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The Effect of Sublingual Testosterone on Ischemic Pain Sensitivity

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ABSTRACT

Sex differences in pain have been reported for over a half-century with males having higher pain tolerance and lower pain sensitivity than females. Testosterone, a male hormone, is associated with pain perception in humans. However, as of yet no study has directly manipulated a participants' testosterone to test for causal relationship between testosterone and pain. A double-blind fully-crossed study was conducted using sublingual administration of 0.5 mg testosterone. Twenty female participants completed two 5-hour sessions over a 3-day period. Participants completed an ischemic pain task, behavioral tasks and self-report measures at baseline and at post-administration to explore the effects of testosterone intervention on self-perceived health, aggression, risk-taking, body self-esteem, self-perceived mate value, sexual attitudes, and disgust. Three multilevel models were conducted to test how the drug intervention influenced levels of testosterone, estradiol, and progesterone. Testosterone was significantly higher for females who received the drug intervention as compared to females who received the placebo ($p < 0.001$). A significant interaction between time and intervention was also found for estradiol ($p < 0.001$) and progesterone ($p < 0.001$) meaning that both hormones were higher in females who received the testosterone intervention. Several one-way repeated

measure analysis of variance (ANOVAs) were carried out to examine the remainder of the outcome variables. Female participants given testosterone reported higher self-perceived physical functioning ($p = 0.04$) and exhibited higher risk-taking behavior when performing the Balloon Analogue Risk Task BART ($p = 0.03$) than those who received the placebo. However, testosterone did not influence the following variables: self-reported aggression, risk-taking behaviors, body image self-esteem, sexual attitudes, mate value, and disgust behaviors ($p > 0.05$). These findings suggest that a single sublingual administration of 0.5 mg testosterone is not powerful enough to alter pain perception in female participants but is sufficient to alter levels of other sex hormones along with risk-taking behavior and perceived physical functioning.

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TABLE OF CONTENTS

List of Figures

List of Tables

Chapter 1: Introduction

Sex Differences

Sex differences are not uncommon among medical and psychological diseases. There are several diseases and medical conditions such as temporomandibular joint disorder (TJD), fibromyalgia, irritable bowel syndrome (IBS), and arthritis that appear disproportionately more frequently in females than in males (Unruh, 1996). With IBS, for example, the female to male patient population ratios can range from 3:1 to 5:1 in certain patient populations (Heitkemper, Jarrett, Bond, & Chang 2003; Longstreth & Wolde-Tsadik, 1993; Toner & Akman, 2000). Symptom presentation of IBS can differ between females and males, with females exhibiting more symptoms of constipation, bloating, and severe abdominal pain while males may report diarrhea more often (Adeyemo, Spiegel, & Chang, 2010; Chang et al., 2006; Lovell & Ford, 2012;). IBS provides an excellent example of how a disease can appear more often in one sex and differ in its symptom presentation between the sexes. Some autoimmune diseases are also more prevalent in females than males, with more women suffering from Sjogren's Syndrome, Systemic Lupus Erythematosus, Multiple Sclerosis, thyroid disease, Sclerodema, and Rheumatoid arthritis (Whitacre, 2001).

It has long been reported that females suffer from depression more often than males (Radloff, 1975). A meta-analysis on sex differences in Post-Traumatic Stress Disorder (PTSD) found that women reported more symptoms associated with PTSD; however, they were less likely to experience a traumatic event (Tolin & Foa, 2006). Autism, a developmental disease characterized by dearth of language and social skills, has been found to be more common among boys than girls; however, there is evidence

that girls suffer from more problems with language and exhibit more signs of anxiety and depression related to autism (Hartley & Sikora, 2009). Taken together, stark sex differences in medical and in psychological diseases illustrates the importance in understanding sex differences in males and females. This is especially important when considering sex differences in pain, which is not just a universal human experience but is nearly universal in most animal species. Therefore, understanding the origins of sex differences in pain can lead to better predictions on when sex differences will be more pronounced and potentially lead to better diagnoses and treatments for pain.

Sex differences in pain have been observed numerous times within the pain literature, with some of the first reported sex differences appearing over 40 years ago (Notermans & Tophoff, 1967). Fillingim, King, Ribeiro-Dasilva, Rahim-Willimas, and Riley III (2009), in a review of sex differences in pain, found that in the last 30 years the literature of sex differences in pain has steadily increased starting in the mid-1990s. A meta-analysis on experimental pain studies found medium to large effect sizes with electrical, thermal, and pressure experimental pain paradigms indicating that men were more tolerant of pain and less sensitive (Riley III, Robinson, Wise, Myers, & Fillingim, 1998).

Numerous explanations have been made to explain origin of sex differences in pain. These differences include variations in brain morphology, genetics, social and psychological contributions, and hormones. Each of these explanations will be reviewed briefly, however, specific attention will be placed on hormones with an emphasis on testosterone.

Brain Morphology

Pain has been studied extensively in relation to brain morphology. The use of neuroimaging techniques such as electroencephalogram (EEG), Functional magnetic resonance imaging (fMRI), and positron emission tomography (PET) has lead researchers to conclude that certain cortical and subcortical areas of the human brain are responsible for the perception of pain. A meta-analysis performed on pain studies using neuroimaging techniques found that the thalamus, insular, anterior cingulate cortex (ACC), and the primary and secondary somatosensory areas were associated with the perception of an acute pain experience (Apkarian, Bushnell, Treede, & Zubieta, 2005). Pain, therefore, is a complex somatosensory process involving a network of several cortical and subcortical areas of the brain, which has led to the proposal of a "Pain Matrix" within the brain (Melzack, 1999). The Pain Matrix hypothesis for pain processing posits that the sensory network for perceiving pain can be modulated by one or several cortical areas. Yet, the exact interaction of this pain matrix and how the brain integrates the information from the different cortical areas is still debated (Legrain, Iannetti, Plaghki, & Mouraux, 2011; Tracey & Mantyh, 2007). Nevertheless, the identification of specific regions of the brain has led to the analysis of these regions in relation to sex differences in pain.

In humans, PET scans have shown that males had greater activation of the primary and secondary somatosensory areas, the insula, and parietal cortices while females showed greater activation in the perigenual cingulate cortex (Derbyshire, Nichols, Firestone, Townsend, & Jones, 2002). A PET study on IBS patients used a visceral pain stimulus (i.e., rectal inflation or catheter insertion) found that women had greater activation in the ventromedial prefrontal cortex, right ACC, and left amygdala

(Naliboff et al., 2003). On the other hand, men were found to have higher activation in the dorsolateral prefrontal cortices (DLPFC), insula, and dorsal pons/periaqueductal gray. Another PET scan study found that females had greater activation of the contralateral prefrontal cortex in a thermal pain task than men (Paulson, Minoshima, Morrow, & Casey, 1998). fMRI studies have also found sex differences in pain. For example, an fMRI study examining muscle pain induced by a saline injection found that men had greater activation in the mid-cingulate cortex and the DLPFC while females had greater activation in the cerebellar cortex and an increase in activation in the hippocampus during muscle pain and a decrease during cutaneous pain (Henderson, Gandevia, & Vaughan, 2008). Taken together, this body of research provides support to a neural origin to pain differences based on sex. As Fillingim et al. (2009) notes, though, sex differences in brain regions should be considered with caution since the pain induction techniques and the brain imaging techniques vary from study to study.

Genetics

Genetic explanations for sex differences in pain are limited, with insufficient support for genetic contributions in sex differences in pain. Several genes have been identified in animal models and humans that are associated with the perception of pain (see Foulkes & Wood, 2008 for a review). However, genetic explanations for sex differences in pain are limited. One study has found a link between a specific gene and sex differences in pain. The melanocortin-1 receptor (MC1R) is responsible for skin pigmentation that when activated produces melanin in skin, but invariant (i.e., mutant) versions of this gene produce light skin and red hair. In females who have this invariant version, had increased sensitivity to pain and an increase in analgesic responsiveness,

making them less sensitive to analgesics (Mogil et al., 2005). This finding presents new research methods to understanding sex differences in pain and treating pain.

Social and Psychological Contributions

Gender roles. Despite the physiological, hormonal, and genetic differences that have been reported, social and psychological influences have been found to modulate the perception and expression of pain in humans. The use of the dichotomous variable "sex" has been disputed in pain research in that its use is often confused with gender or social roles in which masculinity and femininity are learned and reinforced in children at a young age (Fillingim et al., 2009; Myers, Riley III, & Robinson, 2003). Sex differences in pain, therefore, might be the result of males and females being socialized to react to pain as expected of their gender role (i.e., boys do not cry and girls tell an adult).

Robinson et al. (2001) tested this assumption by developing the Gender Role Expectation of Pain questionnaire (GREP) and found that men and women both reported that men are expected to underreport their pain and that women are more sensitive and less tolerant of pain than men. Another study found that when controlling for an individual's GREP score, sex differences were eliminated in pain sensitivity and pain tolerance (Wise et al., 2002). It is important to note that when they performed hierarchical regression analysis, sex difference was maintained even after controlling for participants GREP scores. High self-reported masculinity by males correlated with higher pain tolerance, but no such relationship was found in women (Otto & Dougher, 1985). However, these results are not conclusive, with some studies reporting a relationship between gender roles and pain, but gender roles were unable to explain the sex differences (Myers, Robinson, Riley III, & Sheffield, 2001) and other findings showing

no relationship between gender and pain (Fillingim, Edwards, & Powell, 1999). Altogether, gender socialization should be considered when explaining sex differences in pain.

Psychological Disorders. Psychological factors (i.e., depression/anxiety) have also been found to contribute to sex differences in pain. Depression has been previously found to exacerbate pain reports in experimental studies in that individuals suffering from depression report more pain than individuals without depression (Bär et al., 2005; Piñerua-Shuhaibar et al., 1999). This is important when considering sex differences in pain because women are more often than men diagnosed with depression than men (Munce & Steward, 2007), and women report more pain associated with their depression than men (Marcus et al., 2008). How depression or mood might influence pain perception and expression differently in men and women is not known (Fillingim et al., 2009). However, differences in depression are no doubt important to understanding sex differences in pain.

Anxiety is another mental illness that is diagnosed in women more than in men (Regier et al., 1993). Women with high anxiety often report increased pain in both experimental and clinical settings (Rhudy & Williams, 2005; Robin, Vinard, Vernet-Maury, & Saumet, 1987). Women who reported being victims of physical and/or sexual abuse reported more somatic symptoms associated with pain (Riley III, Robinson, Kvaal, & Gremillion, 1998). Therefore, the anxiety level of the participant, especially if they are female, should be considered when studying sex differences in pain. Anxiety and depression should be potentially controlled when analyzing these differences in pain. However, depression and anxiety occur more often in females. Whether this is due to

socialization or biology is debatable, but biological causes for sex differences should not be completely ruled out.

Distraction and Coping Styles. Differences in distraction and coping styles have been implicated in sex differences in pain. Distraction, or the focusing of the participant/patient's attention away from the painful stimulus, has been researched as a potential aid to those that are experiencing pain. The belief is that if a participant/patient is not focusing on the pain, then they will perceive the pain as being less intense.

Research on distraction is mixed. Several studies conducted using chronic pain patients, patents undergoing a dental procedure, and normal college students have showed that there is no effect for distraction when engaging in a pain task (Aitken, Wilson, Coury, & Moursi, 2002; Goubert, Crombez, Eccleston, & Devulder, 2004; McCaul, Monson, & Maki, 1992). However, an MRI study examining the Anterior Cingulate Gyrus (ACG) found that when men and women engaged in a cold pressor task while distracted reported their pain as being less intense (Frankenstein, Richter, McIntyre, Rémy, 2001).

In another study, men who focused their attention on their pain as oppose to avoiding their pain reported less pain intensity while no effect was found in women (Keogh, Hatton, Ellery, 2000). This has led to further research demonstrating that men and women differ in their coping strategies. Men who focus on their pain sensations during a pain task feel less pain, but when focusing on the emotions they feel during a pain task they feel more pain (Keogh & Herdenfeldt, 2002). The opposite pattern was found with females, in that women who focused on the emotional component of pain reported less pain and women who focused on the sensations reported more pain.

In a chronic pain study with adolescents, males relied more on behavioral distraction coping strategies whereas females relied more on social support and emotion-focused coping strategies (Keogh & Eccleston, 2006). Again, as with depression and anxiety, it difficult to ascertain with certainty whether sex differences in distraction or coping styles are the result of biology/socialization or an interaction of the two.

Hormones

Estrogen. Logically, hormone variations across the sexes have been used to account for these differences. For example, estrogen has been implicated as pain pro-nociceptive agent. Several pain-inducing medical conditions (e.g. migraine headaches, Temporomandibular Joint Dysfunction [TJD], Irritable Bowel Syndrome [IBS]) either appear or worsen around puberty for females when estrogen level is naturally increased: such conditions are mitigated after menopause when estrogen is naturally decreased (Brandes, 2006; Mulak, Taché, & Larauche, 2014; Warren & Fried, 2001). The use of oral contraception that promotes estrogen in the body has been found to be associated with increased risk of TJD in females (LeResche, Saunders, Von Korff, Barlow, & Dworkin, 1997). In a study looking at transgender females using a hormone replacement therapy in the form of estrogen supplementation and anti-androgens, participants reported increased pain associated with their chronic pain condition (Aloisi et al., 2007).

Estrogens appears to promote pain, but the male androgens, specifically, testosterone appear to have the opposite effect, in that it dampens pain. It is therefore important to focus on testosterone and its association with pain to better understand how sex differences in pain may arise.

Testosterone. In humans, testosterone has been linked to the initial masculinization of the male brain (Morris, Jordan, & Breedlove, 2004) and further sexual differentiation of males at puberty with the development of secondary sexual characteristics (Hiort, 2002). Specifically, testosterone has been found to allocate energy to the development/growth of muscle tissue and skeletal cells (Kasperk, Wergedal, Farley, Linkhard, & Turner, 1989; Power & Florini, 1975).

Along with altering the physical appearance of males, testosterone also alters behaviors. Testosterone has also been implicated in courtship/mating behaviors (Hutchison, 1970; Lindzey & Crews, 1986; Wiley & Goldizen, 2003), territorial aggression (Hau, Wikelski, Soma, & Wingfield, 2000; Soma, Sullivan, & Wingfield, 1999), ornamentation (Ligon, Thornhill, Zuk, & Johnson, 1990; Parker, Knapp, & Rosenfield, 2002; Setchell, Smith, Wickings, & Knapp, 2008) and social rank (Muller & Wrangham, 2004; Rose, Holaday, & Bernstein, 1971) in several species. In humans, testosterone has been linked to dominant, antisocial, and aggressive behaviors (Archer, 2006; Mazur & Booth, 1998; Rowe, Maughan, Worthman, Costello, & Angold, 2004).

Testosterone and the immune system. Testosterone has been negatively correlated with parenting effort, immunity, and overall survival (Sinervo & Svensson, 1998; Wingfield, Hegner, Dufty, & Ball, 1990). In male birds for example, testosterone is at its highest during the mating season, and during this time the immune system is compromised in males with higher instances of infection and greater vulnerability to parasites (Deerenberg, Arpanius, Daan, & Bos, 1997; Owen-Ashley, Hasselquist, Wingfield, 2004; Saino, Bolzern, Møller, 1997; Sheldon & Verhulst, 1996 Zuk & Johnsen, 1998). The human immune system is also suppressed by the actions of

testosterone (see Muehlenbein & Bribiescas, 2005 for a review). One study examined males with higher fat-free mass and high limb muscle volume, which was previously associated with attractiveness, and found that males had lower C-reactive protein and white blood cell count (Lassek & Gaulin, 2009). Males given a flu vaccination had a reduction of testosterone the weeks following the vaccination. Finally, Men with respiratory infections or who had more flu/cold like symptoms were also found to have lower testosterone (Gettler, McDade, Agustin, Feranil, & Kuzawa, 2014; Muehlenbein, Hirschtick, Bonner, & Swartz, 2010). These studies provide evidence that, like with birds, the human immune system is suppressed by the actions of testosterone.

Testosterone, has many pleiotropic effects on the human body with some of those effects being beneficial to the individual (i.e., mating advantages), while others may be detrimental (i.e., immune suppression). Again, testosterone allocates energy, and in males mating effort is prioritized over the well-being of the body. It therefore stands to reason, by the actions of testosterone, that pain is also being suppressed in males. It has been recently argued that sex differences in pain might originate in differences in immune system functioning between the sexes, which may be modulated by the expression of sex hormones (see Rosen, Ham, & Mogil, 2017 for a review). Whether sex differences in pain originate in the immune system is not quite known, but based on the actions of testosterone on the immune system, it is important to know how testosterone modulates other bodily functions, specifically pain.

Testosterone and pain. Several studies have been conducted using animal models that have tested the role of testosterone and pain. In a study looking at gonadectomized male rats and gonad intact male rats, gonad intact rats showed a

decreased reaction (i.e., paw jerking, licking) after several formalin injections of testosterone (pain induction task) whereas gonadectimized rats had an increased reaction (Aloisi, Ceccarelli, Fiorenzani, De Padova, & Massafra, 2004; Ceccarelli, Scaramuzzino, Massafra, Aloisi, 2003). Another study looking at rats found the expression of c-Fos was unchanged in the hypothalamus, a region of the brain associated with pain, of the gonad intact males whereas its expression was increased in gonadectomized male rats (Aloisi, Ceccarelli, Fiorenzani, De Padova, & Massafra, 2004). In an experiment involving house sparrows, males given exogenous testosterone held their feet in hot water longer than controls but males who were given an androgen antagonist pulled their feet out much sooner than controls (Hau, Dominquez, & Evrard, 2004). These studies provide support that testosterone acts as an analgesic; animal models with higher testosterone than controls are less likely to express painful behaviors. Evidence is also provided showing that testosterone interacts with regions of the brain that are responsible for pain perception.

In humans, research on testosterone and pain are limited; however, there have been studies in clinical chronic pain and experimental acute pain that have found a link between the two. People who use opioids for chronic pain or abuse opioids show lower basal testosterone levels (Abs et al., 2000; Finch, Roberts, Price, Hadlow, & Pullan, 2000; Malik, Khan, Jabbar, & Iqbal, 1992; Rasheed, & Tareen, 1995). In opioid-induced hypogonadic men with chronic pain, those given exogenous testosterone reported a significant improvement in their pain in several pain measurements as well as in sexual functioning (Aloisi et al., 2011; Basaria et al., 2015). Furthermore, in a groundbreaking study involving transgender individuals and chronic pain, females transitioning to males

undergoing androgen replacement therapy reported a significant reduction in their chronic pain (Aloisi et al., 2007). On the contrary, males transitioning to females taking estrogen, or an anti-androgen reported an exacerbation of their chronic pain.

Experimental studies have also found a link between testosterone and pain. Choi et al. (2006) found that in female subjects who had high levels of basal testosterone who performed a pain task in their follicular stage of their menstrual cycle had greater activation of the left precentral gyrus and reduced activation of right thalamus, providing evidence that testosterone dampened pain in these females. Female oral contraception users with low testosterone were discovered to have lower threshold for pain by reporting pain at lower temperatures in a noxious thermal task than females with higher testosterone, and that activation of the rostral ventromedial medulla was reduced (Choi et al., 2006). Brain activation has also been found to differ in males as well. Males in a high placebo condition (strongly led to believe that an analgesic would be effective) had higher levels of testosterone, decreased pain, and stronger activation in the premotor areas, ACC, and the prefrontal cortex (Choi et al., 2011). Another study examined competitors in Kumdo, a Korean martial art, and found that pain was decreased after competition. This was positively related to an increase in testosterone post competition (Choi et al., 2013).

Based on the evidence from chronic pain studies and experimental studies, it is evident that pain is influenced by the presence and level of testosterone. The male androgen acts as an analgesic in humans to modulate pain expression in males. However, there are limitations to these human studies. First, there are limited studies that have examined the relationship between testosterone and pain in humans. No study has

experimentally manipulated the participant's testosterone levels to establish a causal link between the actions of this hormone and pain. While increased testosterone does alter chronic pain in opioid induced hypogonadic men and transgender males (Aloisi et al., 2011; Aloisi et al., 2007; Basaria et al., 2015), it is not known if testosterone alters acute pain in healthy individuals.

Testosterone Administration Methods

To better understand the relationship between testosterone and pain, it is vital to establish causal relationships by administering testosterone to participants. However, it is important that this is done safely and with minimal risk to the participants. Several methods exist for administering testosterone and dosages vary within and between methods.

Intramuscular injections. Studies examining men receiving intramuscular injections of anabolic-steroids with dosages ranging from 40 mg to 600 mg found not to moderate changes in behaviors (Bhasin et al., 1996; Su et al., 1993; Yates, Perry, MacIndoe, Holman, & Ellingrod, 1999). In females who received 40 mg of testosterone through intramuscular injections, anger proneness increased after 3 months, but overall aggressive behaviors did not (van Goozen, Frijda, & van de Poll, 1995).

Topical application. Another method of administration is topical application. Dosages for these studies also vary. In a study examining depression, men who received 100 mg of testosterone topically over several weeks reported less depression than men that received a placebo (Pope, H. G., Cohane, G. H., Kanayama, G., & Hudson, J. I. 2003). Men who were given 150 mg of testosterone topically selected images of themselves that were altered to appear more dominant. Finally, 50 mg of topically

applied testosterone has been shown to increase prosocial behaviors (i.e., decreased lying) in males (Wibral, Dohmen, Klingmüller, Weber, & Falk, 2012).

Sublingual administration of testosterone. A major concern when giving exogenous testosterone to participants is safety. Exogenous testosterone is known to have many detrimental side-effects (Kindlundh, Isacson, Berglund, & Nyberg, 1998; Nieminen, Rämö, Vitasalo, Heikkilä, Karjalainen, Mäntysaar, & Heikkilä, 1996). In the literature, sublingual administration using a 0.5 mg dosage has been used to safely increase female participants' testosterone while at the same time still being powerful enough to alter behaviors. This method, first used by Tuiten et al. (2000), was found to increase female participants' testosterone by 10-fold after 15 minutes of administration. Within 90 minutes after administration, the subjects returned to baseline levels of testosterone. After 4 hours of administration, subjects reported increased vaginal responsiveness, increased vaginal sensations, and sexual lust.

Because of the ease of administration, consistency in dosage, and relatively fast induction of behavior change, sublingual administration has many advantages over other methods. Sublingual administration in female has shown to reduce empathy (Hermans, Putman, & van Honk, 2006; van Honk et al., 2013), impair moral judgment (Montoya et al., 2013), reduce unconscious fear (van Honk, Peper, & Schutter, 2005), and alter stress response (Hermans et al., 2007). These studies have helped establish a causal link between testosterone and several behaviors. Based on the results reported in the literature, it can be argued that the induction method produces prototypical "male-like" behaviors in females. As such it is important to examine pain behaviors using this method of

testosterone induction to see how females react to pain after elevation in their testosterone level.

Current Study

There are many unanswered questions when concerning testosterone and pain. The current study attempted to answer some of those questions by exploring a causal link between testosterone and pain by experimentally manipulating participants' testosterone level. The study has the potential to illuminate the role of testosterone in pain and could be a stepping stone in a line of research that could not only treat pain, but also aid in the diagnosis of pain conditions in males and females. This is especially relevant considering the opioid epidemic in the United States (Manchikanti et al., 2012). It is important to note, to our knowledge this is the 1st study that has directly manipulated testosterone in humans while examining pain perception. The main hypothesis of this study is that when a female participant is given the testosterone intervention, they will exhibit better pain tolerance than a participant who receives a placebo.

Due to the exploratory nature of this project, several sub-hypotheses were proposed. As discussed above, testosterone influences a range of human behaviors, some of which have not been addressed using experimental manipulation. In keeping with the theme of the main hypothesis, several of these sub-hypotheses are concerning overall health. Sub-hypothesis 1: Sex differences in mortality indicate that women live longer than men (Owens, 2002), but men overwhelmingly report their health to be better than females and less instances of illnesses (Olsen & Dahl, 2007). Since testosterone alters psychosocial behavior, it is possible that testosterone is altering self-perceived health in men. In this study, we examined whether administration of testosterone in females would

also alter self-perceived health. Sub-Hypotheses 2: Similarly, disgust sensitivity varies by sex, in general, females are more sensitive to disgust stimuli than males (Davey, 1994; Haidt, McCauley, & Rozin, 1994; Schienle, Stark, Walter, & Vaitl, 2003). However, evidence indicates that females are more sensitive to disgusting stimuli with regards to sexuality (Tybur, Bryan, Lieberman, & Hooper, 2011; Tybur, Lieberman, & Griskevicius, 2009). Again, it was hypothesized that testosterone might be influencing the perception of disgust, which was explored in this study. Sub-hypothesis 3: Body image is another trait that varies between the sexes with males perceiving themselves to be more attractive than females (Feingold & Mazzella, 1998). Body dissatisfaction and lower self-esteem have been associated with one another in females, but in males, body dissatisfaction does not seem to influence self-esteem (Furnham, Badmin, Sneade, 2002). Perception of body image could also be influenced by testosterone which was explored in this study. Sub-hypothesis 4: Sex differences have been reported in responses to sexual stimuli with males being more concerned with regards to the actor they were observing while women were more interested in the context of the sexual stimuli (see Rupp & Wallen, 2008 for a review). Testosterone could be differentially influencing the interest in specific sexual stimuli which was investigated in this study.

Chapter 2: Methods

Participant Characteristics

A convenience sample was recruited from the University of New Mexico (UNM) Psychology SONA system. The SONA system consists of subject pool drawn from Introduction to Psychology classes at UNM. Twenty healthy female participants (M_{Age} = 18.7 [0.92]) took part in this study. Of the 20 participants in this study, 17 reported to be exclusively heterosexual, 2 to be bisexual, and 1 to be mostly homosexual. These participants were not taking any form of hormonal contraceptive and therefore were in their natural menstrual cycle. All females were targeted in their luteal phase of their cycle, which was determined from their last reported menstruation using a forward counting method and only women who reported having a regular menstrual cycle were eligible. Typically, ovulation is thought to occur between the 10^{th} and the 14^{th} day of the menstrual and therefore, we generally aimed for the 17^{th} day of their cycle. All participants were asked to inform the experimenter if menstruation had occurred before the start of their first session. If menstruation had occurred, participants were re-scheduled for another date. Exclusion criteria included individuals with a history of chronic pain, and/or peripheral nerve damage. Participants were excluded if they were taking blood thinners, corticosteroids, oxyphenbutazone, triamcinolone or any other prescription or supplement drugs that might alter their baseline testosterone level. Participants were not allowed to participate if they reported not feeling well. Pregnant female subjects were also excluded from this study using urine pregnancy tests.

Sampling Procedures

The study consisted of 2 experimental sessions that were approximately 5 hours per session. Participants who met the initial inclusionary criteria were invited to the lab for a pre-lab session. During this session participants were informed of the risks and benefits of their participation in the study and to verify their time commitment. Once the prospective participants had read and stated they understood what was required of them, they were allowed to sign the consent form and schedule their first lab visit.

On their first lab visit, participants were pre-screened for pregnancy, tree nut allergies, and any self-reported use of drugs (e.g., insulin, blood-thinners, corticosteroids, oxyphenbutazone, triamcinolone) that may alter their testosterone level. For both sessions, female participants were continually screened for pregnancy. During the course of the experiment, no female subjects tested positive for pregnancy. All participants were asked about any new medication used before the start of each session. Since exercise, sexual behaviors, and competitive activities may increase testosterone, all participants were instructed to avoid these activities on the day of their participation. Health status of all female participants was also carefully monitored to ensure they were all physically capable to participant in this study.

Participants were randomly assigned to either a placebo or a testosterone group before arrival. The experimenters were blinded to this assignment. Randomization of the placebo and experimental drugs were controlled by research pharmacist. All participants filled out a short survey for basic demographic information at the first experimental session after completion of the consent form.

Participants provided an initial saliva sample to establish their baseline testosterone level. Once they had given this sample, participants were either given the

drug intervention or a placebo. Upon being given the intervention, participants completed the first Balloon Analogue Risk Task (BART). They then provided the last saliva sample 15 minutes following the intervention. Participants remained in the lab for the duration of this 5-hour session. They were allowed to watch Netflix and listen to music as they waited. However, the content they viewed or listened to was limited to G or PG ratings in order to avoid potential fluctuations in their testosterone level. Participants were instructed to turn their cell phones off to ensure that their mood was not significantly altered. At the 4-hour mark, participants completed the pain task, questionnaires, the Three Domain Disgust Videos (TDDV) Disgust task, and the BART, respectively. Once this was completed, subjects were paid based on the money they earned during the BART. Each participant was also paid $5 for each session. The sessions were 3 days apart between the experimental sessions to ensure participants remain in their luteal phase. Participants were reminded about their informed consent before the start of their second session to ensure they understood their continued rights as research participants. In addition to being paid for their participation, participants were also awarded 3 research credits for each session for a total of 6 credits.

Pain Tasks

The ischemic discomfort task uses a sphygmomanometer (blood pressure cuff) placed 5 cm below the participant's elbow. Participants were instructed to raise their arm vertically in the air and hold in place for 1 minute to desanguinate the limb. The cuff was then inflated to 200 mmHg over the course of 20 seconds. The subjects were asked to lower their arm and perform handgrip exercise for a 30 second period. This procedure was previously found to be safe and effective means in producing pain (Johnson &

Tabasam, 2003; Ring et al., 2007). Participants were then asked to report when they first felt discomfort, first felt pain, and when they wanted to stop the task. This "stop time" was used as an indicator of pain tolerance. The more tolerant they were of pain, the later their stop time. Participants also reported their pain using a visual analogue scale (VAS) every 30 seconds. Participants were told they could discontinue the experiment at any time and were not allowed to exceed 6 minutes in the pain task. If a participant made it to 6-minute mark, the experimental task was automatically discontinued.

Behavioral Tasks

Balloon Analogue Risk Task (BART). The BART is a computerized measure of risk-taking behavior (Lejuez et al., 2002). In this task, participants are asked to inflate 60 virtual balloons using a pump. Each pump earns the participant 5 cents from which the participant can either choose to collect the money at any time or continue to pump in order to gain more money but at the risk of popping the balloon and losing any money earned. At the end of the task, participants collect the money earned in their bank. However, if the balloon "pops" as a result of inflating it too much, the participant does not earn any money from that balloon and a new balloon appears. The "explosion point" varied depending on the type of balloon the participant viewed. An adjusted average number of pumps was computed for each session completed. This adjusted average consisted of the average pumps of each trial in which the balloon did not explode.

Three Domain Disgust Videos (TDDV). The TDDV Task is comprised of 20 short videos that are based on the Three Domain Disgust Scale (Del Giudice, unpublished). Like the Three Domain Disgust Scale (Tybur, Lieberman, & Griskevicius, 2009), this task is comprised of three domains of disgust: pathogen (Testosterone Group

α = .69, Placebo Group α = .91), moral (Testosterone Group α = .58, Placebo Group α = .85), and sexual (Testosterone Group α = .91, Placebo Group α = .89) . The participants viewed 5 short videos in each domain in addition to 5 neutral videos. Using a 9-point Likert Scale, participants rated the videos from "not at All Disgusting" to "extremely disgusting." The TDDV Task was found to have a similar factor structure as the Three Domain Disgust Scale, and the pattern of sex difference was also similar (i.e., females were more sensitive to sexual disgust stimuli than males).

Self-Report Questionnaires

SF-36 Health Survey. The SF-36 Health Survey is a 36-item survey, which is commonly used to assess self-reported physical and mental health in the medical field (Appendix A: Turner-Bowker, DeRosa, & Ware Jr., 2008). There are two broad domain scale measures that assess physical and mental health. The survey also has 8 sub-scales which include: physical functioning (PF), role-physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role-emotional (RE), and mental health (MH).

Buss-Perry Aggression Questionnaire-Short Form. The original Buss-Perry Aggression Questionnaire (Appendix A: Buss & Perry, 1992) was a 29-item measurement of aggression with 4 subscales: physical (Testosterone Group α = .87, Placebo Group α = .70) , verbal (Testosterone Group α = .50, Placebo Group α = .21), anger (Testosterone Group α = .42, Placebo Group α = .64), hostility (Testosterone Group α = .60, Placebo Group α = .45), and total aggression (Testosterone Group α = .91, Placebo Group α = .87). For the purposes of this study, a refined 4 factor short-form (i.e., 12 items) was used (Bryant & Smith, 2001). This new refined questionnaire was

generalizable to subjects in three different countries and was equivalent for both males and females.

Domain-Specific Risk-Attitude Scale. To measure risk taking behaviors we used the domain-specific risk-attitude scale developed by Weber, Blais, and Betz (2002). This scale assesses 5 domains of risk taking behaviors, which include: financial (Testosterone Group α = .69, Placebo Group α = .69) , health/safety (Testosterone Group α = .59, Placebo Group α = .61), recreational (Testosterone Group α = .75, Placebo Group α = .79), ethical (Testosterone Group α = .90, Placebo Group α = .84), social risks (Testosterone Group α = .74, Placebo Group α = .64), and total aggression (Testosterone Group α = .88, Placebo Group α = .84). The scale contains 50 statements pertaining to the different risk-taking domains in which the subjects use a Likert scale to state how likely or how unlikely they were to perform the activity (Appendix A).

Body-Esteem Scale. The Body-Esteem Scale is a 35-item survey that assesses how participants perceive their own body (Appendix A: Franzoi & Shields, 1984). The scale consists of 3 sub-scales: weight concern (Testosterone Group α = .89, Placebo Group α = .88), physical condition (Testosterone Group α = .86, Placebo Group α = .86), and sexual attractiveness (Testosterone Group α = .76, Placebo Group α = .76). This survey has been used consistently in the literature over the last 30 years, and has only been recently revised (Frost, Franzoi, Oswald, & Shields, 2018).

Self-Perceived Mating Success Scale. This is a 10-item survey, which assesses the participants' perceived mating success using a 7-point Likert scale (Appendix A: Landolt, Lalumière, and Quinsey, 1995). An example of one of the questions is "I am able to attract individuals I find desirable as relationship partners." Two of the items are

reverse scored and all scores added together to form a composite score (Testosterone Group α = .78, Placebo Group α = .77) called "mate value."

Three Domain Disgust Scale. The Three Domain Disgust Scale (Appendix A) is a 21-item measurement consisting of three sub-scales: moral (Testosterone Group α = .79, Placebo Group α = .84), sexual (Testosterone Group α = .89, Placebo Group α = .89), and pathogen (Testosterone Group α = .68, Placebo Group α = .75: Tybur, Lieberman, & Griskevicius, 2009). This scale used a 7-point Likert scale in which the participants were asked to rate items as "Not Disgusting at All" to "Extremely Disgusting." An example of an item would be "Hearing two strangers have sex." In development, a consistent sex difference was found using this scale in which female participants were more sensitive to sexual disgust than males.

Interest in Visual Sexual Stimuli. This scale is a 10-item measurement that uses a 7-point Likert scale that assesses interest in sexual stimuli (Appendix A: Bailey, Gaulin, Agyei, & Gladue, 1994). An example of an item is, "If I met someone I found very attractive right now, I would fantasize about what they would look like without clothes on." Items 5 and 9 were reverse scored and all items were summed together to form a score on this scale referred to as sexual attitudes (Testosterone Group α = .86, Placebo Group α = .91) in the analysis.

Hormonal Assessment

Each subject was given a saliva oral swab for saliva collection. Participants were instructed to lightly chew on the cotton swab for approximately 1 minute then instructed to place the swab in a test tube where it will be stored 4° C. Three hormones were measured from the participant's saliva: testosterone, estradiol, and progesterone. All

saliva assays were processed at the Hominoid Reproductive Ecology Laboratory located on UNM Main Campus. Saliva swab tubes were centrifuged for 15 minuets at 4° C. Once saliva samples were purified, Salimetrics enzyme-linked immunosorbent assay (ELISA) diagnostic kit was used to extract testosterone, estradiol, and progesterone levels. For testosterone, interassay coefficients of variation (CVs) were 11.67% for a high control, a0.96 % for a low control, and the intraassay CV was 4.65%. For estradiol, interassay CVs were 2.64% for a high control, 3.35 % for a low control, and the intraassay CV was 1.95%. For progesterone, interassay CVs were 0.98% for a high control, 35.25 % for a low control, and the intraassay CV was 3.89 %. Testosterone measurement using salivary sample has been found to be a reliable indicator of assessing hormonal level of individuals and has been used for diagnoses of endocrine dysfunction in both males and females (Cardoso, Contreras, Tumilasci, Elbert, Aguirre, Aquilano, & Arregger, 2011; Karrer-Voegeli, Rey, Reymond, Meuwly, Gaillard, & Gomez, 2009; Morely, Perry, Dollbaum, & Kells, 2006; Shirtcliff, Granger, & Likos, 2002).

Testosterone Administration

The Testosterone and placebo were dispensed in oil-based sublingual product prepared by the UNM Investigational Drug Service Pharmacy (see Appendix B for more details). It was thought that using the 0.5 mg dosage for this study would reduce the risk of any potential adverse effects as these methods have also been safely used in other research designs. A medical doctor on staff prescribed the testosterone. Either the experimental testosterone or a placebo was prepared on the day of the experimental session which was picked up by a member of the research team. The experimenter and participants were blinded on whether they received testosterone or placebo. Prior studies

have found that 0.5 mg of testosterone is a safe and effective means to manipulate testosterone level in females and produce behavioral effects (Herman, Putman & van Honk; 2006; Hermans, Ramsey, & van Honk, 2008; Montoya et al., 2013; Tuiten, et al., 2000; van Honk et al., 2004). From the pilot study (Strenth, Kruger, Thompson, Vigil, Reeves, in preparation) and previous studies, we found that females quickly metabolize testosterone after administration and many returned to their baseline level by 3 hours and 30 minutes after the administration.

Statistical Analysis

Linear mixed effect models were used for the analysis of testosterone, estradiol, and progesterone outcome variables in R version 3.4.3 (R Core Team, 2017) using the *nlme* package (Pinheiro, Bates, debRoy, Sarkar, & R Development Core Team, 2013). A two-level random intercept model was fit using 80 observations. The model included the main effects of time-point (pre vs. post), the intervention (placebo and testosterone), and the time * intervention interaction at the first level. The first level was nested in the participants, which served as the second level. The testosterone variable was non-normal and was log transformed to correct for this.

Several one-way repeated measures analysis of variance (ANOVAs) were conducted to examine the within-subject effect of the drug intervention on the remainder of the outcome variables. These analyses were carried out using SPSS Version. 25. The Sphericity assumption was met for all analyses.

Chapter 3: Results

Testosterone, Estrogen, and Progesterone

Table 1 displays the two-level multilevel model summary table for the testosterone dependent variable. There was a significant main effect of time (β = 0.18, *SE* = 0.05, *p* = 0.002) and a significant interaction between time and the intervention (β =1.16, *SE* = 0.07., *p* < 0.001). A test of the simple effects found a significant effect for the testosterone intervention when moving from pre to post time-points (M_D = -1.34, *t*[57] = -25.38, *p* < 0.001, See Figure 1). Table 2 displays the two-level multilevel mode summary table for the estradiol dependent variable. A significant interaction between time and the intervention variable was found when predicting estradiol (β = 1.08, *SE* = 0.25, *p* < 0.001). A test of the simple effects found a significant effect for the testosterone intervention when moving from pre to post time-points for estradiol (M_D = -0.90, *t*[57] = -5.02, *p* < 0.001, See Figure 2). Finally, Table 3 displays the two-level multilevel model summary table for the progesterone dependent variable. A significant interaction between time and intervention was found (β =453.02, *SE* = 97.33, *p* < 0.001). Finally, A test of the simple slopes found a significant effect for the testosterone intervention when moving from pre to post time-points for progesterone (M_D = -423.64, *t*[57] = -6.16, *p* < 0.001, See Figure 3)

Pain

Three one-way repeated measure ANOVAs were carried out comparing the placebo with the testosterone intervention on the three pain variables: discomfort, pain, and stop. Table 4 displays the means, standard deviations, and within-subject test of the

pain variables. The placebo group did not differ from the testosterone group on any of the pain variables ($p > 0.05$).

Health

Eight Three one-way repeated measure ANOVAs were carried out comparing the placebo with the testosterone intervention on the eight health variables: PH, RP, BP, GH, VT, SF, RE, and MH. Table 5 displays the means, standard deviations, and within-subject test of the health variables. There was a significant effect of drug intervention on PH (F [1, 19] = 4.74, $p = 0.04$, $\eta^2 = 0.20$). Female participants who received the testosterone intervention reported higher PH than females who received the placebo. The placebo group did not differ from the testosterone group on any of the remaining health variables ($p > 0.05$).

Aggression

Five one-way repeated measure ANOVAs were carried out comparing the placebo with the testosterone intervention on the five aggression variables: hostility, anger, verbal, physical, and total aggression. Table 6 displays the means, standard deviations, and within-subject test of the aggression variables. The placebo group did not differ from the testosterone group on any of the aggression variables ($p > 0.05$).

Risk-Taking

Seven one-way repeated measure ANOVAs were carried out comparing the placebo with the testosterone intervention on the five risk-taking variables: recreational, health, ethical, financial, social, total risk and the BART. Table 7 displays the means, standard deviations, and within-subject test of the risk-taking variables. There was a significant effect of drug intervention on the BART (F (1, 19) = 5.11, $p = 0.03$, $\eta^2 =$

0.21). Female participants who received the testosterone intervention had a higher adjusted average number of pumps when inflating the balloons than females who received the placebo. However, the placebo group did not differ from the testosterone group on any of the remaining health variables ($p > 0.05$).

Body Self-Esteem

Three one-way repeated measure ANOVAs were carried out comparing the placebo with the testosterone intervention on the three body self-esteem variables: PC, WC, and SA. Table 8 displays the means, standard deviations, and within-subject test of the body self-esteem variables. The placebo group did not differ from the testosterone group on any of the body self-esteem variables ($p > 0.05$).

Mate Value and Sexual Attitudes

Two one-way repeated measure ANOVAs were carried out comparing the placebo with the testosterone intervention on the mate value and sexual attitudes variables. Table 9 displays the means, standard deviations, and within-subject test of the body self-esteem variables. A difference between the placebo and testosterone group approached significance for the mate value variable (F [1, 19] = 3.83, $p = 0.06$, $\eta^2 = 0.17$) with females receiving the testosterone intervention reporting higher mate value. The placebo group did not differ from the testosterone group on the sexual attitudes scale ($p > 0.05$).

Disgust

Six one-way repeated measure ANOVAs were carried out comparing the placebo with the testosterone intervention on the six disgust variables: moral, sexual, pathogen, TDDV moral, TDDV sexual, and TDDV disgust. Table 10 displays the means, standard

deviations, and within-subject test of the disgust variables. The placebo group did not differ from the testosterone group on any of the disgust variables ($p > 0.05$).

Chapter 4: Discussion

The current study found additional support for the alteration of endogenous testosterone in female participants by sublingual administration of exogenous testosterone. Additionally, this study has provided evidence that this method of testosterone administration alters the sex hormones estradiol and progesterone. In examining pain variables, our intervention did not alter times in which the participants first reported pain, first reported discomfort, or when they wanted to stop the pain task. PF was altered due to the intervention with participants reporting higher physical functioning than females who received placebo. The placebo and the testosterone group also differed in the BART with female participants given the testosterone intervention increased their pumps for each balloon indicating higher risk-taking behavior. A difference between the placebo and testosterone intervention approached significance when examining the mate value variables. However, all other variables: aggression, risk-taking, body self-esteem, sexual attitudes, and disgust were non-significant.

Testosterone, Estradiol, and Progesterone

Testosterone is readily converted into estradiol by both males and females whether the source is endogenous or exogenous (Campfield, Saul, & Swerdloff, 1982; Gibori & Kraicer, 1973; Hillier & Ross, 1979; Longcope, Kato, & Horton, 1969; Sokol, Palacios). This is not surprising since testosterone is a precursor to estradiol and is converted by enzyme aromatase (Ishikawa, Glidewell-Kenney, & Jameson, 2006). Therefore, with this type of administration, one would expect that part of the exogenous testosterone would be converted into estradiol.

It is unclear as to why progesterone was also significantly increased in females. Previous studies that examined the relationship between exogenous testosterone and progesterone have found that the male sex hormone does not influence the production of progesterone (Hillier & Ross, 1979; Richardson & Masson, 1981). However, little has been published on this relationship. Unlike estradiol, progesterone is produced early on in the steroidogenesis pathways, which takes cholesterol and converts into the many steroid hormones found in the body (see Miller & Auchus, 2011 for a review). Meaning that neither hormone should influence the other. It is possible that the surge in testosterone due to the intervention disrupted the normal regulatory pathway that controls steroidogenesis in the hypothalamic-pituitary-gonadal (HPG) axis. As a result, this leads to not only increase in testosterone and estradiol but also augmentation of other hormones as well.

Another possible explanation for elevated levels of estradiol and progesterone could be due to the actions of sex hormone binding globulin (SHBG). SHGB is a protein that binds to the majority of circulating androgens and estrogens and reduces their bioavailability (Anderson, 1974). Concentrations of SHBG are positively associated with concentrations of estrogen, and thus are higher in adult females versus males (Goto et al., 2014; Edlefsen et al., 2010). This protein has a higher affinity to bind to androgens than to other sex hormones. Therefore, it is possible that female participants may have elevated SHBG in their systems such that exogenous testosterone administered would be bound by the SHGB making it appear that other hormones such as estradiol and progesterone are higher in concentration. Future research should consider measuring SHGB in relation to this method of testosterone administration.

Time course effects were not explored in this study, so it is unknown whether this increase in estradiol, and progesterone was temporary, relative to the increase in testosterone or whether these increases were similar. Like testosterone, it is possible that elevations in estradiol and progesterone might affect behavior at a much later time. Whereas the behavioral effects of testosterone might manifest around 4 hours, the elevations in estradiol and progesterone might influence behavior before or after 4 hours. This study showed an initial increase in estradiol and progesterone, however, as testosterone is converted to estradiol, it could be possible to see another rise in estradiol and progesterone. Future testosterone administration studies should explore the relationship between these three hormones over time. However, the increases in estradiol and progesterone does call into question whether the effects found in previous studies are the result of testosterone alone or whether it is actually contribution of all three hormones.

How these hormones interact with each other when elevated is not known. It was previously noted that estradiol tends to exacerbate pain when elevated. Testosterone might dampen pain, but this may be relative to the level of estradiol. The fact that pain and several other behaviors were unaffected by the intervention may be the result of the individual effects of each hormone canceling each other out. Therefore, estradiol and progesterone might need to be relatively low in relationship to testosterone for pain to be dampened.

Pain

Prior research examining opioid-induced hypogonadism in men, and transgender men found that testosterone alleviated chronic pain symptoms in these individuals (Aloisi

et al., 2011; Aloisi et al., 2007; Basaria et al., 2015). The current study did not find that the testosterone intervention altered pain tolerance. However, testosterone should not be ruled out for altering pain perception. The aforementioned studies administered testosterone multiple times and at a much higher dose whereas we used a very small dose in comparison. For pain to be altered, organizational changes to the body as a result of high dosages of testosterone may be required. Future research on this topic should explore the relationship between the variations in dosages and the cumulative effect of multiple doses.

The current study only used one type of pain task, and it is possible that testosterone may alter specific domains of pain. For example, pregnant women have been found to be more sensitive to heat pain than cold pain (Carvalho et al., 2006). The ischemic pain task used in this study is thought to produce a deep muscular pain. This type of pain might be a symptom of a more serious injury and may not be dampened by testosterone. A more superficial pain (e.g. heat/cold pain) may be dampened more by the effects of testosterone than a muscular pain.

This study found no effect of exogenous testosterone on pain in the short-term, however, this study does contribute to the scientific literature by providing more evidence on the use of testosterone as an aid to pain. When considering treatment modalities for pain, an acute administration of testosterone might not make a difference in pain perception in the short-term, but it is possible that at higher doses over the course of time could be used in conjunction with opioids to either reduce pain or reduce the use of opioids in individuals suffering from chronic pain or extreme trauma. More research is

needed, and the positive effects of testosterone need to be weighed against its side-effects. Yet, it still might be possible to use this hormone in the management of pain.

Health

Men report better health and less diseases than women even though male's mortality is higher than females (Olsen & Dahl, 2007; Owens, 2002). Women given testosterone reported greater physical functioning (e.g. climbing stairs, bending, kneeling, and walking moderate distances) than women who received placebo. Testosterone, therefore, maybe altering the perceptions of the individual; in someone who has high testosterone believes they are more capable of physical tasks that would normally be painful. There were no other significant differences between the placebo and testosterone interventions when addressing the other sub-scales of the SF-36 Health Survey. A study examining the effect of exogenous testosterone in older men and the SF-36 Health Survey found that both the placebo group and the testosterone groups had declining perceived physical and mental health after a 12-month period (Kenny, Bellantonio, Gruman, Acosta, & Prestwood, 2002). However, decline in perceived health might be due more to the complications of old age. A study on hypogonadal men given testosterone, found that testosterone supplementation improved energy, good feelings, and friendliness (Wang et al., 1996). More research is needed to elucidate the relationship between perceived health and testosterone.

Considering possible treatments in relation to the findings of this study, it might be feasible to use testosterone to treat pain catastrophizing. Pain catastrophizing consists of repeated thoughts of worry that tend to exacerbate pain which can be debilitating, and these thoughts are common among those who suffer from chronic pain (Keogh &

Asmundson, 2004; Sullivan et al., 2001). In this study, testosterone increased perceived physical functioning in normal female participants. Testosterone could be used as a treatment for individuals suffering from chronic pain to treat pain catastrophizing for chronic pain patients, which may motivate these patients to engage in behaviors or activities that they previously thought may cause pain. As of yet, pain catastrophizing has not been examined using testosterone.

Risk-Taking

When female participants received testosterone, their average pumps for the BART increased significantly, meaning participants engaged in riskier behaviors in order to attain larger monetary rewards in the BART. This finding confirms previous research showing that high endogenous levels of testosterone are associated with increased risk-taking behaviors (Ronay & Hippel, 2010; Stanton, Liening, & Schultheiss, 2011; van Honk Schutter, Hermans, Tuiten, & Koppeschaar, 2004; Vermeersch, T'Sjoen, Kaufman, & Vincke, 2008). This is the first study to show that exogenous testosterone alters risk-taking when participants are using the BART.

However, despite the significant findings with the BART, the risk-taking subscales for the Domain-Specific Risk-Attitude Scale were all non-significant. It is possible that this behavior scale, which used a 6-point Likert-scale, was not sensitive enough to detect the changes in behavior caused by the testosterone intervention. Several flaws have been pointed out concerning the use of self-report measures: such as participants lacking the ability to accurately self-report and the tendency for participants to respond in ways perceived as socially acceptable (John & Robins, 1994; Paulhus, 1991). The BART, therefore, might have been a more reliable to assess risk-taking

behaviors than the Domain-Specific Risk-Attitude Scale. This is evident by the low Cronbach's alphas found for the sub-scales of this scale.

Aggression

None of the sub-scales to the Buss-Perry Aggression Questionnaire Short-Form were altered due to the intervention. This is a surprising finding considering body of research linking aggression with testosterone (see Archer, 2006 for a review). Again, this questionnaire uses a 5-point Likert scale, and may not have been sensitive to detect variations in aggression due to the testosterone intervention. Like with the Domain-Specific Risk-Attitude Scale, participants could have also been reluctant to self-report on behaviors that are not socially acceptable.

Body Self-Esteem, Mate Value, and Sexual Attitudes

The current study did not find any significant differences between the placebo and testosterone intervention for any of the measures of body self-esteem and sexual attitudes. A difference between the placebo and testosterone intervention approached significance for the mate value variable. Previous research on sexual motivations and body image has suggested that for women, estradiol and progesterone play a more significant role in these behaviors than testosterone (Carr-Nangle, Johnson, Bergeron, & Nangle, 1994; Eisenbruch, Simmons, & Roney, 2015; Roney & Simmons, 2013). Previous research has linked attractiveness with endogenous levels of estradiol and progesterone (Jasienska, Ziomkiewicz, Ellison, Lipson, Thune, 2004), however, a large study on attractiveness and hormones recently found no relationship between attractiveness, progesterone, and estradiol (Jones et al., 2018). More research is needed to confirm what role, if any, testosterone plays in sexual motivations and body image.

Disgust

None of the disgust variables were influenced by the testosterone intervention. Again, it is possible that estradiol and progesterone play a bigger role in disgust sensitivity than testosterone. A study on pregnant women found women were more sensitive to disgusting stimuli during the first trimester of pregnancy (Fessler, Eng, & Navarrete, 2005). This could be an indication that estradiol and progesterone are influencing perceptions of disgust. Future research should examine how these hormones influencing disgust.

Limitations

The intervention proved to not be influential to many of the outcomes investigated in this study. A reason for this might be due to the sample size. Many of the outcomes investigated in this study have not been examined using this method administration or dosage. Although the sample size used in this study is comparable to previously published studies (Hermans, et al., 2006; van Honk et al., 2013), the effects under investigation were probably smaller requiring a larger sample size in order to capture them.

Thirty-five within-subject analyses were performed, and it is possible that significant findings found for PF and BART are product of random chance rather than actually being significant differences between the groups (Tukey, 1991). That being said, the findings from this current study concerning these two variables should be considered in light of this.

In the pain tasks, all of these experimental procedures were carried out by a male experimenter. Previous research has shown that women report pain differently depending

on the sex of the experimenter whether short or long exposure (Vigil & Coulombe, 2011; Vigil et al., 2015; Vigil, Rowell, Alcock, Maestes, 2014;). It is possible that female participants' pain response was being influenced by the presence of the male experimenter, which could have superseded the effect of the drug intervention. Testosterone administration studies that examine pain should try in the future to have mixed sex experimenters to see if the effect of the administration differs between the sexes.

All female participants were examined during the luteal phase of their menstrual cycle however, it is not known whether this method of administration varies across the menstrual cycle. For example, a meta-analysis on menstrual cycle effects on pain found women were more sensitive to pain during the luteal phase (Rilley III, Robinson, Wise, & Price, 1999). It is possible that the females in this study were already "primed" to be more sensitive to pain. The momentary flux in testosterone might have done little to influence this menstrual cycle effect on pain. More research is needed to explore how different phases of the menstrual cycle influence testosterone administration.

Several measures were used in this study and it is possible that some of those measures were measuring trait behaviors while others were measuring state behaviors. A personality trait can be defined as aspect of a person's personality that does not change and is consistently the same, whereas a state attribute is how that individual feels in that moment (Watson & Pennebaker, 1989) The measures of aggression, body self-esteem, risk-taking, and some of the measures of the SF-36 Health Survey may have been capturing trait-like behaviors. This indicates that the administration of testosterone would not have as much effect on altering these behaviors. The null effects found with these

variables might be due to the fact that one would not expect these behaviors to vary due to temporary variations in hormonal levels. The measures of interest in sexual stimuli, disgust, pain, and the BART, on the other hand, might be more appropriate to use in this investigation since it could be argued that these are more "state-like" behaviors and are more susceptible to variations in testosterone.

It is unknown whether a ceiling effect or floor effect exists with this type of administration. It is possible that for some of the participants that the sudden increase in testosterone was not as effective for some as it was for others. Testosterone, when increased may not continue to alter behaviors past a certain point. There are no reported ceiling effects or floor effects for this method of administration, but nevertheless, more research is needed to explore the limits of this method.

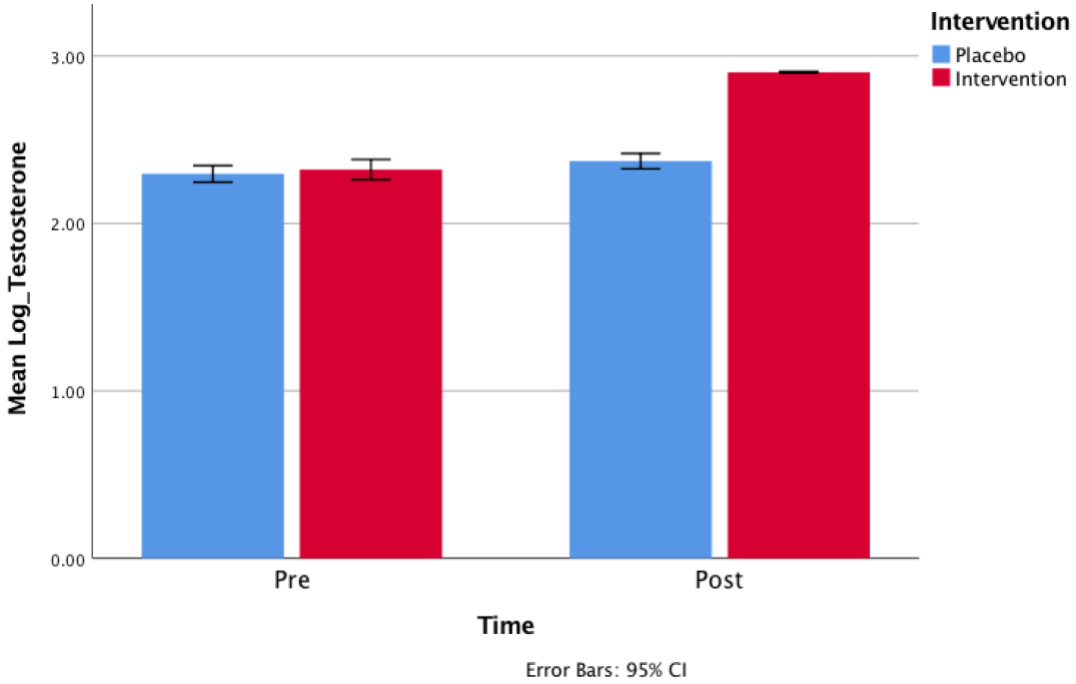
Conclusions

The sublingual administration of testosterone altered not only endogenous levels of testosterone, but also that of estradiol and progesterone. In light of these findings, future administration studies should consider whether testosterone alone is influencing behavior or whether it is a combination of all three hormones. Pain was not influenced by exogenous testosterone, but it is possible that a small single dosage is not powerful enough to alter pain in females. More research is needed to explore whether larger dosages are required to alter pain. The findings with the PF variable provides further evidence that testosterone may be altering one's perceived health. Additional support is also provided showing that testosterone alters risk-taking behaviors. While most of the effects explored in this study were none significant, more research is needed using this

method of administration to capture the effects of aggression, body self-esteem, sexual attitudes, and disgust.

Figure 1.

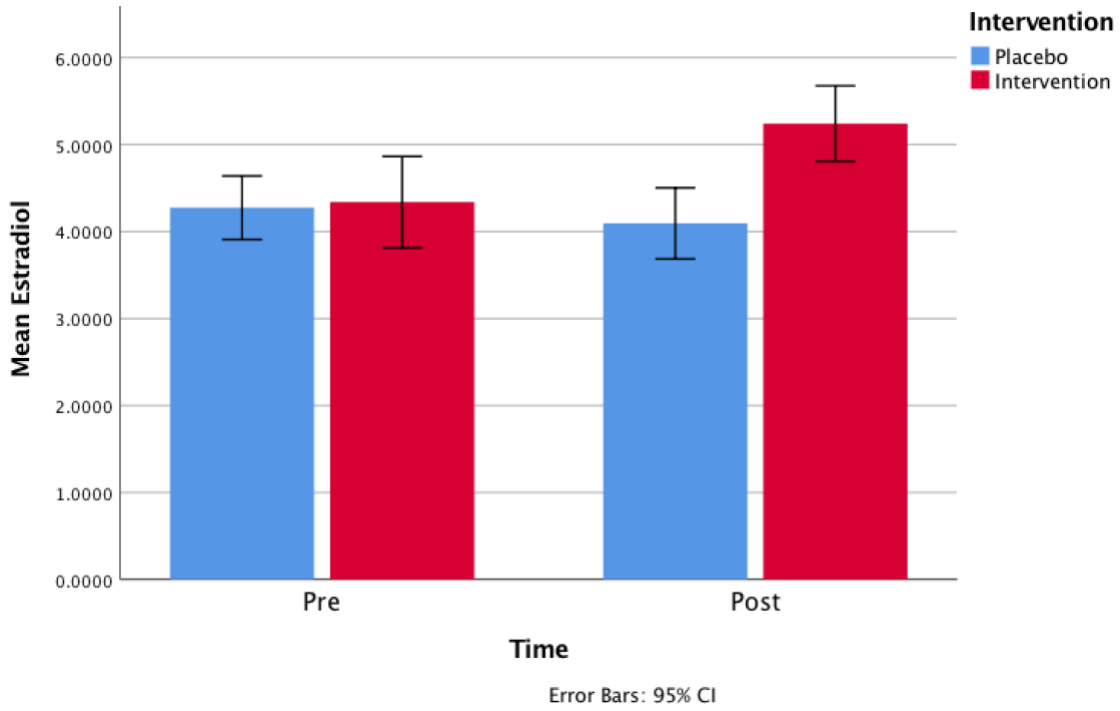
Bar Means of Log Transformed Testosterone by Time and Intervention



Note. Testosterone is log transformed in this graph. Error bars are 95% confidence intervals.

Figure 2.

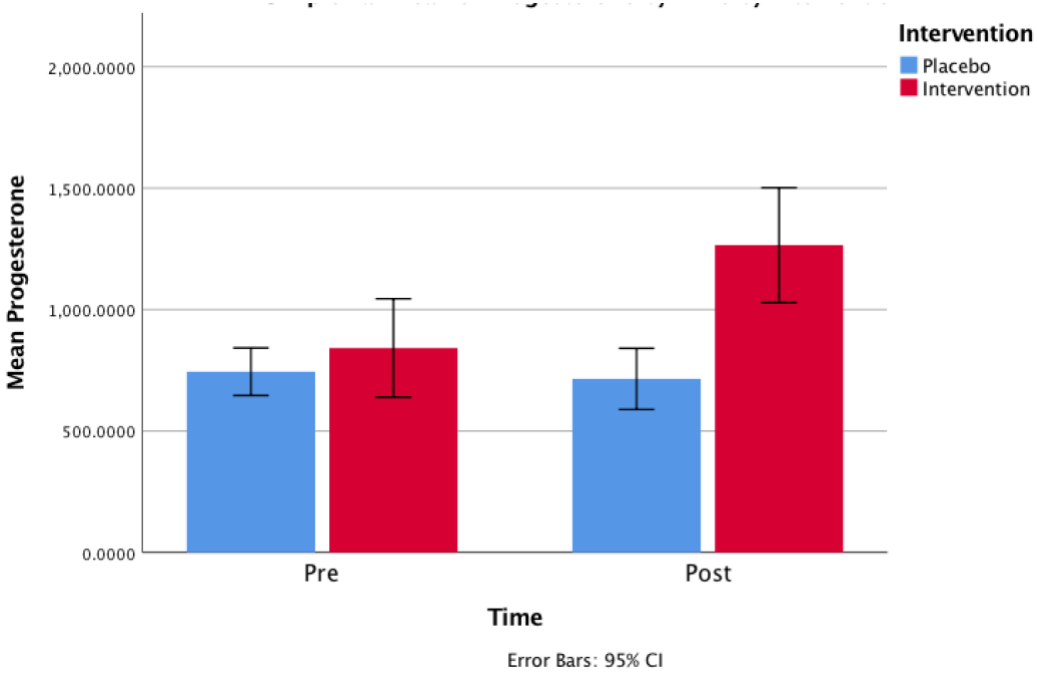
Bar Means of Estradiol by Time and Intervention



Note. Error bars are 95% confidence intervals.

Figure 3.

Bar Means of Progesterone by Time and Intervention



Note. Error bars are 95% confidence intervals.

Table 1

Multilevel Model Summary Table: Testosterone (Log)

Dependent Variable: Testosterone (Log)	Coefficient (SE)	t test	p value	R^2_{GLMM}	R^2_{GLMC}	Log Likelihood	Bayesian Inf. Crit.
Intercept	5.29 (0.04)	105.88	< 0.001***	0.876	0.931	17.58	-8.87
Time	0.17 (0.05)	3.32	0.001***	-	-	-	-
Intervention	0.06 (0.05)	1.13	0.260	-	-	-	-
Time*Intervention	1.16 (0.07)	15.60	< 0.001***	-	-	-	-

Note. The testosterone outcome variable was log transformed for this analysis. The Time variable is a dummy coded variable where pre-administration is equal to zero and post-administration is equal to one. R^2_{GLMM} is the predicted variance for the fixed effects and R^2_{GLMC} is the predicted variance for the fixed effects and the random effects. For mixed-models, R^2_{GLMM} and R^2_{GLMC} are the equivalent to R^2 reported in linear models (Nakagawa & Schielzeth, 2013). The Log Likelihood and the Bayesian Information Criterion variables are used for model fit comparisons.

*p < 0.05; **p < 0.01; ***p < 0.001

Table 2

Multilevel Model Summary Table: Estradiol

Dependent Variable: Estradiol	Coefficient (SE)	t test	p value	R^2_{GLMM}	R^2_{GLMC}	Log Likelihood	Bayesian Inf. Crit.
Intercept	4.27 (0.20)	20.44	< 0.001***	0.194	0.703	-86.82	199.93
Time	-0.18 (0.18)	-1.00	0.320	-	-	-	-
Intervention	0.06 (0.18)	0.35	0.724	-	-	-	-
Time*Intervention	1.08 (0.25)	4.26	< 0.001***	-	-	-	-

Note. The Time variable is a dummy coded variable where pre-administration is equal to zero and post-administration is equal to one. R^2_{GLMM} is the predicted variance for the fixed effects and R^2_{GLMC} is the predicted variance for the fixed effects and the random effects. For mixed-models, R^2_{GLMM} and R^2_{GLMC} are the equivalent to R^2 reported in linear models (Nakagawa & Schielzeth, 2013). The Log Likelihood and the Bayesian Information Criterion variables are used for model fit comparisons.

*p < 0.05; **p < 0.01; ***p < 0.001

Table 3

Multilevel Model Summary Table: Progesterone

Dependent Variable: Progesterone	Coefficient (SE)	t test	p value	R^2_{GLMM}	R^2_{GLMC}	Log Likelihood	Bayesian Inf. Crit.
Intercept	744.09 (83.60)	8.90	< 0.001***	0.271	0.785	-7.99	42.28
Time	-29.38 (68.83)	-0.43	0.67	-	-	-	-
Intervention	97.87 (68.83)	1.42	0.16	-	-	-	-
Time*Intervention	453.02 (97.33)	4.65	< 0.001***	-	-	-	-

Note. The Time variable is a dummy coded variable where pre-administration is equal to zero and post-administration is equal to one. R^2_{GLMM} is the predicted variance for the fixed effects and R^2_{GLMC} is the predicted variance for the fixed effects and the random effects. For mixed-models, R^2_{GLMM} and R^2_{GLMC} are the equivalent to R^2 reported in linear models (Nakagawa & Schielzeth, 2013). The Log Likelihood and the Bayesian Information Criterion variables are used for model fit comparisons.

Table 4

Descriptive Statistics and Within-Subjects Main Effects for Pain Variables

	Descriptive Statistics				Within-Subjects Effects			
Outcome: Placebo vs. Treatment	M_P	SD_P	M_T	SD_T	F	df	p-value	η^2
Discomfort	48.86	46.31	43.38	28.83	0.310	(1,17)	0.59	0.01
Pain	92.84	42.16	88.25	45.45	0.365	(1,16)	0.55	0.02
Stop	224.93	94.08	224.21	91.14	0.005	(1,19)	0.95	0.00

Note. M_P = Mean of the placebo group. M_T = Mean of the testosterone group. SD_P = Standard deviation of the placebo group. SD_T = Standard deviation of the testosterone group. η^2 = partial eta-squared. *p < 0.05; **p < 0.01; ***p < 0.001

Table 5

Descriptive Statistics and Within-Subjects Main Effects for SF-36 Health Survey Sub-Scale Variables

	Descriptive Statistics				Within-Subjects Effects			
Outcome: Placebo vs. Treatment	M_P	SD_P	M_T	SD_T	F	df	p-value	η^2
PF	88.24	22.08	90.25	19.50	4.74	(1,19)	0.04*	0.20
RP	90.00	16.27	88.13	20.17	0.53	(1,19)	0.47	0.03
BP	77.80	24.55	82.90	18.49	0.91	(1,19)	0.35	0.05
GH	76.15	21.60	78.65	20.78	2.52	(1,19)	0.13	0.12
VT	64.69	14.80	63.44	19.05	0.35	(1,19)	0.56	0.02
SF	83.13	25.09	88.13	16.95	1.15	(1,19)	0.30	0.06
RE	84.17	19.48	83.33	20.23	0.11	(1,19)	0.74	0.006
MH	78.25	14.44	80.00	13.86	1.35	(1,19)	0.26	0.07

Note. PF = Physical Functioning. RP = Role Physical. BP = Bodily Pain. GH = General Health. VT = Vitality. SF = Social Functioning. Role-Emotional = RE. MH = Mental Health. M_P = Mean of the placebo group. M_T = Mean of the testosterone group. SD_P = Standard deviation of the placebo group. SD_T = Standard deviation of the testosterone group. η^2 = partial eta-squared.
*p < 0.05; **p < 0.01; ***p < 0.001

Table 6

Descriptive Statistics and Within-Subjects Main Effects for Buss-Perry Aggression Short-Form Sub-Scale Variables

	Descriptive Statistics				Within-Subjects Effects			
Outcome: Placebo vs. Treatment	M_P	SD_P	M_T	SD_T	F	df	p-value	η^2
Hostility	5.85	2.13	5.55	2.35	0.46	(1,19)	0.51	0.02
Anger	4.80	2.14	4.45	2.01	1.21	(1,19)	0.29	0.06
Verbal	5.65	2.28	5.20	2.26	1.57	(1,19)	0.23	0.08
Physical	7.70	3.20	7.30	3.83	0.41	(1,19)	0.53	0.02
Total Aggression	24.00	8.72	22.50	9.37	1.13	(1,19)	0.30	0.06

Note. M_P = Mean of the placebo group. M_T = Mean of the testosterone group. SD_P = Standard deviation of the placebo group. SD_T = Standard deviation of the testosterone group. η^2 = partial eta-squared.
*p < 0.05; **p < 0.01; ***p < 0.001

Table 7

Descriptive Statistics and Within-Subjects Main Effects for Risk-Taking Variables

	Descriptive Statistics				Within-Subjects Effects			
Outcome: Placebo vs. Treatment	M_P	SD_P	M_T	SD_T	F	df	p-value	η^2
Recreational	31.40	7.32	31.80	6.43	0.13	(1,19)	0.72	0.007
Health	20.10	5.12	20.15	5.17	0.003	(1,19)	0.95	0.00
Ethical	17.10	5.60	18.05	8.40	0.64	(1,19)	0.43	0.03
Financial	19.50	4.55	18.65	4.49	1.49	(1,19)	0.24	0.07
Social	27.60	5.63	27.05	6.52	0.15	(1,19)	0.70	0.008
Total Risk	115.70	17.22	115.70	21.64	0.00	(1,19)	1.00	0.00
BART	13.90	3.94	16.8	6.13	5.11	(1,19)	0.03*	0.21

Note. M_P = Mean of the placebo group. M_T = Mean of the testosterone group. SD_P = Standard deviation of the placebo group. SD_T = Standard deviation of the testosterone group. η^2 = partial eta-squared.

*p < 0.05; **p < 0.01; ***p < 0.001

Table 8

Descriptive Statistics and Within-Subjects Main Effects for Body Self-Esteem Subscales

	Descriptive Statistics				Within-Subjects Effects			
Outcome: Placebo vs. Treatment	M_P	SD_P	M_T	SD_T	F	df	p-value	η^2
PC	32.75	6.54	33.65	5.99	0.70	(1,19)	0.41	0.04
WC	35.05	6.99	35.55	7.66	0.23	(1,19)	0.64	0.01
SA	44.95	6.49	45.85	6.53	1.07	(1,19)	0.31	0.05

Note. M_P = Mean of the placebo group. M_T = Mean of the testosterone group. SD_P = Standard deviation of the placebo group. SD_T = Standard deviation of the testosterone group. η^2 = partial eta-squared.
*p < 0.05; **p < 0.01; ***p < 0.001

Table 9

Descriptive Statistics and Within-Subjects Main Effects for Mate Value and Sexual Attitude Variables

	Descriptive Statistics				Within-Subjects Effects			
Outcome: Placebo vs. Treatment	M_P	SD_P	M_T	SD_T	F	df	p-value	η^2
Mate Value	55.00	9.97	57.00	9.94	3.83	(1,19)	0.06	0.17
Sexual Attitudes	39.50	12.94	39.50	11.06	0.00	(1,19)	1.00	0.00

Note. M_P = Mean of the placebo group. M_T = Mean of the testosterone group. SD_P = Standard deviation of the placebo group. SD_T = Standard deviation of the testosterone group. η^2 = partial eta-squared.
*p < 0.05; **p < 0.01; ***p < 0.001

Table 10

Descriptive Statistics and Within-Subjects Main Effects for Disgust Sub-Scale Variables

	Descriptive Statistics				Within-Subjects Effects			
Outcome: Placebo vs. Treatment	M_P	SD_P	M_T	SD_T	F	df	p-value	η^2
Moral	26.70	7.80	27.45	7.47	0.30	(1,19)	0.59	0.02
Sexual	27.10	10.99	29.10	9.84	2.49	(1,19)	0.13	0.12
Pathogen	26.85	7.54	26.60	6.99	0.06	(1,19)	0.81	0.003
TDDV Moral	28.80	7.97	30.20	5.25	1.45	(1,19)	0.24	0.07
TDDV Sexual	28.45	7.65	29.85	8.54	0.68	(1,19)	0.42	0.04
TDDV Pathogen	28.50	9.86	30.20	6.35	2.90	(1,19)	0.11	0.13

Note. M_P = Mean of the placebo group. M_T = Mean of the testosterone group. SD_P = Standard deviation of the placebo group. SD_T = Standard deviation of the testosterone group. η^2 = partial eta-squared.
*p < 0.05; **p < 0.01; ***p < 0.001

Appendix A: Self-Report Measures

SF-36 Health Survey

1. In general, would you say your health is:
    a. Poor
    b. Fair
    c. Good
    d. Very good
    e. Excellent
2. Compared to one week ago, how would you rate your health in general now?
    a. Much better now than one week ago
    b. Somewhat better now than one week ago
    c. About the same as one week ago
    d. Somewhat worse now than one week ago
    e. Much worse now than one week ago

The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

3. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports.
    a. Yes, limited a lot
    b. Yes, limited a little
    c. No, not limited at all
4. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf
    a. Yes, limited a lot
    b. Yes, limited a little
    c. No, not limited at all
5. Lifting or carrying groceries
    a. Yes, limited a lot
    b. Yes, limited a little
    c. No, not limited at all
6. Climbing several flights of stairs
    a. Yes, limited a lot
    b. Yes, limited a little
    c. No, not limited at all
7. Climbing one flight of stairs
    a. Yes, limited a lot
    b. Yes, limited a little
    c. No, not limited at all
8. Bending, kneeling, or stooping
    a. Yes, limited a lot
    b. Yes, limited a little
    c. No, not limited at all

9. Walking more than a mile
    a. Yes, limited a lot
    b. Yes, limited a little
    c. No, not limited at all
10. Walking several hundred yards.
    a. Yes, limited a lot
    b. Yes, limited a little
    c. No, not limited at all
11. Walking one hundred yards.
    a. Yes, limited a lot
    b. Yes, limited a little
    c. No, not limited at all
12. Bathing or dressing yourself
    a. Yes, limited a lot
    b. Yes, limited a little
    c. No, not limited at all

For the next 4 questions consider the following: during the past week, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

13. Cut down on the amount of time you spent on work or other activities.
    a. All of the time.
    b. Most of the time.
    c. Some of the time.
    d. A little of the time
    e. None of the time.
14. Accomplished less than you would like
    a. All of the time.
    b. Most of the time.
    c. Some of the time.
    d. A little of the time
    e. None of the time.
15. Were limited in the kind of work or other activities.
    a. All of the time.
    b. Most of the time.
    c. Some of the time.
    d. A little of the time
    e. None of the time.
16. Had difficulty performing the work or other activities (for example, it took extra effort).
    a. All of the time.
    b. Most of the time.
    c. Some of the time.
    d. A little of the time
    e. None of the time.

For the next 3 questions consider the following; during the past week, how much of the time have you had any of the following problems with your work or regular daily activities as a result of an emotional problems (such as feeling depressed or anxious)?

17. Cut Down on the amount of time you spent on work or other activities.
    a. All of the time.
    b. Most of the time.
    c. Some of the time.
    d. A little of the time
    e. None of the time.
18. Accomplished less than you would like.
    a. All of the time.
    b. Most of the time.
    c. Some of the time.
    d. A little of the time
    e. None of the time.
19. Did work or other activities less carefully than usual.
    a. All of the time.
    b. Most of the time.
    c. Some of the time.
    d. A little of the time
    e. None of the time.
20. During the past week, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?
    a. All of the time.
    b. Most of the time.
    c. Some of the time.
    d. A little of the time
    e. None of the time.
21. How much bodily pain have you had during the past week?
    a. All of the time.
    b. Most of the time.
    c. Some of the time.
    d. A little of the time
    e. None of the time.
22. During the past week, how much did pain interfere with your normal work (including both work outside the home and housework)?
    a. All of the time.
    b. Most of the time.
    c. Some of the time.
    d. A little of the time
    e. None of the time.

These questions are about how you feel and how things have been with you during the past week. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past week...

23. Did you feel full of life?
    a. All of the time.
    b. Most of the time.
    c. Some of the time.
    d. A little of the time
    e. None of the time.
24. Have you been very nervous?
    a. All of the time.
    b. Most of the time.
    c. Some of the time.
    d. A little of the time
    e. None of the time.
25. Have you felt so down in the dumps that nothing could cheer you up?
    a. All of the time.
    b. Most of the time.
    c. Some of the time.
    d. A little of the time
    e. None of the time.
26. Have you felt calm and peaceful?
    a. All of the time.
    b. Most of the time.
    c. Some of the time.
    d. A little of the time
    e. None of the time.
27. Did you have a lot of energy?
    a. All of the time.
    b. Most of the time.
    c. Some of the time.
    d. A little of the time
    e. None of the time.
28. Have you felt downhearted and depressed?
    a. All of the time.
    b. Most of the time.
    c. Some of the time.
    d. A little of the time
    e. None of the time.
29. Did you feel worn out?
    a. All of the time.
    b. Most of the time.
    c. Some of the time.
    d. A little of the time
    e. None of the time.

30. Have you been happy?
    a. All of the time.
    b. Most of the time.
    c. Some of the time.
    d. A little of the time
    e. None of the time.
31. Did you feel tired?
    a. All of the time.
    b. Most of the time.
    c. Some of the time.
    d. A little of the time
    e. None of the time.
32. During the past week, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?
    a. All of the time.
    b. Most of the time.
    c. Some of the time.
    d. A little of the time
    e. None of the time.

How TRUE or FALSE is each of the following statements for you?

33. I seem to get sick a little easier than other people
    a. Definitely true.
    b. Mostly true.
    c. Don't know.
    d. Mostly false.
    e. Definitely false.
34. I am as healthy as anybody I know.
    a. Definitely true.
    b. Mostly true.
    c. Don't know.
    d. Mostly false.
    e. Definitely false.
35. I expect my health to get worse.
    a. Definitely true.
    b. Mostly true.
    c. Don't know.
    d. Mostly false.
    e. Definitely false.
36. My health is excellent.
    a. Definitely true.
    b. Mostly true.
    c. Don't know.
    d. Mostly false.

e. Definitely false.

Buss-Perry Aggression Scale Short-Form

Using this 5 point scale, indicate how uncharacteristic or characteristic each of the following statements is in describing you.

Given enough provocation, I may hit another person.

1. Extremely Uncharacteristic 2. Somewhat Uncharacteristic 3. Neither 4. Somewhat Characteristic 5. Extremely Characteristic

There are people who pushed me so far that we came to blows.

1. Extremely Uncharacteristic 2. Somewhat Uncharacteristic 3. Neither 4. Somewhat Characteristic 5. Extremely Characteristic

I have threatened people I know.

1. Extremely Uncharacteristic 2. Somewhat Uncharacteristic 3. Neither 4. Somewhat Characteristic 5. Extremely Characteristic

I often find myself disagreeing with people.

1. Extremely Uncharacteristic 2. Somewhat Uncharacteristic 3. Neither 4. Somewhat Characteristic 5. Extremely Characteristic

I can't help getting into arguments when people disagree with me.

1. Extremely Uncharacteristic 2. Somewhat Uncharacteristic 3. Neither 4. Somewhat Characteristic 5. Extremely Characteristic

My friends say that I'm somewhat argumentative.

1. Extremely Uncharacteristic 2. Somewhat Uncharacteristic 3. Neither 4. Somewhat Characteristic 5. Extremely Characteristic

I flare up quickly but get over it quickly.

1. Extremely Uncharacteristic 2. Somewhat Uncharacteristic 3.

Neither 4. Somewhat Characteristic 5. Extremely Characteristic

Sometimes I fly off the handle for no good reason .

1. Extremely Uncharacteristic 2. Somewhat Uncharacteristic 3. Neither 4. Somewhat Characteristic 5. Extremely Characteristic

I have trouble controlling my temper.

1. Extremely Uncharacteristic 2. Somewhat Uncharacteristic 3. Neither 4. Somewhat Characteristic 5. Extremely Characteristic

At times I feel I have gotten a raw deal out of life.

1. Extremely Uncharacteristic 2. Somewhat Uncharacteristic 3. Neither 4. Somewhat Characteristic 5. Extremely Characteristic

Other people always seem to get the breaks.

1. Extremely Uncharacteristic 2. Somewhat Uncharacteristic 3. Neither 4. Somewhat Characteristic 5. Extremely Characteristic

I wonder why sometimes I feel so bitter about things.

1. Extremely Uncharacteristic 2. Somewhat Uncharacteristic 3. Neither 4. Somewhat Characteristic 5. Extremely Characteristic

Domain-Specific Risk-Attitude Scale

For each of the following statements, please indicate the likelihood of engaging in each activity. Provide a rating from 1 to 5, using the following scale:

1	2	3	4	5
Extremely Unlikely		Not Sure		Extremely Likely

Admitting that your tastes are different from those of your friends. (S)

Arguing with a friend who has a very different opinion on an issue. (S)

Asking your boss for a raise. (S)

Betting a day's income at the horse races. (F)

Buying an illegal drug for your own use. (E)

Chasing a tornado by car to take photos that you can sell to the press. (R)

Cheating a fair amount on your income tax. (E)

Cheating on an exam. (E)

Co-signing a new car loan for a friend. (F)

Dating someone that you are working with. (S)

Deciding to share an apartment with someone you don't know well. (S)

Disagreeing with your father on a major issue. (S)

Driving home after you had three drinks in the last two hours. (E)

Eating 'expired' food products that still 'look okay'. (H)

Exploring an unknown city or section of town. (R)

Forging somebody's signature. (E)

Frequent binge drinking. (H)

Going camping in the wild. (R)

Going down a ski run that is too hard or closed. (R)

Going on a safari in Kenya. (R)

Going on a two-week vacation in a foreign country without booking accommodations ahead. (R)

Going whitewater rafting at high water in the spring. (R)

Ignoring some persistent physical pain by not going to the doctor. (H)

Illegally copying a piece of software. (E)

Taking a medical drug that has a high likelihood of negative side effects. (H)

Traveling on a commercial airplane. (R)

Plagiarizing a term paper. (E)

Engaging in unprotected sex. (H)

Investing 10% of your annual income in a blue chip stock. (F)

Investing 10% of your annual income in a very speculative stock. (F)

Investing 10% of your annual income in government bonds (treasury bills). (F)

Investing in a business that has a good chance of failing. (F)

Lending a friend an amount of money equivalent to one month's income. (F)

Moving to a new city. (S)

Never using sunscreen when you sunbathe. (H)

Never wearing a seatbelt. (H)

Not having a smoke alarm in or outside of your bedroom. (H)

Openly disagreeing with your boss in front of your coworkers. (S)

Periodically engaging in a dangerous sport (e.g. mountain climbing or sky diving). (R)

Regularly riding your bicycle without a helmet. (H)

Shoplifting a small item (e.g. a lipstick or a pen). (E)

Smoking a pack of cigarettes per day. (H)

Speaking your mind about an unpopular issue at a social occasion. (S)

Spending money impulsively without thinking about the consequences. (F)

Stealing an additional TV cable connection. (E)

Taking a day's income to play the slot-machines at a casino. (F)

Taking a job where you get paid exclusively on a commission basis. (F)

Trying bungee jumping. (R)

Using office supplies for your personal business. (E)

Wearing unconventional clothes. (S)

Body Esteem-Scale

Instructions: On this page are listed a number of body parts and functions. Please read each item and indicate how you feel about this part or function of your own body using the following scale:

A. I have strong negative feelings.
B. I have moderate negative feelings.
C. I have no feelings one way or the other.
D. I have moderate positive feelings.
E. I have strong positive feelings.

1. Body scent.
2. Appetite.
3. Nose.
4. Physical stamina.
5. Reflexes.
6. Lips.
7. Muscular strength.
8. Waist.
9. Energy level.
10. Thighs.
11. Ears.
12. Biceps.
13. Chin.
14. Body build.
15. Physical coordination.
16. Buttocks.
17. Agility.
18. Width of shoulders.
19. Arms.
20. Chest or breasts.
21. Appearance of eyes.
22. Cheeks/cheekbone.
23. Hips.
24. Legs.
25. Figure or physique.
26. Sex drive.
27. Feet.
28. Sex organs.
29. Appearance of stomach.
30. Health.
31. Sex activities.
32. Body hair.
33. Physical condition.
34. Face.
35. Weight.

Self-Perceived Mating Success Scale

Indicate the degree to which you disagree or agree with each statement below by writing a number between 1 and 7 in the space provided.

1. Strongly Disagree
2. Disagree
3. Slightly Disagree
4. Neutral
5. Slightly Agree
6. Agree
7. Strongly Agree

____ Members of the opposite sex often comment that I would make a good boyfriend/girlfriend.

____ I do not receive many compliments from members of the opposite sex.

____ I am able to attract individuals I find desirable as relationship partners.

____ I receive sexual invitations from members of the opposite sex.

____ I can have as many sexual partners as I choose.

____ I am able to attract individuals I find desirable as sexual partners.

____ Members of the opposite sex that I would like to date, tend to like me back.

____ Members of the opposite sex notice me.

____ I receive many compliments from members of the opposite sex.

____ Members of the opposite sex are not very attracted to me.

____ Members of the opposite sex want to spend time with me and "get to know me."

____ Members of the opposite sex are attracted to me.

Three-Domain Disgust Scale

The following items describe a variety of concepts. Please rate how disgusting you find the concepts described in the items, where 0 means that you do not find the concept disgusting at all and 6 means that you find the concept extremely disgusting.

1. Shop lifting a candy bar from a convenience store.
2. Hearing two strangers having sex.
3. Stepping on dog poop.
4. Stealing from a neighbor.
5. Performing oral sex.
6. Sitting next to someone who has read sores on their arm.
7. A student cheating to get good grades.
8. Watching a pornographic video.
9. Shaking hand with a stranger who has sweaty palms.
10. Deceiving a friend.
11. Finding out that someone you don't like has sexual fantasies about you.
12. Seeing some mold on old leftovers in your refrigerator.
13. Forging someone's signature on a legal document.
14. Bringing someone you just met back to your room to have sex.
15. Standing close to a person who has body odor.
16. Cutting to the front of a line to purchase the last few tickets to a show.
17. A stranger of the opposite sex intentionally rubbing your thigh in an elevator.
18. Seeing a cockroach run across the floor.
19. Intentionally lying during a business transaction.
20. Having anal sex with someone of the opposite sex.
21. Accidently touching a person's bloody cut.

Interest in Visual Sexual Stimuli

Attitudes and Beliefs. Please answer each of the following items. Answer as you feel **today**, which could be different than how you *usually* feel. If it helps, *imagine* what the item asks about to respond. Use the following scale:

1 2 3 4 5 6 7
Agree Not At All Very Strongly Agree

___ 1. Seeing attractive people nude doesn't sexually arouse me.
___ 2. I find the thought of a very attractive body of the opposite sex very exciting.
___ 3. Seeing attractive people (of my preferred sex) in skimpy clothing such as lingerie or tight briefs would be very sexually exciting to me.
___ 4. The thought of touching a very attractive body of the opposite sex gives me tingles.
___ 5. Being around an attractive naked body (of my preferred sex) does not sound very sexually arousing to me.
___ 6. If I met someone I found very attractive right now, I would fantasize about what they would look like without clothes on.
___ 7. If I were to meet someone especially physically attractive, I may follow them briefly to get another look.
___ 8. If I were to fantasize about having sex with someone right now, I would try to picture very vividly in my mind what their body would look like.
___ 9. If I had to choose, right now I'd rather have a long conversation with someone I'm attracted to than see them naked.
___ 10. Seeing the arm or leg muscles of an attractive opposite-sex person subtly flex would be a real turn-on right now.

Appendix B: Testosterone Formulation

Testosterone Pain Study – Methods for Formulation

Formulation:

Other published work in this area has involved the use of testosterone- cyclodextrin complexes prepared by processes for which UNM IDS is not equipped. As an alternative, IDS developed an oil-based testosterone formulation for use in this study. This decision was made based on the IDS pharmacist's past experience as a compounding pharmacist, known chemical properties of testosterone (e.g., it is insoluble in water), and published

Rx Testosterone 10 mg/0.1 mL Sublingual Drops

Testosterone	1 g
Saccharin	100 mg
Silica gel	200 mg
Flavor	qs
Almond oil	qs 10 mL

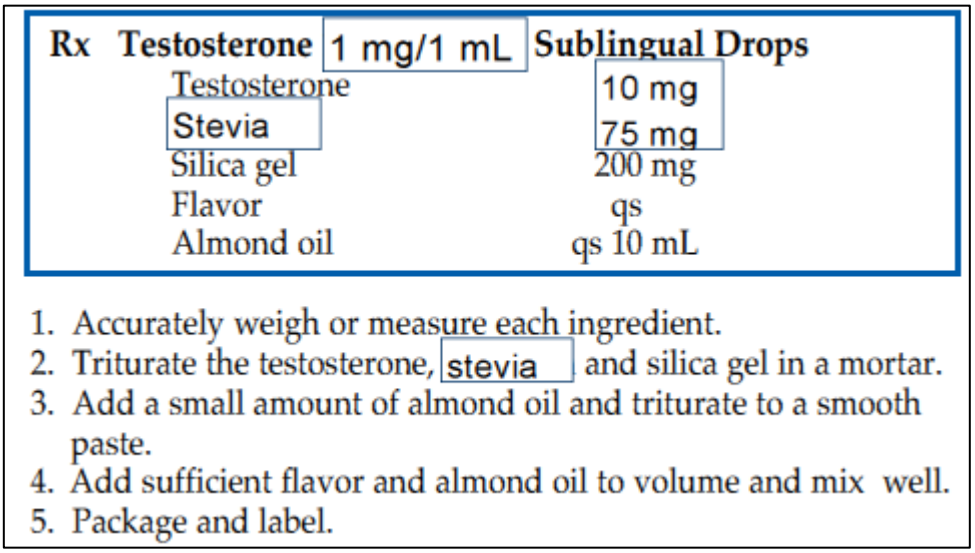
1. Accurately weigh or measure each ingredient.
2. Triturate the testosterone, saccharin and silica gel in a mortar.
3. Add a small amount of almond oil and triturate to a smooth paste.
4. Add sufficient flavor and almond oil to volume and mix well.
5. Package and label.

formulations such as the following:

Source: Secundum Artem Volume 8 Number 2, "Compounding for Male Andropause", available at http://www.perrigo.com/business/pdfs/Sec Artem 8.2.pdf

Note that the final concentration of testosterone in the published formulation is 1 gram (1,000 mg) in 10 mL oil. At this concentration, the 0.5 mg study dose would occupy a volume of 0.005 mL, far below the volume that can be accurately delivered sublingually by a standard oral syringe.

The published formulation was modified for the needs of this study as follows:



Rx Testosterone 1 mg/1 mL **Sublingual Drops**

Testosterone	10 mg
Stevia	75 mg
Silica gel	200 mg
Flavor	qs
Almond oil	qs 10 mL

1. Accurately weigh or measure each ingredient.
2. Triturate the testosterone, stevia and silica gel in a mortar.
3. Add a small amount of almond oil and triturate to a smooth paste.
4. Add sufficient flavor and almond oil to volume and mix well.
5. Package and label.

A 0.5 mg dose by this formulation would occupy 0.5 mL, which is acceptable for sublingual administration. Micronized testosterone USP was used for the active formulation. Placebo doses were prepared by the same method but without the testosterone. The silica gel serves as a suspending agent to keep the active ingredient dispersed throughout the oil base. Silica gel and flavoring were added to both formulations for blinding purposes. Stevia and a food-grade oil-based clementine flavoring were selected for the study formulation. Small batches of stock preparation were prepared ahead of time and doses drawn up on the day of each visit within the beyond-use dating of each batch.

Chain of Custody: Testosterone is a controlled substance on Schedule III and is therefore subject to more stringent state and federal regulations than non-controlled substances. Accordingly, all drug procurement, storage, compounding and dispensation were conducted under the supervision of a licensed pharmacist in the UNM Investigational Drug Service Pharmacy (IDS). Each dispensation of study medication was authorized by a written order signed by a medical doctor on the research team. Strict adherence to a chain-of-custody plan was maintained throughout the study. Only authorized researchers, lab personnel and medical personnel had access to study drug at any time.

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