factors underpinning craving and relapse for cocaine and other substances (H. C. Fox, Hong, Siedlarz, & Sinha, 2008; H. C. Fox, Hong, et al., 2009) and b) strengthening cognitive, behavioral and emotional regulatory processes associated with improved prefrontal network connectivity (Arnsten, 2011b; Arnsten & Jin, 2012; Arnsten & Pliszka, 2011) and substance-abuse outcome (Blume & Marlatt, 2009; Williams, Simpson, Simpson, & Nahas, 2009; Witkiewitz & Marlatt, 2005). Initially, therefore it may be necessary to discuss the relationship between stress system sensitization, anxiety, prefrontal control mechanisms and compulsive cocaine use in order to subsequently determine the efficacy of guanfacine in targeting stress and negative emotion sensitization and regulation through the mediation of peripheral and central sympathetic arousal (Scahill et al., 2009; M. Wang, Ji, & Li, 2004). Research data from our laboratory will be presented in order to assess the effects of guanfacine on stress system dysregulation and regulatory function in co-morbid cocaine dependent men and women.

Stress system dysregulation underlying compulsive cocaine seeking, cocaine craving and relapse

Cocaine dependence has been described as a chronic stress state (H. C. Fox, Hong, et al., 2009; Goeders, 2002; R. Sinha, 2001) characterized socially by a high prevalence of

cumulative lifetime stress (R. Sinha, 2008), early childhood abuse and traumatic stress (Hyman et al., 2008; Hyman, Paliwal, & Sinha, 2007; Viola, Tractenberg, Pezzi, Kristensen, & Grassi-Oliveira, 2013), and bio-physiologically as comprising decreased dopamine (DA) activity in the mesolimbic pathways (Everitt & Wolf, 2002; Kalivas & Stewart, 1991; Piazza & Le Moal, 1997) and a recruitment of the brain stress systems which include mutual anxiogenic pathophysiology (Dunn & Swiergiel, 2008b; Dunn, Swiergiel, & Palamarchouk, 2004; Koob, 2009a). Due to the overlap in brain stress and reward pathways, these neuroadaptations have been associated with the motivational effects of cocaine (Koob, Caine, Markou, Pulvirenti, & Weiss, 1994; Kuhar, Ritz, & Boja, 1991), including behavioral sensitization (I. E. de Jong, Steenbergen, & de Kloet, 2009; Shalev, Grimm, & Shaham, 2002), persistent cocaine craving (H. C. Fox, Hong, Siedlarz, et al., 2008; R. Sinha et al., 2003) and cocaine seeking (Anderson & Pierce, 2005; Bossert, Ghitza, Lu, Epstein, & Shaham, 2005; R. Sinha, Garcia, Paliwal, Kreek, & Rounsaville, 2006).

The activation of the dopaminergic pathway from the ventral tegmental area (VTA) to the nucleus accumbens (NAc) is thought to be critical for cocaine reward (Bardo, 1998; Johanson & Fischman, 1989; Koob, 1992; Tzschentke, 2001). Specifically, both repeated stress and the maintenance of psychostimulant dependence have been associated with alterations to these mesocorticolimbic DA systems (Everitt & Wolf, 2002; Kalivas & Stewart, 1991; Piazza & Le Moal, 1997) particularly in the nucleus accumbens and the medial prefrontal cortex (Koob et al. 1987; Di Chiara & Imperato 1988; Kalivas & Duffy 1990; Koob & Le Moal 1997) via glutamatergic corticolimbic circuitry (Everitt & Robbins, 2005; Saal, Dong, Bonci, & Malenka, 2003) as well as the effects of CRF stress systems on glutamate and dopamine release in the VTA (Ungless, Whistler, Malenka, & Bonci, 2001; B. Wang et al., 2005). According to the allostatic model of addiction a sustained increase in the secretion over time of dopamine may culminate in increased allostatic load and result in a decrease in the function of normal reward-related neurocircuitry and persistence or sensitivity of the stress-related systems (Koob & Le Moal, 2005). Furthermore, chronic cocaine-related adaptations in the noradrenergic system have been implicated in the withdrawal/abstinence and compulsive drug seeking aspects of cocaine dependence (G. Aston-Jones & Kalivas, 2008). Both animal and human studies have shown that neuroadaptations to these core stress systems and the persistent nature of an enhanced stress state may modulate the propensity for individuals to misuse many drugs of abuse including cocaine, alcohol, opioids and nicotine (I. E. M. De Jong & De Kloet, 2004; H. C. Fox, Hong, et al., 2009).

Growing preclinical research has shown that the responsiveness of central noradrenergic systems to stress as well as central activation of noradrenergic transmission, via α_2 antagonism, reinstates extinguished cocaine seeking (Feltenstein & See, 2006; Lee, Tiefenbacher, Platt, & Spealman, 2004; Mantsch et al., 2010; Vranjkovic, Hang, Baker, & Mantsch, 2012). Research from our own laboratory has also indicated that in cocaine dependent individuals, exposure to stressors results in 15% increases in plasma norepinephrine and 20–25% increases in plasma epinephrine, with little indication of normalization/return to baseline even 1 hour post stress induction (R. Sinha et al., 2003). Moreover, these increases in catecholamines were accompanied by augmented craving, anxiety and associated with a greater chance of relapse. Findings from subsequent studies

have also indicated that elevations in sympathetic and HPA axis tone are associated with a dysregulated emotional, interoceptive and biophysiological response to stress provocation, shown to characterize the craving state and predict increased subsequent relapse risk in both cocaine and alcohol dependent individuals (Bergquist, Fox, & Sinha, 2010; Chaplin et al., 2010; H. C. Fox, Bergquist, Hong, & Sinha, 2007; H. C. Fox, Bergquist, Peihua, & Rajita, 2010; H. C. Fox, Hong, Paliwal, Morgan, & Sinha, 2008; R. Sinha, Fox, et al., 2011; R. Sinha et al., 2006). As increased stress-related adrenergic sensitivity may be involved in the transition from controlled to compulsive drug-seeking in cocaine dependent individuals, medications such as guanfacine, which block central norepinephrine activity, may also serve to attenuate stress-related cocaine craving and relapse rates.

The role of anxiety symptomatology in compulsive cocaine-seeking, cocaine craving and relapse

During early recovery from cocaine, clinical studies also highlight persistent and dysfunctional aspects of anxiety processing in dependent individuals (Chaplin et al., 2010; H. C. Fox, Hong, Paliwal, et al., 2008; Harris & Aston-Jones, 1993; Kampman, Volpicelli, et al., 2001; Lejuez et al., 2008). Although there is a paucity of data regarding the prevalence of co-morbid anxiety disorders, possibly due to the fact that cocaine is less commonly thought to be consumed in individuals with a pre-disposition for anxiety, a NESARC survey documented that 31% of individuals with cocaine dependence reported lifetime anxiety disorders (Conway, Compton, Stinson, & Grant, 2006) and paranoia has also been documented as occurring in 68% to 84% of patients using cocaine (Morton, 1999). The clinical relevance of this is highlighted by the fact that severity of withdrawal-related anxiety has been found to impact the course, treatment outcome, and prognosis of both syndromes (Naifeh, Tull, & Gratz, 2012; O'Leary et al., 2000) (Sanchez-Hervas & Llorente del Pozo, 2012), particularly in women (Ambrose-Lanci, Sterling, & Van Bockstaele, 2010; Back et al., 2005; Chaplin, Hong, Bergquist, & Sinha, 2008; H. C. Fox & Sinha, 2009). In both genders, higher resting anxiety in alcoholics has been shown to be associated with greater stress and cue-induced alcohol craving and anxiety and higher ACTH and cortisol levels (R Sinha, Hong, Seo, Fox, & Bergquist, 2010). Higher stress-induced anxiety also predicts less treatment engagement in after care following inpatient treatment (R. Sinha, Fox, et al., 2011). Notably, in substance abusing women, enhanced emotional and anxiety-related sensitivity to stress has been a dissociable and defining factor of the craving state compared with men and may reflect a vulnerability pathway to relapse in women. For example, significantly elevated stress-induced anxiety ratings documented in women compared with men have been observed in social drinkers (Chaplin et al., 2008), alcoholics (H. C. Fox et al., 2007) and co-morbid cocaine and alcohol dependent individuals (H. C. Fox, Hong, et al., 2009). In all cases, this sensitized anxiety response was accompanied by significantly higher ratings of both stress-induced and drug cue-induced craving.

With regard to treatment development, it is notable that despite chronic cocaine-related adaptations to core stress and anxiety pathophysiology, few studies have focused directly on treating withdrawal and stress-related anxiety sensitivity. Chronic cocaine use as well as abuse of other substances, including alcohol and nicotine all reflect up-regulation of CRF

and NE feed-forward circuitry (Smith & Aston-Jones, 2008) (Marcinkiewicz et al., 2009), as well as elevated noradrenergic transporter binding in the hypothalamus, brainstem, hippocampus, midbrain and limbic forebrain regions and a desensitization of the α_2 -adrenoceptors in the prefrontal cortex (PFC) (Baumann, Milchanowski, & Rothman, 2004; Beveridge, Smith, Nader, & Porrino, 2005; Goldstein & Volkow, 2002; Porrino, Lyons, Smith, Daunais, & Nader, 2004). In addition, anxiety involves up-regulated extra-hypothalamic CRF and NE circuits involving the amygdala, bed nucleus of the stria terminalis (BNST) and down-regulated medial prefrontal circuits, which in turn, result in changes in stress-related pathways involving the hypothalamic paraventricular nucleus and locus coeruleus to construct a powerful 'feed forward' loop that contributes to increased anxiety and stress responses (Dunn & Berridge, 1990; Dunn & Swiergiel, 2008a; Dunn et al., 2004; Koob, 2009a) (Kushner, Abrams, & Borchardt, 2000).

Therefore, in addition to playing an integral role in underlying stress-induced craving, these central noradrenergic systems are also key in terms of inducing anxiety, dysphoria, and autonomous panic attacks during early withdrawal from cocaine (McDougle et al., 1994). For example, placebo-corrected adrenergic challenge using α_2 antagonist, yohimbine, has been shown to elicit elevated levels of norepinephrine metabolite, 3-Methoxy-4-hydroxyphenylglycol (MHPG), as well as augmented fear and panic attacks during early recovery in cocaine addicted individuals (McDougle et al., 1994). As such, adrenergic medications that focus on attenuating the up-regulation of central norepinephrine feed forward circuitry, known to underlie chronic cocaine use, withdrawal symptoms, craving, relapse vulnerability and mutual anxiety pathophysiology, may reduce stress-related compulsive cocaine seeking by targeting the negative anxiogenic reinforcing aspects of cocaine.

The role of guanfacine and α_2 receptor agonists in reducing stress-related anxiety, negative mood and compulsive drug seeking

Guanfacine is an α_2 adrenergic agonist, known to inhibit NE centrally (Shaham, Shalev, Lu, De Wit, & Stewart, 2003) by stimulating presynaptic α_2 -adrenergic receptors (Arnsten, 2007) as well as significantly reducing peripheral sympathetic stress system arousal response and drug seeking (Erb, Shaham, & Stewart, 1998) (Erb et al., 2000; Highfield, Yap, Grimm, Shalev, & Shaham, 2001). Enhancement of cognitive performance by guanfacine may be associated with the drug's ability to mimic the enhancing effects of norepinephrine at postsynaptic α_2A -receptors in the PFC (Arnsten, 2011a; Ramos & Arnsten, 2007) and decreasing excitatory postsynaptic transmission in the medial prefrontal cortex (mPFC) and bed nucleus of the stria terminalis (BNST) (Ji, Ji, Zhang, & Li, 2008; Le et al., 2011; Shields, Wang, & Winder, 2009). Although the specific mechanisms of action are not fully known with regard to the anxiolytic effects of guanfacine, the indirect down-regulation of dopamine turnover has been documented (Jetmalani, 2010), as well as feedback inhibition of noradrenaline release via presynaptic α_2 receptors in humans (Mosqueda-Garcia, 1990; Sorkin & Heel, 1986). It may therefore be of benefit to cocaine dependent individuals with a susceptibility to up-regulated stress dysregulation secondary to chronic cocaine abuse as well as in women whose stress-related cocaine craving state may

typically be characterized by elevated levels of anxiety symptomatology. In support of this, there is a burgeoning body of research which, taken together, indicates that chronic relapse-related adaptations in the noradrenergic system can be reversed by decreasing norepinephrine centrally thereby reducing sympathetic arousal and anxiety, and ultimately attenuating compulsive drug seeking in cocaine dependence.

By down-regulating sympathomimetic outflow from the vasomotor center of the brain to the heart and stimulating peripheral alpha (2) receptors (Scahill, 2009; Sica, 2007) guanfacine may decrease the anxiogenic and negative reinforcing components of the craving state for several drugs of abuse, including cocaine. Several animal studies have modeled this noradrenergic mediation of anxiety-like behavior which emerges after withdrawal of cocaine, predicts relapse (Ambrose-Lanci et al., 2010; Kampman, Volpicelli, et al., 2001; O'Leary et al., 2000), and is attenuated by alpha2 adrenergic receptor agonists. For example, several recent studies from the animal and human literature have examined the ability of alpha2 adrenergic agonists including guanfacine, clonidine and lofexidine to attenuate stress-induced craving, cocaine-seeking and relapse as well as other negative reinforcing components of the craving state including negative affect and anxiety (R. Sinha, Shaham, & Heilig, 2011). Shaham and colleagues have shown that α 2-adrenergic receptor agonists (clonidine, lofexidine, guanfacine) modulate the sympathetic stress response, decrease norepinephrine cell firing and release centrally (Shaham et al., 2003; R. Sinha, Fox, et al., 2011), as well as block footshock stress-induced reinstatement of cocaine seeking (Erb et al., 2000; Erb et al., 1998; Highfield et al., 2001). Clonidine at low doses has also been shown to block forced swim-induced reinstatement of cocaine in mice (Mantsch et al., 2010). In addition clonidine has been shown to block stress-induced reinstatement of speedball seeking (Highfield et al., 2001) and yohimbine-induced cocaine reinstatement after extinction (Lee et al., 2004). Guanfacine has also successfully attenuated cue-induced self administration of cocaine in laboratory rats (Smith & Aston-Jones, 2011)

A recent preclinical study by Buffalari and colleagues (Buffalari, Baldwin, & See, 2012), also examined the relationship between cocaine withdrawal anxiety symptoms with reinstatement in laboratory rats by using alpha-2 agonist guanfacine and alpha-2 antagonist yohimbine, to modulate anxiety and impact cocaine seeking. Findings indicated that anxiety-type behaviors, measured using the elevated plus maze and shock probe burying behavior, were significantly correlated with cocaine-primed reinstatement. In addition, yohimbine treatment increased reinstatement to cues while guanfacine reduced yohimbine-related reinstatement, emphasizing both the potential utility of withdrawal-related anxiety and related reinstatement of cocaine seeking as a target for medications development and guanfacine as a possibly treatment.

While the effects of guanfacine on drinking behaviors in humans have been less well studied, several studies have examined its effects on alcohol-seeking in laboratory animals. Furthermore, as alcohol dependence is highly co-morbid with anxiety-related disorders (Kessler et al., 1997; Schneider et al., 2001) and acute alcohol withdrawal and protracted abstinence involves noradrenergic dysregulation (Patkar et al., 2003; Patkar et al., 2004; Rasmussen, Wilkinson, & Raskind, 2006), it is likely that guanfacine may also provide a viable pharmacotherapeutic treatment for attenuating anxiety-related drinking, or co-morbid

drinking, in addicted humans. In support of this, early preclinical studies indicated that both clonidine and guanfacine were able to reduce ethanol intake in ethanol-preferring rats having free choice between 10% ethanol or water (Opitz, 1990) as well as attenuate the appearance and incidence of ethanol withdrawal symptoms (Parale & Kulkarni, 1986; Washton & Resnick, 1981). More recently, preclinical studies have also shown that activation of alpha2 adrenoceptors mediate stress and anxiety induced re-instatement of alcohol seeking. In one study, guanfacine was shown to attenuate yohimbine-induced reinstatement of alcohol in laboratory rats (Le et al., 2011) and in another, pre-treatment with lofexidine was observed to reduce stress-related reinstatement of alcohol seeking as well as decrease alcohol self-administration.

In terms of smoking, while several clinical and preclinical studies have assessed the effects of alpha2 adrenergic stimulation on stress-induced reinstatement and withdrawal related symptoms using clonidine and dexmedetomidine, the effects of guanfacine, *per se*, have not been well assessed. Despite this, early studies investigating the effects of alpha2 agonists on nicotine withdrawal-related symptoms served to highlight the salience of noradrenergic transmission in terms of underpinning the anxiolytic, negative reinforcing and possibly control-related aspects of craving. They also demonstrated the sex-specificity of noradrenergic mediation of the stress-related craving state. For example, Glassman and colleagues first showed that while clonidine demonstrated similar efficacy to alprazolam in reducing anxiety, tension, irritability, and restlessness during nicotine withdrawal in fifteen heavy smokers; only clonidine successfully reduced cigarette craving (Glassman, Jackson, Walsh, Roose, & Rosenfeld, 1984). In a slightly later study, Glassman and colleagues also showed that clonidine was significantly efficacious in reducing nicotine withdrawal and promoting smoking cessation in women as compared to men (Covey & Glassman, 1991; Glassman et al., 1988), and particularly in vulnerable women (Glassman et al., 1993). Recent preclinical research holds support for these studies showing that intra central nucleus of the amygdala (CeA) infusion of clonidine and dexmedetomidine in rats, attenuates stress-induced reinstatement of nicotine seeking, possibly via synaptic connections between noradrenergic terminals and CRF neurons (Yamada & Bruijnzeel, 2011).

A recent meta-analysis reviewing twenty-four studies comprising a total of 1631 participants, also investigated the efficacy of alpha2 agonists for the management of opioid withdrawal (Gowing, Farrell, Ali, & White, 2009)(Gowing et al., 2009). Overall findings indicated that the alpha2-adrenergic agonists, clonidine and lofexidine were both more effective than placebo in managing withdrawal from heroin; although chances of completing withdrawal were no different to those associated with reducing doses of methadone (Gowing et al., 2009). Importantly, however, many clinical trials have indicated that cocaine use is also prevalent in approximately 50% of individuals receiving opioid maintenance treatment (Castells et al., 2009; Grella, Anglin, & Wugalter, 1995; Kosten, Rounsaville, & Kleber, 1987; Peles, Kreek, Kellogg, & Adelson, 2006). Furthermore, the co-abuse of cocaine is known to be associated with poorer outcomes in heroin users, suggesting that addressing both cocaine and opioid dependence may be an optimal strategy. In view of this, findings from our own laboratory indicated that lofexidine successfully attenuated stress and drug

cue related opiate and cocaine craving in opiate dependent individuals also treated with naltrexone (R. Sinha, Kimmerling, Doebrick, & Kosten, 2007).

Guanfacine as a medication for substance abuse compared with other alpha2 adrenergic agonists

In view of these previous clinical and preclinical findings, we subsequently proposed to examine the effects of guanfacine on stress system adaptations underlying the craving state in cocaine dependent individuals who also abuse alcohol and nicotine. Compared with other alpha-2 adrenergic agonists, such as clonidine and lofexidine, guanfacine was deemed to have a more preferable pharmacodynamic profile (Balldin, Berggren, Eriksson, Lindstedt, & Sundkler, 1993; Bearn, Gossop, & Strang, 1996; Chappell et al., 1995; Kahn, Mumford, Rogers, & Beckford, 1997). First, early preclinical studies have indicated that guanfacine is 8 to 10 times more selective than clonidine for alpha2 adrenoceptors (Jarrott, Louis, & Summers, 1982; Seedat, 1985; Summers, Jarrott, & Louis, 1981). Second, clonidine has consistently shown greater side effects compared with both guanfacine and lofexidine in terms of orthostatic hypotension, sexual dysfunction and withdrawal syndrome following cessation, (Gish, Miller, Honey, & Johnson, 2010; Sorkin & Heel, 1986). In addition, guanfacine has been shown to enhance selective executive and inhibitory control processes underlying impulsivity and other behavioral factors associated with outcome in substance abuse (Brady, Gray, & Tolliver, 2011; Sofuoglu, DeVito, Waters, & Carroll, 2013) in non-human primates (Franowicz & Arnsten, 2002), healthy volunteers (Jakala, Riekkinen, Sirvio, Koivisto, Kejonen, et al., 1999; Jakala, Riekkinen, Sirvio, Koivisto, & Riekkinen, 1999) and other clinical populations (Swartz, McDonald, Patel, & Torgersen, 2008). Conversely, although few studies assessing the cognitive profile of lofexidine have been conducted, one study documented decreased cognitive efficiency after lofexidine administration compared with placebo, in fourteen opioid dependent individuals stabilized on methadone (Schroeder et al., 2007). As our studies comprised experimental paradigms conducted across only a few days, we also proposed to use the generic preparation of guanfacine, rather than extended release formula.

Consistent with our previous studies (H. C. Fox et al., 2006; H. C. Fox, Hong, Siedlarz, et al., 2008; H. C. Fox et al., 2005; R. Sinha et al., 2009), we used a personalized guided imagery paradigm in order to induce a distress state in twenty-nine early abstinent treatment-seeking substance abusing men and women. Of the twenty-nine cocaine dependent individuals, seventeen were randomized to guanfacine (2mg or 3 mgs) and twelve to placebo after a 12-day dosing titration period. Two doses were incorporated into the paradigm as there was little previous research regarding the optimal guanfacine dosing levels for drug craving-related outcomes. The laboratory challenge studies were conducted following approximately 21 days of abstinence during which patients resided on an in-patient treatment research unit. All participants were exposed to three 10-min guided imagery conditions (stress, cocaine cue, combined stress and cocaine cue), one per day, consecutively in a random, counterbalanced order. Subjective craving, anxiety and arousal as well as cardiovascular output were assessed at baseline, immediately following imagery

exposure and at repeated recovery time-points until one hour post imagery (H. C. Fox, Seo, et al., 2012).

As anticipated, guanfacine attenuated sympathetic tone in cocaine dependent individuals, characterized by significantly lower heart rate levels ($p=.001$) and blood pressure (SBP: $p=.002$; DBP: $p=.01$) compared with the placebo group. In terms of phasic response, the guanfacine group also demonstrated reduced cue-related cocaine craving and nicotine craving following exposure to all three imagery conditions. In addition, negative reinforcing effects of cocaine, such as anxiety and arousal were also decreased in the guanfacine group compared with the placebos following exposure to the cocaine cue imagery condition (see Figure 1a–d) (H. C. Fox, Seo, et al., 2012). Although guanfacine did not impact phasic heart rate and blood pressure response, its efficacy in lowering autonomic tone may itself represent a key sympathetic mechanism underlying the changes in subjective response to stress and cue. For example, up-regulated heart rate and blood pressure are often characteristic of the non-specific physiological adaptations observed in chronic cocaine dependence, especially during early abstinence (H. C. Fox, Hong, et al., 2009). In addition, high tonic autonomic arousal per se, may act as a cue or trigger for cocaine craving and increased anxiety during early abstinence (Kampman et al., 2006). As such, the guanfacine-related decrease in peripheral physiological arousal observed in this study may contribute to decreasing subjective anxiety, arousal and craving response to provocation.

While the combined doses of 2mgs and 3mgs of guanfacine seemed to produce more robust effects in terms of attenuating cue related cocaine craving and accompanying negative reinforcing aspects, a preliminary dose analysis showed that the higher 3 mg dose of guanfacine was also beneficial in decreasing stress-induced cocaine craving, stress-induced alcohol craving and stress-induced nicotine craving (see Figure 2).

As an extension of the same project, additional data was subsequently collected in 27 cocaine dependent males and 13 cocaine dependent females in order better ascertain sex differences in these cocaine-related stress system neuroadaptations (H.C. Fox, Morgan, & Sinha, in press). As mentioned earlier, many prior studies show robust sex variation in the stress and cue-induced craving state (Brady et al., 2006; Colamussi, Bovbjerg, & Erblich, 2007; H. C. Fox, Hong, et al., 2009; Kajantie & Phillips, 2006; Saladin et al., 2012; Waldrop, Back, Verduin, & Brady, 2007; Waldrop et al., 2010) with women generally reporting significantly higher ratings of anxiety, stress and negative affect (Back et al., 2005; Chaplin et al., 2008; H. C. Fox, Hong, Siedlarz, et al., 2008; H. C. Fox & Sinha, 2009) alongside unique sympathetic dysregulation patterns compared with those of men (H. C. Fox et al., 2006; H. C. Fox, Hong, et al., 2009). Preclinical studies have also shown sex diversity, with female rats displaying longer HPA axis activation and greater norepinephrine response to stressors compared to male rats (Heinsbroek et al., 1990; Heinsbroek, Van Haaren, Van de Poll, & Steenbergen, 1991). We therefore hypothesized that guanfacine's effects would be sex-specific with women potentially showing enhanced benefit from adrenergic medication compared with males.

In response to the three provocation conditions described above, multiple medication by sex interactions revealed a significantly greater benefit of guanfacine in cocaine dependent

women as compared to men (Figure 3). Guanfacine significantly attenuated cocaine craving, alcohol craving, anxiety, and negative emotion in women administered guanfacine compared with women given placebo. This discrepancy was not observed between the male guanfacine and placebo groups. Guanfacine also significantly reduced sympathetic tone as well as stress-induced and cue-induced blood pressure and nicotine craving in both males and females.

The significant reduction observed in craving, anxiety and negative emotion in the guanfacine female group stemmed predominantly from the significantly higher ratings reported in all measures by the placebo females compared with both the guanfacine females and the placebo males. This is again consistent with extensive research showing that both cocaine dependent and non-dependent females report significantly higher, anxiety, stress and negative mood during distress compared with males, (Back et al., 2005; Chaplin et al., 2008; Eisenberg et al., 1991; H. C. Fox, Hong, Paliwal, et al., 2008; Kelly, Tyrka, Anderson, Price, & Carpenter, 2008) and experience negative emotions at a greater frequency and intensity than men (Craske, 2003; Nolen-Hoeksema, Larson, & Grayson, 1999). Findings also support clinical data indicating that US women are markedly over-represented with regard to stress-related psychopathology, including anxiety and mood disorders (Blanchard, 1998; Brady, Grice, Dustan, & Randall, 1993; McCance-Katz, Carroll, & Rounsaville, 1999; Rounsaville et al., 1991). In view of this, potentiated stress and cue-related negative mood and anxiety might represent a salient motivational component of the provoked craving state in dependent women (Chaplin et al., 2008; H. C. Fox, Hong, et al., 2009; H. C. Fox & Sinha, 2009). As an adrenergic agonist, guanfacine targets core anxiety-related CRH and NE sympathetic pathways (Arnsten, 2011a; Sica, 2007; van Zwieten, 1999), and this mechanism may therefore underlie its efficacy in reducing anxiety, negative emotion and thus, craving for multiple drugs of abuse in dependent females.

In summary, research from both our own laboratory and those of others demonstrates that alpha-2 adrenergic agonists such as guanfacine may represent a viable medication for reducing peripheral autonomic and emotional arousal mechanisms pertinent to stress-related compulsive cocaine seeking, especially in cocaine dependent women. It is likely that such attenuation of stress system arousal may be related to central noradrenergic mediation of anxiety-like behavior which emerges after the withdrawal of cocaine (Buffalari et al., 2012; El Hage et al., 2012; Kampman, Alterman, et al., 2001; Kampman et al., 1998), is associated with craving and relapse factors (Ahmadi, Kampman, & Dackis, 2006; Ahmadi et al., 2009; Erb, 2010; H. C. Fox, Hong, Siedlarz, et al., 2008) and is sensitive to gender (Ambrose-Lanci et al., 2010; Back et al., 2005; Chaplin et al., 2008; H. C. Fox, Hong, Siedlarz, et al., 2008). This is clinically important as anxiety sensitivity may be enhanced in females (Chaplin et al., 2008; H. C. Fox, Hong, Siedlarz, et al., 2008; Frye, Petralia, & Rhodes, 2000) and be directly related to their increased relapse severity compared with men (Ambrose-Lanci et al., 2010). Furthermore, findings from this initial body of research are particularly salient as polydrug use is a common feature of cocaine dependence (McCance-Katz et al., 1999; Patkar et al., 2006) and women are especially vulnerable to the acquisition, maintenance and outcome of addiction (Quinones-Jenab, 2006).

Prefrontal regulatory function and cocaine dependence

In addition to reducing peripheral and central arousal mechanisms underlying the affective and anxiolytic aspects of cocaine addiction, guanfacine is also a powerful modulator of catecholaminergic fronto-striatal regulatory circuits (Arnsten & Li, 2005; Ma, Arnsten, & Li, 2005). Dysregulation of emotion and desires/cravings is related to a general diminished ability to recruit frontal systems including the anterior cingulate and prefrontal cortex (Goldstein & Volkow, 2002; Kalivas & Volkow, 2005; Paulus, Tapert, & Schuckit, 2005; R. Sinha, 2001) and often underpins the eventual loss of control over drug seeking and consumption. For example, the ability to regulate affect and desires may underlie thoughtful, more adaptive goal-directed behaviors (Gallagher, McMahan, & Schoenbaum, 1999; Kuhl & Koole, 2004; Tice, Bratslavsky, & Baumeister, 2001), including planning, organizational skills, self control, self-monitoring, and decision making which, in turn, are necessary to change substance abuse behaviors and promote better treatment outcome (Blume & Marlatt, 2009; Verdejo-Garcia & Perez-Garcia, 2007). Specifically, poor inhibitory control processes may be a central mechanism of distractibility and impulsive behaviors (Fishbein et al., 2005; Marlatt & Gordon, 1985; Witkiewitz & Marlatt, 2005) and impulsive behavior may cause one to use cocaine despite the negative consequences (Garavan & Hester, 2007). In addition, poor cognitive control may also be related to an inability to resist environmental cues which might trigger drug use (de Wit & Richards, 2004).

Not only is cognitive, emotional and behavioral self-regulation key to characterizing and determining the trajectory of many substance use disorders (Blume & Marlatt, 2009), but regulatory strategies are psychologically effortful and under demanding or stressful situations volitional behavior may be jeopardized due to a reduction in either mental and/or motivational capacity (Kuhl & Koole, 2004). According to theorists, this may be the result of conflict in different regulatory goals. While the self-monitoring of impulses and urges may be beneficial for an individual to focus on longer-term priorities; uncontrollable, cumulative and persistent stressors shift attention towards more immediate often pleasure-seeking goals (Baumeister, Stillwell, & Heatherton, 1994). Notably then, managing such conflicts in regulatory goals has vital implications for treatment attrition, particularly in a population of dependent individuals defined by a high prevalence of lifetime cumulative stress (Ansell, Rando, Tuit, Guarnaccia, & Sinha, 2012) and chronic stress system up-regulation (H. C. Fox et al., 2010; H. C. Fox, Hong, et al., 2009), where stress may literally deplete the psychological resources required for effective emotional and behavioral control.

In view if this, substance dependent individuals may be extremely vulnerable to stress-induced prefrontal impairment. For example, cocaine use impinges functionally (Goldstein et al., 2009) structurally (Franklin et al., 2002; Lim, Choi, Pomara, Wolkin, & Rotrosen, 2002) and metabolically (Thanos, Michaelides, Benveniste, Wang, & Volkow, 2008; Volkow, Fowler, Wang, & Swanson, 2004) upon regulatory prefrontal executive control systems of the brain as well as memory-related cortico-striatal and hippocampal regions (Rabbitt, 1997; L. Roberts, Robbins, & Weiskrantz, 1998). Furthermore, with regard to the efficacy of guanfacine, these brain areas are also rich in dopamine and norepinephrine innervations (S. Aston-Jones, Aston-Jones, & Koob, 1984; Foote, Bloom, & Aston-Jones, 1983), and critical to the arousal state (Sara, 2009). This is important as optimal levels of

norepinephrine acting at pre-synaptic alpha-2A-adrenoceptors serve to enhance neuronal “signals” in the prefrontal cortex and optimal levels of dopamine at D1 receptors serve to reduce “noise” in the prefrontal cortex by suppressing neuronal processing of irrelevant information (Brennan & Arnsten, 2008; Gamo & Arnsten, 2011; Levy, 2008) and hence strengthen regulatory function and reduce distractibility. In effect, moderate levels of norepinephrine and dopamine under optimal arousal conditions may serve to facilitate the suppression of irrelevant noise while enhancing relevant signals (Gamo & Arnsten, 2011). Cocaine-related changes to these powerful attentional catecholaminergic systems, may therefore impact related regulatory behaviors including executive (Sawaguchi & Goldman-Rakic, 1994; Zahrt, Taylor, Mathew, & Arnsten, 1997) and inhibitory control processes (Woodward, Mansbach, Carroll, & Balster, 1991). In addition, cocaine-related changes to dopamine-dependent cortico-striatal interconnectivity with the prefrontal cortex may also alter stimulus-response associative learning processes which are associated with habit-formation (Everitt, Dickinson, & Robbins, 2001; Everitt & Robbins, 2005; Haber, Fudge, & McFarland, 2000) and may also impinge on one’s ability to regulate both emotion and behavior under challenging circumstances.

Prefrontal regulatory dysfunction as targets for alpha-2 adrenergic agonists

As guanfacine is an alpha2 adrenergic agonist, known to stimulate pre-synaptic receptors in the prefrontal cortex, it may serve to enhance regulatory cognitive-affective function by means of several putative processes and mechanisms. First, as already discussed, the attenuation of central and peripheral sympathetic mechanisms (Erb et al., 2000; Erb et al., 1998; Shaham et al., 2003) may serve to assist with the reduction of anxiety, negative affective state (Ambrose-Lanci et al., 2010; H. C. Fox, Seo, et al., 2012), and hence attenuate potential conflict in regulatory goals (Koole & Jostmann, 2004). This may subsequently facilitate cognitive re-appraisal during negative emotional experiences (Albein-Urios et al., 2012) known to impact drug-seeking behavior. In addition, guanfacine’s ability to optimize catecholamine levels in the prefrontal cortex and strengthen prefrontal connectivity via the stimulation of alpha2 receptors and inhibition of cAMP-potassium channel signaling in postsynaptic spines (Arnsten & Li, 2005; Arnsten & Pliszka, 2011; Ramos, Stark, Verduzco, van Dyck, & Arnsten, 2006; M. Wang et al., 2007) may also improve executive and inhibitory function (Arnsten, 2009, 2011b; Mao, Arnsten, & Li, 1999) and hence goal-directed behaviors integral to outcome factors (Blume & Marlatt, 2009).

In support of this, animal studies using monkeys have indicated that guanfacine-related improvements to delayed response and spatial working memory are accompanied by enhanced regional blood flow to discrete regions of the prefrontal cortex including the dorsolateral prefrontal cortex (Avery, Franowicz, Studholme, van Dyck, & Arnsten, 2000) which is associated with inhibitory control, planning (Lazeron et al., 2000) and associative memory deficits (Petrides & Milner, 1982; Sahakian et al., 1988). Other preclinical studies have also demonstrated guanfacine improved delayed response performance in adult and elderly monkeys (Arnsten, Cai, & Goldman-Rakic, 1988; Mao et al., 1999; Rama,

Linnankoski, Tanila, Pertovaara, & Carlson, 1996; Ramos et al., 2006) as well as rats (Ramos et al., 2006). Furthermore, while Yohimbine (an alpha-2 adrenergic antagonist) has been shown to increase distractibility and impulsiveness in rodents; guanfacine improves attention, working memory, inhibitory control and orbitofrontal reversal learning in non-human primates (Arnsten & Li, 2005; Ma et al., 2005; Steere & Arnsten, 1997).

In humans guanfacine treatment has also been efficacious in decreasing impulsivity in children and adults with ADHD and tic disorders (Chappell et al., 1995; Hunt, Arnsten, & Asbell, 1995; Scahill et al., 2001; F. B. Taylor & Russo, 2001). With regard to healthy volunteers, however, findings demonstrating working memory enhancement have been ambiguous, with several studies showing guanfacine-related improvements in selective function, including planning and associative learning (Jakala, Riekkinen, Sirvio, Koivisto, Kejonen, et al., 1999; Jakala, Sirvio, et al., 1999) and other studies failing to document any improvements (Birnbaum, Podell, & Arnsten, 2000; Muller et al., 2005). It has therefore been suggested that the effects of guanfacine on executive and regulatory mechanisms may be more likely observed in conditions characterized by catecholaminergic dysfunction (Arnsten, Steere, Jentsch, & Li, 1998) (Franowicz & Arnsten, 1998; Milstein, Lehmann, Theobald, Dalley, & Robbins, 2007). As cocaine withdrawal and ADHD both share a common pathophysiology associated with prefrontal dysregulation and interactions with the caudate and catecholamine system (Arnsten, Steere, & Hunt, 1996; El Hage et al., 2012; Ernst, Zametkin, Matochik, Jons, & Cohen, 1998), guanfacine treatment may be particularly effective at enhancing inhibitory control processes in cocaine dependent individuals.

Notably, enhancing these prefrontal cognitive processes that are integral to exerting control over drug-seeking behaviors may highlight one of the major benefits of guanfacine compared with several other adrenergic agents. For example, while a number of clinical studies have evaluated the effects of anxiolytic noradrenergic agents in decreasing cocaine withdrawal-related stress on cocaine outcomes they have not found positive effects on either craving or relapse. While, Kampman and colleagues showed positive effects of propranolol on cocaine severity and withdrawal (Kampman, Alterman, et al., 2001; Kampman et al., 1998), a larger study found no effects of propranolol on cocaine abstinence (Kampman et al., 2006; Kampman, Volpicelli, et al., 2001).

It is also important to emphasize that stress signaling pathways are responsible for taking the prefrontal cortex “off-line” by increasing excess catecholamine release into the prefrontal cortex and modulating ionic regulation of microcircuits (Gamo & Arnsten, 2011). For example, during periods of heightened and uncontrollable stress, potassium channels are opened by elevated cAMP signaling which reduces persistent firing and weakens prefrontal network activity (Arnsten & Jin, 2012). This is extremely pertinent in chronic stress-related disorders such as cocaine dependence due to the fact that, stimulation of alpha-2A receptors on prefrontal spines, by agents such as guanfacine, are known to inhibit cAMP signals and increase delay-related firing (M. Wang et al., 2007). This, in turn, this may serve to improve control-related and purpose-driven regulatory behaviors under challenging and stressful situations, common to dependent populations (R. Sinha, 2008).

Previous research findings from our own laboratory have provided some initial support for this by demonstrating that the ability to optimize dorsolateral and ventromedial function in the face of stress and/or environmental challenge may highlight an important pharmacotherapeutic mechanism associated with guanfacine. In addition to the laboratory component of our double blind placebo controlled study (H. C. Fox, Seo, et al., 2012), a sub-sample of 15 cocaine dependent individuals (9 placebo / 6 guanfacine) also completed an fMRI component. In the fMRI session, six 2-minute imagery scripts (stress – two, cue – two, neutral – two) were presented in a quasi-randomized manner across one testing session. It was ensured that trials of the same imagery conditions were not presented consecutively. Functional MRI scans during six, 5-min trials were acquired, with each trial comprising a 1.5-min quiet baseline period followed by a 2.5-min imagery period (2 min of read-imagery) and a 1-min quiet recovery period as in our previous studies (Jastreboff et al., 2011; C. S. Li, Kosten, & Sinha, 2005; Seo et al., 2011; R. Sinha et al., 2005). During the baseline, participants were instructed to stay still without engaging in any mental activity. During the recovery period, participants were asked to stop imagining and lie still in the scanner. Each script was presented only once and scripts from the same condition were not presented consecutively. Between fMRI blocks, all subjects participated in progressive relaxation for 2 minutes in order to normalize any residual anxiety or craving from previous trials.

Following voxel-based analysis using AFNI, findings showed that guanfacine treatment increased activation in specific regions of the medial and lateral prefrontal cortex in response to stress and drug cue exposure, as well as increasing insula activation during stress imagery exposure compared with placebo. Most importantly, these increases in regional blood flow occurred in prefrontal regions typically implicated with distractibility and alertness (Sara, 2009) as well as the cognitive and emotional regulatory mechanisms underpinning craving, interoceptive function and treatment outcome (Aron, 2007; Kober, Kross, Mischel, Hart, & Ochsner, 2010; C. S. Li, Luo, Yan, Bergquist, & Sinha, 2009; R. Sinha et al., 2005).

Other potential anxiolytics and cognitive enhancers

Much converging evidence suggests that reducing central stress system function and enhancing regulatory processes by stimulating adrenergic transmission within fronto-striatal systems, may be an important mechanism for reducing craving and relapse in cocaine dependent individuals who also abuse alcohol and nicotine. However, in order to fully ascertain the efficacy of guanfacine in terms of outcome and abuse potential, it may be necessary to briefly evaluate these factors against additional agents including other anxiolytics and cognitive enhancers.

As many of the subjective and reinforcing effects of cocaine have traditionally been attributed to dopaminergic deficiencies within the mesocorticolimbic pathways (Koob, 2003; Volkow, Fowler, Wang, & Goldstein, 2002), potentiating dopamine transmission via “agonist therapy” has provided an important therapeutic target for reducing withdrawal symptoms and preventing relapse (Verrico, Haile, Newton, Kosten, & De La Garza, 2013). However, many of these candidate medications have been limited due to their high abuse liability and high prevalence of side effects (Diana, 2011; Thanos et al., 2004). While the

development of both partial agonists and dual DA/5HT (serotonin) releasers has provided some feasible means of preventing deleterious effects caused by the activation of mesolimbic dopamine neurons (Grabowski, Shearer, Merrill, & Negus, 2004; Rothman & Baumann, 2003; Rothman et al., 2005), there are still problems regarding long-term use.

For example, while the “anti-stimulant” effects of increasing levels of 5-HT with dopamine agonists have been shown to decrease cocaine self-administration behavior in rats and rhesus monkeys (Carroll, Lac, Asencio, & Kragh, 1990; Peltier & Schenk, 1993; Rothman, Blough, & Baumann, 2008) findings in humans have been mixed (Batki, Washburn, Delucchi, & Jones, 1996; Covi, Hess, Kreiter, & Haertzen, 1995; Shorter & Kosten, 2011). Furthermore, 5-HT releasing agents, including SSRIs such as fenfluramine, have also been associated with unpleasant side effects and rare but serious conditions such as cardiac valve disease (Fitzgerald et al., 2000; Rothman et al., 2000), serotonergic depletion and neurotoxicity, and primary pulmonary hypertension (PPH) (Rothman & Baumann, 2002). Although important steps have been made to develop monoamine releasers which isolate the desirable qualities of DA stimulation on cocaine self administration while eliminating the reinforcing stimulant effects, such as PAL-287 (Rothman & Baumann, 2009; Rush & Stoops, 2012), future studies still need to assess the potential of these medications with regard to increasing risk for cardiac valve and pulmonary heart disease.

In contrast, while initial reactions to guanfacine are common, most symptoms are mild and include fatigue, sedation, light-headedness, dizziness and vertigo, and tend to disappear either on continued dosing or following dose adjustment (Strang, Bearn, & Gossop, 1999). In fact, one major advantage of guanfacine over other alpha2 adrenergic agonists such as clonidine, is that it is less sedating with less hypotensive potential in both children and adults (Balldin et al., 1993; Bearn et al., 1996; Chappell et al., 1995; Kahn et al., 1997; Scahill et al., 2001). No serious side effects have been noted in adult populations, between the ages 18–65 and there are no reported differences in responses between elderly and younger populations. The most serious side effects in pediatric patients are reports of mania and aggressive behavior in pediatric subjects with ADHD (Horrigan & Barnhill, 1998). This side effect has not been documented within adult populations and there is no evidence that guanfacine poses a greater risk than those seen in children and adults with ADHD. In our own laboratory studies using guanfacine for cocaine dependence, the most common side effects of tiredness and fatigue were reported as being mild to moderate and dissipated within the initial two weeks of inpatient stay. There were also no significant differences in reported side-effects between the experimental group and the placebos (H.C. Fox et al., in press; H. C. Fox, Seo, et al., 2012).

Other anxiolytic medications have frequently been used as relapse prevention medications, typically administered in order to reduce cocaine reinforcement following the attainment of a short abstinence period (Kampman, 2008). However, while these agents show promise in terms of preventing relapse to cocaine, they are often associated with high levels of sedation and subsequent problems pertaining to attention, memory and language. For example, in two clinical trials, the GABA uptake inhibitor tiagabine, demonstrated promise with regard to decreasing cocaine use (Gonzales et al., 2003), potentially via anxiolytic mechanisms (Schwartz & Nihalani, 2006). However, several studies also documented clear evidence for

tiagabine-induced cognitive impairment in adults and children (Ijff & Aldenkamp, 2013). Similarly, while GABAB receptor agonist, baclofen, has been observed to reduce cocaine administration (D. C. Roberts, 2005; D. C. Roberts & Brebner, 2000) and cocaine seeking in rats (Di Ciano & Everitt, 2003) as well as craving for cocaine, tobacco and marijuana in humans (Brebner, Childress, & Roberts, 2002; Ling, Shoptaw, & Majewska, 1998); it has also worsened cognitive performance during marijuana withdrawal in humans (Haney et al., 2010) and induced sedation in mice (X. Li et al., 2013). In addition, while controlled pilot trials for topiramate have shown it to be efficacious in terms of maintaining abstinence (Kampman et al., 2004), it is also known to induce sedation and memory problems, particularly with regard to verbal fluency and reaction time (Sommer, Mitchell, & Wroolie, 2013).

In view of this, noradrenergic medications which attenuate sympathetic function are also worth reporting as several have shown some ability to decrease anxiety and cocaine use as well as limit the effects of psychostimulants without being mediated by severe side effects (Blanc et al., 1994). For example, several studies have shown that alpha1 antagonist prazosin versus placebo decreases anxiety and arousal symptoms, particularly nightmares, and sleep disturbances in PTSD and other anxiety disorders (Boynton, Bentley, Strachan, Barbato, & Raskind, 2009; Fraleigh, Hendratta, Ford, & Connor, 2009; Raskind et al., 2007; H. R. Taylor, Freeman, & Cates, 2008). Both prazosin and doxazosin have also been shown to attenuate stress-induced alcohol craving (H. C. Fox, Anderson, et al., 2012), fewer drinking days compared with placebo during a 6-week pilot study (Simpson et al., 2009), and a greater number of cocaine negative urines in a 13-week placebo controlled pilot study (Shorter, Lindsay, & Kosten, 2013) with minimal side-effects. Similarly, in alcohol-related preclinical work, prazosin is effective in decreasing alcohol consumption in dependent animals (Rasmussen, Alexander, Raskind, & Froehlich, 2009).

In addition to alpha receptors, other studies have indicated that nonselective beta adrenergic blockers such as propranolol may additionally represent a promising pharmacotherapeutic strategy for abstinence initiation in individuals with severe cocaine withdrawal symptoms and heightened anxiety. Clinical trials in humans have documented increases in cocaine treatment retention and attenuation of severity of withdrawal symptoms (Kampman, Alterman, et al., 2001; Kampman et al., 2006; Kampman et al., 1999). Again, however, while findings for adrenergic medications show initial promise, beta adrenergic blockers have been shown to induce sedation and impair memory consolidation as a possible function of their therapeutic effects (Kampman, 2008; McGaugh, 1989) and alpha1- adrenergic receptor blockers have also been associated with sedation and behavioral inactivity (Lapiz & Morilak, 2006), perhaps indicating less promise in terms of cognitive enhancement, although this has yet to be determined.

As executive functions such as inhibitory / regulatory control may be an essential component of behaviors underlying treatment outcome (Blume & Marlatt, 2009; H. C. Fox, Jackson, & Sinha, 2009), it may become necessary to start assessing the benefits of cognitive enhancers as potential therapies for substance abuse. Several agents including guanfacine, such as glutamatergic mediators (memantine, minocycline), monoamine transporter inhibitors (methylphenidate, atomoxetine) and cholinergic agents (galantamine,

varenicline) may show some promise (see (Sofuoglu et al., 2013) for full review). Moreover, cognitive enhancing agents that also target depressive and anxiety symptomatology may be particularly efficacious. For example, selective NET inhibitors such as atomoxetine have been used successfully to improve attention and visual memory performance in children with ADHD (Shang & Gau, 2012) as well as outcome in ADHD, with (Gabriel & Violato, 2011) and without (Durell et al., 2013) comorbid partially responsive anxiety symptoms. However, although atomoxetine may show initial potential in terms of attenuating some of the negative reinforcing effects of cocaine as well as enhancing regulatory function, the drug has yet to be tested in clinical trials for substance abuse. Similarly, preclinical studies using modafinil have shown both dose and delay dependent cognitive improvements as well as cognitive enhancing properties in substance abusers (Heinzerling et al., 2010; Mereu, Bonci, Newman, & Tanda, 2013) alongside low abuse potential. This is thought to be due to fact that modafinil has a markedly lower affinity for DAT binding compared with other stimulants (Minzenberg & Carter, 2008). However, the literature remains ambiguous with regard to modafinil's anxiolytic properties, and several studies have indicated that modafinil may *increase* levels of anxiety in a range of human populations (Randall, Shneerson, Plaha, & File, 2003; Taneja, Haman, Shelton, & Robertson, 2007; Wong et al., 1999) making it a potentially less viable medication than guanfacine for substance abusing females.

Long-term maintenance of guanfacine

One of the major benefits of guanfacine in terms of the long-term potential may be based around the fact that guanfacine represents a medication targeting core regulatory stress systems underlying combined anxiety and addiction pathology. Substance abuse and anxiety disorders are highly co-morbid and treatment and health care burdens are higher for co-morbid groups. Using an integrated medication with the potential to uniquely target common stress systems through which substance abuse and anxiety disorders co-occur at highly prevalent rates, may therefore help individuals address both disorders simultaneously. Most importantly, several studies comparing integrated with non integrated treatment programs have reported significantly greater improvement in substance abuse outcomes for individuals receiving long-term integrated treatments (Barrowclough et al., 2001; Drake, Yovetich, Bebout, Harris, & McHugo, 1997; Godley, Godley, Pratt, & Wallace, 1994) as compared with short-term intensive treatment (Brunette, Drake, Woods, & Hartnett, 2001). The requirement for longer term treatments in co-morbid substance abusers are also highlighted by the fact that short periods of abstinence are typically followed by a more challenging and qualitatively different phase of sustained abstinence (Kampman et al., 2006; Marlatt & George, 1984). Moreover, the potential utility of extended release guanfacine in this context may be highlighted by the fact that optimal cognitive skills may be considered a lynch pin of successful relapse prevention (Blume, Schmaling, & Marlatt, 2005; Marlatt & Gordon, 1985).

In light of these studies, as guanfacine is a non-stimulant agent with minimal treatment-limiting side effects, the extended release formula may additionally offer long term therapeutic potential in substance abusers co-morbid for anxiety and dysregulatory behaviors. In support of this, to date, studies examining the long-term tolerability of extended release guanfacine in children with ADHD have been successful in maintaining the

attenuation of symptoms safely, over two years, with minimal and transient side-effects (Biederman et al., 2008; Sallee et al., 2009). Extended release guanfacine administered across eight weeks, has also been shown to safely improve traumatic stress, anxiety and ADHD symptoms in children and adolescents (Connor, Grasso, Slivinsky, Pearson, & Banga, 2013).

Summary

Cocaine dependence is a chronic stress state characterized by compulsive and often uncontrollable, drug seeking and drug use despite debilitating negative consequences (Goldstein & Volkow, 2002). Moreover, compared with many other drugs of abuse, there are few efficacious medications that address the high rates of craving and cocaine relapse (Kang et al., 1991; C. P. O'Brien, 2005; R. Sinha, 2001). Notably, the chronic use of cocaine is associated with robust adaptations to core neural stress systems that mediate stress sensitivity, anxiety pathophysiology and prefrontal regulatory function (H. C. Fox & Sinha, 2009). Specifically, these include up-regulated extra-hypothalamic CRF and norepinephrine circuits involving the amygdala, bed nucleus of the stria terminalis (BNST) and down-regulated medial prefrontal circuits, which in turn result in changes to hypothalamic paraventricular nucleus and locus coeruleus (LC) connections. Over time, these changes may reflect a powerful feed forward loop which contributes to sex-specific changes in anxiety and stress sensitivity (Dunn & Berridge, 1990; Dunn & Swiergiel, 2008b; Dunn et al., 2004; Koob, 2009b; Kushner et al., 2000). These catecholaminergic fronto-striatal circuits are also important components of executive and regulatory processes known to underpin goal-directed behaviors, critical to treatment outcome (Blume & Marlatt, 2009).

As an alpha2 adrenergic agonist, guanfacine's ability to target such overlapping stress, reward and anxiety pathophysiology suggest that it may be a useful long-term agent for attenuating the stress and cue-induced craving state in women especially, but also in men. This is supported by recent research findings from our own laboratory (H.C. Fox et al., in press). The ability of guanfacine to improve regulatory mechanisms that are key to exerting cognitive and emotional control over drug-seeking behavior (Verdejo-Garcia & Perez-Garcia, 2007) also suggest that guanfacine may be an effective medication for reducing craving and relapse vulnerability in many drugs of abuse. As cocaine dependent individuals are typically polydrug abusers and women may be at a greater disadvantage for compulsive drug use than men (Becker & Hu, 2008), it is plausible that medications which target catecholaminergic fronto-striatal regulatory circuits and simultaneously reduce stress system arousal may provide added benefits for attenuating cocaine dependence.

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Figure 1.

Differences between guanfacine and placebo in subjective craving and mood following exposure to stress (SS), drug cue (DD) and combined stress and drug cue (SD)

Note. SS: Stress/Stress condition; SD: Stress/Drug cue condition; DD: Drug cue/Drug cue condition. Group differences: **, $p < .01$; ***, $p < .0001$

Figure 2.
Subjective craving responses following exposure to stress imagery, by guanfacine dose

a) Cocaine Craving

b) Alcohol Craving

c) Anxiety:

I: Imagery exposure; R: recovery time-points

Figure 3.

Medication (guanfacine Vs placebo) differences by gender following exposure to all three imagery conditions combined

I: Imagery exposure; R: recovery time-points