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Pharmacological Challenge Studies with Acute Psychosocial Stress

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Abstract

Chronic stress is known to affect many psychiatric disorders, and studies of responses to acute stress may reveal processes that ultimately lead to maladaptive responses to chronic stress. Many studies have used simulated public speaking tasks to induce stress in the laboratory and, of interest to this review, the tasks have been used to assess the effects of both therapeutic and nonmedical drugs on stress reactivity. Here we review 38 studies that examined effects of single doses of drugs on subjective, cardiovascular and hormonal responses to an acute social stressor in healthy volunteers. Most studies have used the Trier Social Stress Test (TSST), or variations on it involving public speaking or mental arithmetic. Pharmacological studies with the TSST (ph-TSST) have been conducted for three main reasons: i) to determine the clinical effectiveness of psychiatric medications to reduce stress responses, ii) to investigate the neurochemical mechanisms involved in the stress response, and iii) to determine whether drugs of abuse relieve, or occasionally worsen, responses to acute stress. The review indicates that standard anxiolytic medications consistently reduce subjective responses to the TSST, whereas single doses of antidepressants produce mixed effects. Mechanistic studies indicate that several neurotransmitter systems are involved in the stress response, including serotonin, norepinephrine, GABA, glutamate, opioids, and endocannabinoids. Among drugs of abuse, alcohol and cannabinoids exert some stress-dampening effects, whereas caffeine, nicotine, and amphetamines tend to increase stress responses. Comparing outcome measures of the responses to stress, subjective ratings of anxiety are among the most sensitive indices of the stress response, with cortisol levels second and cardiovascular responses least sensitive. We conclude that the TSST is a valuable tool to study the clinical effectiveness of medications for stress-related disorders, and that it is important to use standardized procedures to enable comparisons across studies.

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Keywords

Social Stress; TSST; Psychoactive drugs; Pharmacology

Introduction

Stress is a critical determinant of many psychiatric disorders (Selye, 1936; McEwen, 2000; Charney, 2004; de Kloet et al., 2005; Kendler, 2016). Studying responses to acute psychosocial stressors, and the effects of drug pretreatments on these responses to these stressors, may provide a window to understanding the consequences of chronic stress and ways to modulate its maladaptive effects. The Trier Social Stress Test (TSST; Kirschbaum et al., 1993) and similar public speaking tasks are commonly used in laboratory studies to assess acute responses to stress, and to investigate effects of psychoactive drugs on the stress response (Kudielka et al., 2007). In these drug challenge studies, subjects are pre-treated with a drug or a placebo, and then participate in the task, which involves a brief preparation period followed by a speaking monologue and a math task performed in front of an audience that provides no positive feedback. The outcome measures usually include three categories: i) self-reports of anxiety or tension, ii) cardiovascular responses such as heart rate and blood pressure, and iii) levels of the stress hormone cortisol in saliva or blood. The procedure is believed to induce an acute social evaluative threat, and researchers have studied the effects of drugs on public speaking tasks for three main reasons: i) to determine the clinical effectiveness of approved or potential psychiatric medications in reducing responses to acute stress, ii) to investigate the neurochemical receptor mechanisms involved in the stress response, and iii) to determine whether drugs of abuse are effective in ‘self-medicating’ or relieving negative aspects of acute stress responses. In this review, we discuss studies that have used drug challenge procedures with the TSST or similar tasks in each of these categories. We review the extent to which the TSST findings correspond to clinical expectations, or inform us about underlying neurochemical or hormonal processes involved in the response. We also review the extent to which the three categories of outcome measures (subjective, cardiovascular and hormonal) are related to each other, or independent. Campbell and Ehlert (2012) examined the correspondence between physiological and subjective responses in 49 studies that used the TSST. They found that cortisol responses and perceived emotional stress variables were correlated in just 25% of the studies, suggesting that these measures are controlled by separate factors, which is a theme throughout this review. We also review key components of the procedure, or of the subject populations, that may affect the outcome and interpretation of the studies.

The results of studies using the TSST have been summarized in several recent reviews (Kudielka et al., 2007; Allen et al., 2017; Goodman et al., 2017; Zorn et al., 2017; Liu et al., 2017). These reviews confirm that the task reliably induces several indices of responses to social stress, and they identify several variables that can influence TSST responses, including, for example, sex, menstrual cycle phase and hormones, age, genotype, time of day of testing, psychiatric diagnosis, symptomatic state (Zorn et al., 2017) and even the presence of a pet dog (e.g., Kertes et al., 2017). The fact that many variables can influence the stress response somewhat complicates the interpretation of pharmacological challenge studies with

the TSST (referred to here as ph-TSST), because the drugs could affect the perception or impact of the stress indirectly, by influencing other variables. Here, we review recent ph-TSST to identify evidence of anxiolytic or stress-dampening effects, and to determine the co-relationships among different outcome measures of the stress response.

We have grouped the ph-TSST studies into three categories of i) approved or potential psychiatric medications (Table 1), ii) mechanistic studies (Table 2), and iii) drugs of abuse (Table 3). We conducted a PubMed search using the words [TSST OR Trier OR social stress OR public speaking] AND [alcohol OR benzodiazepine OR barbiturate OR stimulant OR opioid OR cannabinoid OR caffeine OR antidepressant OR anxiolytic OR analgesic OR serotonin OR GABA OR noradrenaline OR caffeine OR nicotine] AND (healthy OR human OR volunteer). Of the 110 results we selected 38 studies that met our inclusion criteria of studies with healthy volunteers who received a drug or placebo pretreatment before a public speaking task, providing measures of subjective ratings, cardiovascular measures or hormonal responses. The findings are separated into three sections based on the apparent purpose of the studies, but there is much overlap between the sections (e.g., medications that are abused).

The procedures used in the studies reviewed here follow essentially the same basic design, but differ in outcome measures, demographic characteristics of the participants, drug and doses, and phase of the stress response studied (i.e., anticipation, stress response and recovery). Most studies used the TSST, but some used variations involving either a simulated public speaking task or mental arithmetic task instead of the full TSST. In this review we will not focus on methodological differences unless they appear to influence the interpretation. Most of the studies use a between-subject design in which participants are randomly assigned to receive either placebo or a drug. Some, but not all, of the studies include a no-stress control session. The subject samples include healthy men and women, cigarette smokers, and alcohol drinkers. The measures of subjective or mood response to the stress procedure include visual analog measures (VAMS) of anxiety, calm, tension, confidence and other adjectives, the Spielberger Trait Anxiety Inventory (STAI; Spielberger et al., 1983), and self-report measures of somatic symptoms such as perspiration, dry mouth, palpitation, among others (Zuardi et al., 1993; Hetem et al., 1996). Other self-report measures include ratings of how threatening subjects considered the procedure to be. Physiological indices of stress include heart rate (HR), blood pressure (BP), electrodermal activity (EDA; skin conductance or other measures of sweating), and plasma epinephrine levels. Hormonal measures include cortisol (usually salivary), adrenocorticotropic hormone (ACTH) and salivary alpha amylase. In some studies, researchers recorded the participants' performance during the tasks to determine whether the drug impaired, or improved, their performance. With so many possible sources of variability it becomes difficult to compare directly across studies. Nevertheless, some patterns emerge from the range of studies.

A. Approved or potential psychiatric medications

1. Benzodiazepines—Benzodiazepines are the current standard of care for anxiety disorders and, as such, would be expected to reliably dampen responses to an acute laboratory stressor. Surprisingly, however, benzodiazepines have mixed effects on responses

to social evaluative stress tasks. Several early studies examined the effects of the prototypic benzodiazepine diazepam on responses to stress. McNair et al. (1982) tested the effects of 5 and 10 mg diazepam in healthy young adults on subjective anxiety and palmar sweating before and during a public speaking task, and found that the higher dose reduced subjective anxiety before and during the task, but did not change palmar sweating. Graeff et al. (1985) found no effect with diazepam (10mg) on subjective ratings of a speech stressor, whereas Zuardi et al. (1993) reported that diazepam (10mg) decreased ratings of anxiety before, during, and after a stressful speech task without changing HR or BP. These studies were conducted before the TSST procedures had been standardized, and methodological differences make it difficult to account for between study differences. These early studies are also limited by the lack of cortisol levels.

Other benzodiazepines have yielded mixed results, and suggest that this class of drugs dampens some, but not all dimensions of the stress response. Two studies (Rohrer et al., 1994, Fries et al., 2006) examined responses to alprazolam (0.5mg, 1mg) compared to placebo in healthy men. The 0.5mg dose of alprazolam, which is equivalent to about 10mg of diazepam, reduced ACTH and cortisol levels both studies, but did not affect change in HR in response to stress. Fries et al. (2006) found that alprazolam did not affect ratings of state anxiety, although it decreased ratings of wakefulness and increased ratings of good mood. In another study (Guimarães et al., 1987), lorazepam (1mg) decreased subjective ratings of anxiety, but tended to *increase* HR responses to stress. Lastly, Zuardi et al. (2017) found that clonazepam (1 mg) decreased ratings of anxiety during and after a public speaking task, but increased HR response to the stress.

In summary, the prototypic anxiolytic benzodiazepines reduced subjective ratings of anxiety in most studies, but the drugs' effects on the cardiovascular responses to stress are inconsistent. Notably, few studies have measured the effects of benzodiazepines on cortisol, but the one study that did measure cortisol reported the expected decrease. The lack of standardization of the public speaking procedure, and the variability in scales or questionnaires to measure subjective experiences leave a number of questions unanswered. These methodological differences make it difficult to compare across studies and drugs, and it is not known how methodological factors influenced the findings. For example, the subjective experience of the stress task may depend on the adjectives used to describe the state (e.g., anxiety, stress, arousal, tension), and it may depend on when the ratings were conducted (i.e., just before or during the task, or retrospective ratings after the task is completed). One interesting finding from these studies is that the HR response to acute stress appears to be independent of the subjective experience of anxiety or tension during the task. This is consistent with the conclusions drawn by Campbell and Ehlert (2012) that physiological indices of the stress response do not necessarily covary closely with subjective reports. Nevertheless, is possible that more sensitive tools, such as ambulatory EKG monitors measuring heart rate variability, may reveal drug effects on cardiovascular responses to stress in future studies.

Gabapentin, another GABAergic drug with some clinical efficacy as an anxiolytic (Berlin et al., 2015), has been tested using the TSST. Gabapentin modulates the activity of enzymes involved in GABA biosynthesis, increasing GABAergic neurotransmission, although its

exact mechanism is still a subject of debate (Taylor, 1997; Houghton et al., 2016). De Paris et al. (2003) tested the effects of gabapentin (400mg, 800mg) on responses to the TSST. Both doses of gabapentin increased feelings of calm (and decreased hostility) before, during, and after the speech task. As in the case of the benzodiazepines, neither dose affected HR or BP responses to stress, and cortisol was not measured. Several clinical studies have reported that gabapentin reduces anxiety associated with surgery and physical pain (Wallace et al., 2008; Clarke et al., 2013), suggesting that the anxiety states encountered in medical practice may have some similarities with the social evaluative threat induced by the TSST. One study assessed the effects of flumazenil (1mg), a GABA antagonist, on responses to social stress (Kapczinski et al., 1994). Somewhat surprisingly, although flumazenil blocks GABA whereas gabapentin is an agonist, the two drugs had similar effects on psychosocial stress response. Flumazenil decreased anxiety and tension before the task, and reduced reports of heart palpitations. Cardiovascular and endocrine measures were not collected, although this study did include a non-stressful control task to demonstrate the effects were specific to stress. Taken with the gabapentin findings, this suggests that, paradoxically, a change in GABA signaling in either direction can reduce subjective responses to acute social stress.

2. Antidepressants—Stress plays a critical role in the etiology and pathophysiology of depression (van Praag, 2004; de Kloet et al., 2005). Therefore, it has been of interest to examine the acute effects of anti-depressant drugs on the TSST. Although the clinical benefits of anti-depressant drugs do not emerge until several weeks after initiation of treatment, there is evidence that acute doses of the drugs can alter affective processing in ways that predict clinical outcomes (Harmer et al., 2003). Yet, the same drugs also have the potential to induce anxiety. Guimarães et al. (1987) compared the effects of the primarily norepinephrine (NE) reuptake inhibitor maprotiline (50mg) to the effects of the primarily serotonin reuptake inhibitor chlorimipramine (25mg, also referred to as chlomipramine/ clomipramine) on a public speaking task in healthy volunteers. Maprotiline decreased subjective reports of anxiety, but also increased ratings of sedation and lethargy, raising question about the specificity of the anxiolytic effect. Cortisol was not measured and the drugs did not affect HR. In contrast, chlorimipramine (25mg), increased subjective ratings of anxiety, muscle tension, and agitation, and sustained the increase in systolic BP induced by the task. The authors speculate that the increase in anxiety may have been due to a metabolite of chlorimipramine. Interestingly and consistent with this, patients taking chlorimipramine show an increased incidence of panic attacks when starting the medication (Gloger et al., 1981; Ramos et al., 1993). Similar results were obtained with acute doses of the most selective serotonin reuptake inhibitor, escitalopram (10mg, 20mg; Garcia-Leal et al., 2010); the drug increased anxiety, and the higher dose (20mg) also increased plasma cortisol responses to stress. From a neurobiological perspective, these results suggest that the acute inhibition of 5HT reuptake may exert anxiogenic effects. The maprotiline results may be related to observations that NE reuptake inhibitors slow the firing rate of neurons in the locus ceruleus that mediate the stress response (Nybäck et al., 1975). However, the results should be interpreted with caution because neither maprotiline nor chlorimipramine have selective effects on any one neurotransmitter, and both act as antagonists at histamine H1 receptors, muscarinic acetylcholine receptors, and a1-adrenergic receptors.

Nefazodone is a discontinued antidepressant drug that acts as a weak serotonin-norepinephrine-dopamine reuptake inhibitor and 5HT2A receptor antagonist. Silva et al. (2001) examined the anxiolytic effect of nefazodone (100mg, 200mg) in healthy volunteers using either a public speaking task or a fear conditioning procedure. Unexpectedly, nefazodone (200 mg) increased anxiety during anticipation of stress, in the speaking task, but it decreased anxiety in the conditioning task, suggesting that unconditioned anxiety (public speaking) and conditioned anxiety (anticipation of an aversive stimulus) are mediated by separate processes. These findings raise interesting questions about separate circuits underlying different types of stress.

Thus, broadly speaking, clinically effective anxiolytic drugs that act via GABAergic mechanisms appear to dampen subjective, and sometimes also hormonal, responses in the laboratory stress procedures. In contrast, single doses of antidepressant drugs that act through serotonergic mechanisms appear to have anxiogenic effects, while one early study suggested that a noradrenergic antidepressant might have some anxiolytic effect. There is growing recognition that symptoms of depression and anxiety have significant overlap, and researchers have questioned whether they indeed reflect separate underlying disorders (Kendler, 2016; MacNamara et al., 2017). Yet, it is difficult to compare the effects of classic anxiolytic and anti-depressant drugs using the TSST because of the substantial differences in time course of effects. It remains to be determined whether antidepressant drugs would decrease responses to acute stress after chronic administration, coinciding with their delayed actions for clinical efficacy. The studies reviewed here suggest that, of the three main indices of stress, subjective and mood ratings appear to be the most sensitive indicators of effects of drugs on the stress response, followed by changes in cortisol levels. There is little evidence that HR or BP responses are sensitive indices of drug effects in ph-TSST studies.

B. Mechanistic studies

1. Analgesics—Analgesics by definition reduce reactivity to physical pain, but there is growing evidence that they may also reduce reactivity to psychological or social ‘pain’ (Eisenberger and Lieberman, 2004). Social pain and physical pain have overlapping neural processes with important evolutionary functions, and it is recognized that opioids as well as anti-depressants have regulatory effects on both physical and social forms of pain. Further, there is a large body of evidence implicating the opioid system in maternal attachments and responses to isolation distress in rodents (Panksepp et al., 1978, 1980), and that opioids modulate responses to social stress in humans (Zubieta et al., 2003; Chong et al., 2006; Bershad et al., 2015). One ph-TSST study assessed the effects of buprenorphine (0.2mg, 0.4mg) on subjective, cardiovascular and endocrine responses to the TSST in healthy adult volunteers (Bershad et al., 2015). Buprenorphine is a partial agonist at the mu receptor and an antagonist at the kappa receptor. Both doses abolished the salivary cortisol responses to stress, and the higher dose (0.4mg) reduced how threatening the subjects found the task. However, the drug did not dampen momentary ratings of anxiety during the task or cardiovascular responses. In a follow-up study, Bershad et al. (under review) assessed the effects of hydromorphone (2 mg, 4 mg), a pure mu-agonist, at doses equipotent to buprenorphine on ratings of “feel drug”. Like buprenorphine, hydromorphone reduced cortisol responses to stress, but the drug did not reduce either ratings of mood or task

appraisal, or HR or BP responses to stress. The difference between buprenorphine and hydromorphone on ratings of threat appraisal raises the possibility that the ability of buprenorphine to dampen subjective ratings of threat are related to its kappa action, which hydromorphone lacks.

There is also limited evidence that non-opioid analgesics, such as acetaminophen, reduce responses to social rejection and other types of negative social stimuli (de Wall et al., 2010, 2015; Mischkowski et al., 2016). We (Bershad et al., under review) found that acetaminophen (1000mg) reduced pre-task ratings of how challenging participants expected the TSST to be, but it did not reduce anxiety during the task. It also did not affect HR or BP responses to stress, and tended to increase, rather than decrease, cortisol responses. This is another example of the dissociation between subjective and physiological responses to stressful tasks. One way to view the dissociation between subjective and physiological responses may be that the subjective experience of threat reflects the perception of the stressor, whereas increases in cardiovascular responses may be considered the organism's immediate response to the perceived threat and the increase in cortisol may be part of an adaptive system aimed at reinstating homeostatis (de Kloet et al., 2005). One might speculate that the conscious perception of the stressor plays an important role in the memory and cognitions about stressful experiences that affect future behavior, whereas the physiological responses to stress may have more important implications for adverse health consequences of chronic stress. Understanding how these stress systems work together will help to clarify the pathogenesis of maladaptive stress responses, or treatment of stress-related disorders.

2. Serotonergic drugs—Several ph-TSST studies have been conducted to investigate the role of the serotonin system in stress responses. The serotonin system is the subject of intense scientific interest because of its involvement in depression and other stress-related disorders (Ramaker and Dulawa, 2017; Slattery and Cryan, 2017). Thus, studying this system provides an opportunity to understand the neural mechanisms underlying the stress response. This has led to several studies investigating effects of specific receptor agonists and antagonists on responses to acute stressors.

Several studies have examined effects of serotonin agonists, or drugs that increase synaptic levels of serotonin, on public speaking tasks. Hetem et al. (1996) studied the effects of the serotonin releaser and reuptake inhibitor d-fenfluramine (15 mg, 30 mg) on a simulated public speaking task using measures of anxiety, cardiovascular function, and self-reported somatic symptoms of anxiety (e.g., muscle tension, perspiration, etc.). The higher dose of d-fenfluramine reduced subjective reports of anxiety during and following the speech task for self-reported anxiety, but did not reduce somatic symptoms of anxiety. The drug also did not affect stress-induced increases in BP. Zuardi et al.(1993) examined the effects of the 5HT1A partial agonist ipsapirone (5 mg) vs. placebo in a between subjects design. Ipsapirone reduced feelings of anxiety during the speech task and reduced the stress-induced increase in systolic BP. Like fenfluramine, ipsapirone did not affect HR or self-reported somatic symptoms. De Rezende et al. (2013) examined the effects of sumatriptan (50 mg, 100 mg), a 5HT1D/5HT1B agonist used to treat migraines. Sumatriptan (100 mg) *increased* feelings of anxiety and decreased feelings of sedation while subjects were anticipating the speech task

and during the speech itself. Neither dose altered physiological responses to stress. Thus, there is some evidence that serotonin reuptake blockers and 5HT1A agonists, but not 5HT1B agonists, reduce response to acute stress.

As for serotonin antagonists, Graeff et al. (1985) examined the effects of metergoline (12 mg), a nonspecific serotonin antagonist that has been used clinically to treat migraine headaches, on a public speaking task. Metergoline increased rating of state anxiety (STAI-S scores) before the simulated public speaking task and at 24 hours after drug administration compared to placebo but did not affect somatic symptoms, HR, or EDA compared to placebo. Guimarães and colleagues (1997) tested the effect of a 5HT2A/5HT2C antagonist ritanserin (2.5 and 10 mg) on simulated public speaking in a between subjects design, assessing anxiety using the STAI and VAMS, somatic symptoms, and physiological responses using HR and EDA. The high dose of ritanserin increased anxiety and feelings of discontentment on the VAMS after the speech task, and both doses increased anxiety after the task as measured by the STAI. The drug did not, however, reduce stress-induced HR and EDA. Thus, serotonin antagonists appear to increase anxiety responses to stress.

Another way to modify serotonin function is by reducing serotonin levels with a dietary tryptophan (TRP) depletion procedure. TRP is a critical precursor for serotonin synthesis, and decreasing levels of TRP decreases levels of serotonin in the brain. Monteiro-dos-Santos et al. (2000) used TRP depletion with a public speaking task, and measured anxiety (VAMS, STAIS), HR and BP. TRP depletion increased anxiety on the STAI-S during the speech task for female subjects only, although baseline differences made this difficult to interpret. TRP depletion did not affect other measures of the stress response. Thus, although the effects were modest, the effects of TRP depletion on the stress response most closely resembled the effects of serotonin antagonists like metergoline and ritanserin.

Thus, serotonergic drugs have mixed effects on anxiety induced by public speaking. The effects depend on the drug and its profile of receptor action (i.e., 5HT1A or 5HT1B), and perhaps also the subject sample or the measure used to assess anxiety (e.g., VAMS or STAI-S; Zuardi et al., 1993; Hetem et al., 1996). In general, drugs that reduce serotonin function increase anxiety during stress tasks, whereas drugs that increase levels of serotonin are more likely to be anxiolytic. The serotonergic drugs have limited effects on cardiovascular responses to public speaking tasks, although Zuardi et al. (1993) found that ipsapirone reduced in systolic BP response to the speech task. Although several studies included measures of somatic symptomatology (a questionnaire that assess palpitations, perspiration, etc) or EDA, these measures did not reveal any drug effects. Notably, most of these studies did not include measures of cortisol responses to stress, leaving unanswered an important question about the adaptive hormonal response to acute social stress. As noted above in another section, the methodological variations across studies make it difficult to compare responses to different drugs directly, and emphasize the important of using a standardized procedure, such as the TSST.

3. Cannabidiol—Cannabidiol (CBD) is a constituent of the cannabis plant that has received a lot of attention recently for its potential anxiolytic effects, either alone or in combination with THC. Some cannabis users claim that they use cannabis to reduce the

negative subjective experiences of daily life stressors, and this effect is sometimes attributed to CBD (Hurd, 2017). Two studies have examined the effects of CBD on a public speaking task in healthy human volunteers. Zuardi et al. (1993) used a between subject design to compare the effects of CBD (300 mg) to placebo. CBD reduced anxiety following the speech task, but not during either the preparation before the task or during the task, as measured with the VAMS. CBD did not alter cardiovascular function, and cortisol was not measured. In a second study, Zuardi et al. (2017) compared effects of several doses of CBD (100 mg, 300 mg, 900 mg) using a variant of a public speaking task in which 12 participants were tested at once. They found a nonlinear dose-response function such that only the moderate dose (300 mg) reduced ratings of anxiety during and after a public speaking task, despite slightly increasing BP during the task. One other study (Bergamaschi et al., 2011) investigated the effects of CBD (600 mg) compared to placebo on the simulated public speaking task in individuals with social phobia. CBD reduced reports of anxiety, cognitive impairment, and discomfort during the task compared to placebo, although the CBD treated subjects still reported more anxiety during the task than a group of healthy controls (who did not receive CBD). Similar to the first CBD study (Zuardi et al., 1993), CBD did not affect cardiovascular functioning or EDA. Thus, there is some evidence that CBD may have anxiolytic effects during acute social stress. The mechanism underlying this effect, and of CBD, remain unclear.

4. Lamotrigine—Lamotrigine is a sodium channel blocker that indirectly decreases glutamate release, and is prescribed to treat both seizures and mood disorders (Lees and Leach, 1993). Makatsori et al. (2004) examined the effect of lamotrigine (300 mg) on cardiovascular and hormonal responses (no subjective ratings) to the TSST in healthy volunteers. Lamotrigine decreased diastolic BP and decreased salivary cortisol response to TSST. Interestingly, the drug also decreased growth hormone responses following the TSST. Unfortunately, subjective anxiety was not measured in this study, which would be a critical metric in understanding the stress-dampening effects of the drug.

5. Propranolol—Propranolol is a beta blocker and anti-hypertensive that is commonly used to treat performance anxiety. It has been tested in several ph-TSST studies. Alexander et al. (2007) studied the effects of propranolol (40 mg) on the TSST. Although this study did not assess subjective effects throughout the study sessions, participants did rate the anticipated stressfulness of the TSST, and there was no effect of propranolol. Propranolol decreased systolic BP and lowered HR compared to placebo during both TSST and a non-stress control session. Andrews and Pruessner (2013) found that propranolol (80 mg) decreased HR and marginally decreased systolic BP compared to placebo, but that it increased cortisol and had no effect on subjective effects. Dreifus and colleagues (2014) examined the effects of propranolol (60 mg) and found a decrease in systolic BP, but no change in diastolic BP or cortisol response. Participants in the propranolol group reported less anxiety after the TSST, and found the TSST to be less stressful than the placebo group. Overall it seems that propranolol consistently lowers systolic BP in response to a stress task, but has mixed effects on other markers of stress like subjective effects and cortisol response. These studies raise interesting questions about the role of cardiovascular or other physiological changes in the subjective experience of stress or anxiety. Early studies by

Schachter and Singer (1962) demonstrated that increases in physiological arousal are strongly influenced by the emotional context of the environment. Thus, it is possible that a drug which reduces the peripheral cardiovascular responses to a social stressor may indirectly also reduce the subjective experience of the stressor. This raises further questions about the extent to which the subjective, cardiovascular and hormonal responses to acute stress are related, and how each of these adapt to repeated or chronic stress.

C. Drugs of abuse

Stress is known to play an important role in the etiology of drug abuse (Sinha, 2001). Specifically, it is widely believed that people use drugs to 'self-medicate', i.e., to relieve unpleasant psychological states (Khantzian, 1985; 2013), including states of stress or anxiety related to discrete life events (Cappell and Herman, 1972; Sayette, 1999). Thus, several studies have examined the effects of drugs of abuse on reactivity to the TSST, as one test of the self-medication theory. The potential stress-dampening effects have been studied with a range of drugs with markedly different pharmacological profiles. In contrast, several other studies have examined the possibility that certain nonmedical drugs, such as caffeine and nicotine, increase responses to acute stress. Here, we review studies that have investigated the effects of alcohol, caffeine, nicotine, amphetamine, tetrahydrocannabinol (THC), and MDMA in healthy volunteers using public speaking stress tasks.

1. Alcohol—It is commonly believed that people drink to reduce tension (Cappell and Herman, 1972), and laboratory-based studies using the TSST provide some support for stress-dampening effects of single doses of alcohol. Levenson et al. (1980) examined the effects of alcohol (1 g/kg or placebo) on physiological and subjective responses to a speaking stress task in young adults. Alcohol decreased both subjective (ratings of anxiety during the task) and cardiovascular (HR) indices of stress. Bradlyn et al. (1981) conducted a similar study in moderate drinkers and the alcohol-treated subjects were rated by a panel of two judges to be less anxious. Sher and Walitzer (1986) examined the effects of two doses of alcohol (0.42 g/kg, 0.85 g/kg) on cardiovascular and subjective responses to a speech stressor. Both doses of alcohol reduced the stress-induced increase in HR, and the higher dose reduced subjective ratings of anxiety. Zimmerman et al. (2007) examined the effects of alcohol (0.6 g/kg) on responses to the TSST using cortisol as an indicator of stress reactivity. Stress increased cortisol, but alcohol did not reduce this effect. Subjective ratings and cardiovascular responses were not reported.

In studies with alcohol, there have been concerns that the participants' expectancies of receiving alcohol influence the stress-dampening effect, independently of its pharmacological effects. The Levenson et al. (1980) study described above included a condition where subjects were led to believe they received alcohol but they did not. The expectancy did not reduce responses to the stress task. Bradlyn et al. (1981) similarly found that expectancy of alcohol alone did not reduce stress-induced anxiety. In another study, however, Balodis et al. (2011) found that the expectancy of receiving alcohol had effects similar to actually receiving alcohol. The TSST significantly increased salivary levels of both cortisol and the enzyme alpha-amylase, as well as subjective self-ratings of anxiety and tension. Unlike in previous studies, participants who only expected to receive alcohol

exhibited the same stress-dampening effects (ratings of tension and anxiety) and a reduced increase in cortisol following the TSST, compared to subjects who actually received alcohol. Thus, the expectation of receiving alcohol altered subjective and physiological responses to the stressor. The fact that expectancies can influence responses to stress, including both subjective and physiological responses, raises interesting questions about the role of cognitions and beliefs in responses to stress. If the stress response can be dampened by the expectation of ingesting an anxiolytic substance, this suggests that stress responses are to some extent under cognitive control. Such expectancies and cognitions may contribute to nonpharmacological, or behavioral approaches to preventing and treating adverse responses to stress.

In an interesting variant on the TSST procedure with alcohol, Childs et al. (2011) administered intravenous alcohol immediately *after* subjects completed the speech component of the TSST. Whereas a drug administered before the TSST may affect either the perception of the stressor or the body's reaction to it, a drug administered immediately after the stressful task acts only on the body's responses to the stressor. This study examined the effects of alcohol only on reactions after the stressful experience had occurred. Alcohol administered intravenously immediately after the TSST dampened the cortisol responses, although it prolonged the negative subjective responses to the stress. This is consistent with the fact that the cortisol response is delayed, and part of a cascade of responses to acute stress. This finding suggests that the cortisol response to stress can be modified even after the initial experience of the stressor.

Taken together, these studies provide some support for the idea that alcohol has a stress-dampening effect, on measures of HR and subjective ratings and, to a lesser extent, cortisol levels. The studies with alcohol have focused on the role of expectancies, showing that just the expectancy of receiving alcohol can also dampen responses to stress.

2. Caffeine—Caffeine is a stimulant-like drug with anxiogenic properties that may contribute to risk for psychiatric disorders (Broderick and Benjamin, 2004). Two studies have examined the effect of caffeine on responses to the TSST (Lane et al., 1990; Lovallo et al., 2006). Lane et al. (1990) examined effects of acute caffeine (3.5 mg/kg or about 250 mg) on cardiovascular and hormonal (but not subjective) responses to a public speaking task in light caffeine users (<1 dose per day) and heavy caffeine users (3–5 doses per day). Caffeine increased plasma norepinephrine and BP and stress potentiated the effects of caffeine on epinephrine and cortisol. The level of habitual caffeine consumption did not alter responses, suggesting that tolerance does not develop to these effects. Lovallo et al. (2006) examined responses to the TSST in men and women who had consumed either caffeine (750 mg per day in three doses) or placebo for 1 week before the session. The group who had consumed caffeine exhibited a greater stress-induced increase in cortisol than the placebo group. Although these findings suggest that caffeine exacerbates physiological response to stress, they leave unanswered the question of whether caffeine increases subjective responses to the stressor.

3. Nicotine—Nicotine is of interest because it appears to have both stimulant-like and calming effects. Pharmacologically nicotine is considered a stimulant drug, and in studies

with laboratory animals, it increases activity of brain areas directly involved in stress responses (Jiang and Role, 2008; Mineur et al., 2016). Yet, smokers often also report that nicotine has a calming effect (Parrott, 1994). The design and interpretation of studies with nicotine in humans are also complicated by the presence of tolerance and withdrawal in regular smokers, which could independently influence responses to stress. The effects of nicotine on the TSST have been examined in two studies (Girdler et al., 1997; Wardle et al., 2011). Girdler et al. (1997) studied the effect of transdermal nicotine on a public speaking task in men and women who were either smokers (nicotine dose 21 mg/24hr) or nonsmokers (nicotine dose 7 mg/24 hr). Nicotine had little effect on responses to stress, although it increased HR reactivity to stress relative to placebo in men only. Wardle et al. (2011) studied responses to the TSST during acute withdrawal from smoking. Regular smokers either smoked as usual or abstained from smoking for 12 hours, and those who abstained were treated with either a nicotine patch (about 14 mg/24 hr) or a placebo patch before completing the TSST. The placebo patch group reported more subjective negative affect and greater increases in HR, BP, and cortisol after the TSST than the other groups. Thus, the *absence* of nicotine worsened the stress responses in these dependent smokers. Thus, there is no clear evidence that nicotine either increases or decreases responses to acute social stress in healthy adults.

4. Other drugs—Other studies have examined the effects of amphetamine, delta-9-tetrahydrocannabinol (THC) and 3,4-methylenedioxymethamphetamine (MDMA) on responses to the TSST. Childs et al. (2016) examined the effects of d-amphetamine (5 mg, 10 mg) on the TSST or a nonstress control in healthy volunteers. Amphetamine increased HR and cortisol levels in both the stress condition and the non-stress condition, but had little effect on the magnitude of the stress response. Interestingly, d-amphetamine did increase ratings of how stressful the subjects judged the TSST to be, and the higher dose prolonged the duration of feelings of tension after the TSST. It is possible that shared sympathetic or neuroendocrine mechanisms blur the distinction between effects of the stressor and response to a stimulant drug. In another study, Childs et al. (2017) found non-linear dose related effects of oral delta-9-tetrahydrocannabinol (THC; 7.5 and 12.5 mg) on response to the TSST in healthy adults, again including a no-stress control condition. Here, the lower dose reduced subjective distress after the TSST and attenuated post-task appraisals of the task as threatening and challenging, whereas the higher dose increased negative mood overall and increased pre-task ratings of the task as threatening and challenging. The higher dose of THC also impaired TSST performance and attenuated BP reactivity to the stressor. These opposing effects (anxiolytic at low doses and anxiogenic at high doses) are consistent with marijuana users' reports that the drug can both decrease and increase feelings of anxiety. Finally, Bershad et al. (2017) studied the effects of 3,4-methylenedioxymethamphetamine (MDMA; 0.5 and 1.0 mg/kg) on the TSST. The study was based on reports that MDMA has 'prosocial' effects and decreases reactivity to negative social stimuli (Bedi et al., 2009; Hysek et al., 2012; Frye et al., 2014; Kirkpatrick et al., 2014; Wardle and de Wit, 2014; Bershad et al., 2016). Thus, it was hypothesized that the drug would dampen reactivity to the social evaluative stress component of the TSST. However, the drug did not reduce responses to the TSST, on subjective, cardiovascular or hormonal measures.

Understanding the effects of drugs of abuse on responses to acute stress is important for several reasons. It is often assumed that people use drugs in part to relieve negative states or to cope with life stressors, but this idea has not been rigorously tested under controlled conditions. Conversely, the habitual use of drugs such as nicotine or caffeine may worsen responses to acute stressors and add to, rather than relieve, the overall burden of life stress. Studies such as those summarized here advance our understanding of how drugs affect different indices of stress, and how individual differences contribute to these effects.

Conclusions

This review focused on ph-TSST studies that were conducted for one of three reasons: i) to determine the clinical effectiveness of approved or potential psychiatric medications in reducing responses to acute stress, ii) to investigate the neurochemical receptor mechanisms involved in the stress response, and iii) to determine whether drugs of abuse are effective in 'self-medicating' or relieving responses to acute stress. In general, classic anxiolytic drugs such as the benzodiazepines reduce subjective ratings of anxiety, and to a lesser extent reduce cortisol levels, but have little effect on stress-induced increases in HR and BP. In contrast, single doses of serotonergic antidepressant drugs do not reduce responses to stress and indeed are occasionally anxiogenic, while limited evidence suggests that single doses of noradrenergic medications reduce the stress response. Whether chronic administration of serotonergic antidepressants results in attenuated responses to acute stress remains to be determined.

Mechanistic ph-TSST studies indicate that several neurotransmitters contribute to the stress response. Mu-opioid agonists reliably block cortisol responses to stress, but have mixed effects on subjective reports. Serotonergic drugs exert mixed effects on subjective responses to stress, with little effect on physiological stress responses. Different noradrenergic agents reduce responses to stress on subjective, cardiovascular and hormonal responses to stress. These findings raise interesting questions about which components of the stress response are affected by different drugs, how these differential actions affect future behavior and which mechanisms are important for long-term adverse consequences of stress. For example, the subjective experience of stress relief (i.e., anxiolytic effect) may motivate drug-seeking in the short-term to reduce stress, whereas the failure to recover from the hormonal response to stress may predict long-term adverse outcomes. The perception of a stressor is followed by a quick response of the sympathetic nervous system and longer-lasting, perhaps restorative response of the hypothalamic-pituitary axis system. The subjective experience of arousal or anxiety may result from the initial perception of the stressor, or from the sympathetic component of the stress response or from the hormonal response, and drugs may have actions at any of these stages. Whether an increase in physiological arousal (related to sympathetic activity or changes in cortisol levels) results in feelings of stimulation or anxiety likely depends on both the context and cognitions, including expectancies, and this idea is supported by the alcohol studies involving expectancies. Ph-TSST studies that separate these components of the stress response may help to understand adverse consequences of stress, and pharmacological and nonpharmacological approaches to minimizing these.

Overall, the studies summarized here illustrate the value of public speaking tasks to investigate effects of drugs under controlled conditions. This review points to the need for a standardized procedure such as the TSST to enable comparisons across studies. It also points to the need to control for cognitions and expectancy effects, and the inclusion of a no-stress control condition to separate drug effects unrelated to the stress. Inclusion of all three categories of stress response: subjective, cardiovascular measures as a proxy for sympathetic response and hormonal measures as an index of response of the hypothalamic-pituitary axis response, are needed to provide a complete profile of the action of a drug. Additional well-controlled ph-TSST studies will help us understand aspects of the acute stress response, and to develop effective treatments for stress-related disorders.

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Highlights

- Researchers conduct drug challenges studies with acute psychosocial stress to: i) determine the effectiveness of psychiatric medications, ii) investigate the neurochemical mechanisms involved in stress, and iii) determine whether drugs of abuse relieve responses to stress.
- Most anxiolytic medications reduce subjective responses to stress, whereas single doses of antidepressants do not.
- Several neurotransmitter systems are involved in the stress response, including serotonin, norepinephrine, GABA, glutamate, opioids, and endocannabinoids.
- Some nonmedical drugs such as alcohol and cannabinoids reduce responses to stress, whereas other drugs (caffeine, nicotine, and amphetamines) do not.
- Subjective ratings of anxiety are the most sensitive indices of drug effects on stress, and cortisol levels second to those.
- Cardiovascular indices of stress are not related to either subjective or hormonal responses.

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Table 1

Approved or potential psychiatric medications.

Drug, Dose, and Reference	Sample	Subjective Ratings	Cardiovascular Effects	HPA Axis Effects	Other Effects of Drug on Stress Response
Diazepam (5 mg, 10 mg) McNair et al. 1982 §	121 men	High dose decreased ratings of "tension/ anxiety" and increased ratings of fatigue before, during, and after the task	N/R	N/R	Low dose but not high dose decreased finger sweat print means during the task,
Diazepam (10 mg) Zuardi et al. 1993 §	10 men and women	Decreased anxiety before, during, and after task; Increased physical sedation before task; Increased dizziness before and during task	No effect on BP or HR	N/R	N/R
Diazepam (10 mg) Graeff et al. 1985 §	12 men and women	No effect on anxiety ratings	No effect on HR	N/R	No effect on EDA
Alprazolam (1 mg) Fries et al. 2006	46 men	No effect on ratings of "good mood", state anxiety or "agitation"	No effect on HR	Reduced ACTH and cortisol responses after task	No effect on epinephrine or norepinephrine levels after task
Alprazolam (0.5 mg) Rohrer et al. 1994§	20 men	N/R	Decreased systolic and diastolic BP; No effect on HR	Drug reduced ACTH and cortisol responses	No effect on prolactin levels after task
Lorazepam (1 mg) Guimarães et al. 1987 §	10 men and women	Decreased ratings of anxiety during task	No effect on BP; Increased HR following task	N/R	No effect on pupillary diameter or salivation
Clonazepam (1 mg) Zuardi et al. 2017§	6 men, 6 women	Decreased ratings of anxiety during and after task; Increased ratings of sedation after task	No effect on BP or HR	N/R	N/R
Gabapentin (400 mg, 800 mg) de-Paris et al. 2003 §	32 men	High dose decreased excitement and increased calm feelings before, during, and after task; Both doses decreased hostility before and after task	No effect on BP or HR	N/R	N/R
Flumazenil (1 mg) Kapczinski et al. 1994 §	20 men, 20 women	Decreased tension and anxiety before task	N/R	N/R	Decreased self-reported heart palpitations; No effect on EDA
Maprotiline (50 mg) Guimarães et al. 1987 §	10 men and women	Decreased subjective ratings of anxiety during and after task	No effect on BP or HR	N/R	Decreased salivation after task; No effect on pupillary diameter
Clomipramine (25 mg) Guimarães et al. 1987 §	10 men and women	Increased anxiety ratings during task	Increased duration of systolic BP rise after task	N/R	Increased pupillary diameter after task; decreased salivation after task
Escitalopram (10 mg, 20 mg) Garcia-Leal et al. 2010 §	43 men	Low dose increased anxiety before and 15, 30, and 60 mins after task; High dose increased anxiety only at 60 mins after task	No effect on HR or BP	High dose increased plasma cortisol immediately after task	High dose increased prolactin immediately after task
Nefazodone (100 mg, 200 mg) Silva et al. 2001 §	9 men, 25 women	High dose increased anxiety before and during task; Both doses increased reports of physical sedation before, during, and after task	N/R	N/R	

Note. N/R = Not Reported, HR = Heart Rate, BP = Blood Pressure, EDA = Electrodermal Activity (e.g., skin conductance).

[δ] Not full TSST, but some type of speech or public evaluation stressor.

Table 2

Mechanistic studies.

Drug, Dose, and Reference	Sample	Subjective Ratings	Cardiovascular Effects	HPA Axis Effects	Other Effects of Drug on Stress Response
Buprenorphine (0.2 mg, 0.4 mg sublingual) Bershad et al. 2015	32 men, 16 women	No effect on ratings of anxiety; Decreased ratings of how threatening the task was going to be	No effect on BP or HR	Both doses blocked cortisol response	N/R
Hydromorphone (2 mg, 4 mg) Bershad et al. 2017	30 men, 20 women	No effect on subjective ratings	No effect on HR or BP	High dose decreased cortisol response	Both doses reduced pupillary dilation after task
Acetaminophen (1000 mg) Bershad et al. 2017	30 men, 20 women	No effect on anxiety or task appraisal	No effect on BP or HR	Increased cortisol response to task	No effect on pupillary response
d-fenfluramine (15 mg, 30 mg) Hetem et al. 1996 §	27 men, 16 women	High dose decreased anxiety during task; low dose decreased anxiety after task	No effect on BP or HR	N/R	N/R
Ipsapirone (5 mg) Zuardi et al. 1993 §	10 men and women	Decreased anxiety during task	Decreased BP; No effect on HR	N/R	N/R
Sumatriptan (50 mg, 100 mg) de Rezende et al. 2013 §	36 men	High dose increased anxiety and decreased sedation before and during task	No effect on HR or BP	No effect on cortisol response	No effect on EDA
Metergoline (12 mg) Graeff et al. 1985 §	12 men and women	Increased anxiety before task	No effect on HR	N/R	No effect on EDA
Ritanserin (2.5mg, 10 mg) Guimarães et al. 1997 §	13 men, 32 women	High dose increased anxiety and discontentment	No effect on HR	N/R	No effect on EDA
Tryptophan depletion Monteiro dos Santos et al. 2000 §	15 men, 15 women	Trend toward increased anxiety during task in women only	No effect on HR or BP	N/R	N/R
Cannabidiol (300 mg) Zuardi et al. 1993 §	10 men and women	Decreased ratings of anxiety	No effect on BP or HR	N/R	N/R
Cannabidiol (100 mg, 300 mg, 900 mg) Zuardi et al. 2017§	17 men, 18 women	Moderate dose (300 mg) decreased ratings of anxiety during and after task; low dose and high dose had similar effects	Moderate dose slightly increased BP during task; No effect on HR	N/R	N/R
Lamotrigine (300 mg) Makatsori et al. 2004	19 men	N/R	Decreased diastolic BP	Decreased cortisol response after task	Decreased growth hormone after task
Propranolol (40 mg) Alexander et al. (2007)	8 men, 8 women	No effect on anticipated stressfulness of task	Decreased systolic BP during and after task; Decreased HR	N/R	Reduced stress-induced impairment of cognitive flexibility
Propranolol (80 mg) Andrews & Pruessner (2013)	30 men	No effect on ratings of stress	Marginally decreased systolic BP; Increased in HR	Increased cortisol response after task	Reduced SAA

Drug, Dose, and Reference	Sample	Subjective Ratings	Cardiovascular Effects	HPA Axis Effects	Other Effects of Drug on Stress Response
Propranolol (60 mg) Dreifus et al. 2014	24 men, 25 women^	Reduced anxiety; Decreased ratings of stressfulness of task	Decreased systolic BP after task	No effect on cortisol response	N/R

Note. N/R = Not Reported, HR = Heart Rate, BP = Blood Pressure, EDA = Electrodermal Activity (e.g., skin conductance), SAA = Salivary Alpha Amylase.

§ Not full TSST, but some type of speech or public evaluation stressor.

^ Indicates the number of subjects who completed the speech stressor.

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Table 3

Drugs of abuse.

Drug, Dose, and Reference	Sample	Subjective Ratings	Cardiovascular Effects	HPA Axis	Other Effects
Alcohol (1 g/kg) Levenson et al. (1980)[§]	48 men[^]	Decreased anxiety	Reduced HR during task	N/R	Reduced ear pulse transmission time during task
Alcohol (0.9 ml/lb) Bradlyn et al. (1981)[§]	28 men	No change in anxiety from before to after task	N/R	N/R	No effect on EDA; Decreased ratings of "anxious" during task by video coders
Alcohol (0.425 g/kg, 0.85 g/kg) Sher & Walitzer (1986)[§]	96 men	High dose reduced anxiety	Both doses of decreased HR after task	N/R	N/R
Alcohol (0.6 g/kg) Zimmerman et al. (2007)	9 men	N/R	N/R	No effect on cortisol response	Decreased ghrelin secretion
Alcohol (0 sober; 0 placebo; 0.8g/kg), Balodis et al. (2011)	29 men, 58 women	Both placebo and alcohol decreased tension and anxiety	N/R	Placebo and alcohol decreased cortisol response	No effect on SAA
Caffeine (3.5 mg/kg) Lane et al. (1990)[≠]	25 men	N/R	Increased BP before and during stress	Increased epinephrine and cortisol response	N/R
Caffeine (250 mg) Lovallo et al. (2006) [≠]	48 men, 48 women	N/R	N/R	Increased cortisol response	N/R
Nicotine (21 mg/24 h patch for smokers; 7 mg/24 h patch for non-smokers) Girdler et al. (1997)[§]	30 men, 46 women; smokers and non-smokers	N/R	Increased HR reactivity to task in men only	N/R	N/R
Nicotine (14.5 mg/24 h patch or smoke as usual) Wardle et al. (2011)	39 men, 10 women; regular smokers	No effect on positive or negative affect	No effect on HR or BP	Increased cortisol response after task	N/R
Amphetamine (5 mg, 10 mg) Childs et al. (2016)	28 men, 28 women	High dose increased post-task ratings of stressful; Both doses increased ratings of self-efficacy after task	Both doses increased HR	Both doses increased cortisol	N/R
THC (7.5 mg, 12.5 mg) Childs et al. (2017)	29 men, 13 women	Low dose decreased ratings post-task ratings of stressful and challenging	High dose reduced BP after task; No effect on HR	No effect on cortisol response	High dose slightly increased in number of pauses during task; No effect on mental arithmetic performance
MDMA (0.5 mg/kg, 1.0 mg/kg) Bershad et al. (2017)	30 men, 9 women	High dose increased subjective ratings of stress, tension, and insecurity after both TSST and a control task	Both doses increased HR after both TSST and a control task; High dose increased BP after both TSST and a control task	Both doses increased cortisol response after both TSST and a control task	N/R

Note. N/R = Not Reported, HR = Heart Rate, BP = Blood Pressure, EDA = Electrodermal Activity (e.g., skin conductance), SAA = Salivary Alpha Amylase.

§ Not full TSST, but some type of speech or public evaluation stressor.

≠ Not full TSST, but some type of mental arithmetic task with an audience component.

^ Indicates the number of subjects who completed the speech stressor.