Investigating Potential Linkage Between Catecholamines and Anxiety Diagnosis

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Introduction

The prevalence of adolescent and adult anxiety disorders continues to rise from previous generations. Diagnoses among children aged 6-17 years increased from 5.5% in 2007 to 6.4% in 2011-2012 (CDC, 2021). The percentage increase is even more pronounced in reported cases among young adults aged 18-25 years from 7.97% in 2008 to 14.66% in 2018 (Goodwin et al., 2020). Lifetime prevalence for anxiety disorders worldwide are estimated between 16.6% and 28.8% (Walters et al., 2012). Almost half of all Americans will experience an anxiety disorder sometime in their life (Kessler et al., 2005). Anxiety is attributed with higher mortality rates and negative health consequences including depression, substance abuse, and panic attacks (Goodwin et al., 2020).

While anxiety is associated with acute periods of anxiousness, generalized anxiety disorder (GAD) is defined by chronic anxiousness. To diagnose an individual with GAD at least three of six symptoms such as restlessness, fatigability, difficulty concentrating, muscle tension, irritability, or sleep disturbance must be present for a duration of six months or longer (Harvard Health, 2019). Studies based on GAD lifetime prevalence in the general population have provided estimates varying from 1.6 to 5.1% and a 2:1 female-to-male predominance ratio (K.-P. Lesch, 2001). GAD is often associated with high comorbidity rates for other psychiatric disorders including major depressive disorder, dysthymia, social phobia, and panic disorder (Beesdo et al., 2010; Harvard Health, 2019; K.-P. Lesch, 2001; Skre et al., 1994). Additionally, individuals with GAD frequently undergo symptoms of high heart rate, indigestion, irritable bowel syndrome, and chronic pain syndrome (Harvard Health, 2019; K.-P. Lesch, 2001). Although the majority of the research used is related to GAD, the approach I will be taking targets any anxiety disorder in general.

Currently, the predominant methods for diagnosing anxiety disorders are through parent-reports for children or self-report questionnaires in young adults and older generations. The preferred method of testing in the United States is the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) diagnostic criteria (Wittchen et a., 2001). The DSM-5 tests for excessive anxiety for a period of six months or longer, functional impairment, the six symptoms of GAD noted above, and disturbances not attributable to substance use or other mental disorders (SAMHSA, 2016).

Although there have been significant improvements in mental health awareness such as Mental Health Awareness Month to recognize mental illness and prioritize health, and the

Mental Health Access Improvement Act intended to help millions of Medicare beneficiaries receive mental health services, incidence of anxiety symptoms has risen from 3.9 to 5.8/1000 Persons Year at Risk (PYAR) and diagnoses have fallen from 7.9 to 4.9/1000PYAR from 1998 to 2008 (Walters et al., 2012). Unfortunately, it's difficult to know precise data because of the variability between individual responses on anxiety questionnaires. A quantitative test or a biomarker, such as a catecholamine, would provide additional quantitative data. This would help reduce variability in qualitative responses and would help ensure that children, adolescents, and adults get properly diagnosed. Abnormal catecholamine levels can possibly influence anxiety (Harvard Health, 2019). By investigating a potential correlation between anxiety and catecholamine levels, hopefully anxiety can be addressed at an earlier stage, allowing early intervention and preventing more severe symptoms.

Catecholamines

Catecholamines, including dopamine, norepinephrine, and epinephrine, modulate stress-induced sympathetic activity. The neurotransmitter, dopamine, can work as a reinforcement signal to motivate behavioral responses in order to obtain rewards. Dopamine strengthens synapses in the brain's hippocampus and prefrontal cortex to amplify memories regarding rewarded behavior. Dopamine levels influence a person's emotional responses and mood, sleep, memory, learning, and motor control and have been associated with the development of anxiety through abnormal dopamine levels (Olguín et al., 2015). Some findings suggest dopamine is involved in anxiety modulation, including the mesolimbic, mesocortical and nigrostriatal dopaminergic system. One study found that higher dopamine release in the amygdala and rostral anterior cingulate cortex (rACC) led to lower self-reported trait anxiety (Berry et al., 2019). Dopamine D1 and D2 receptor mechanisms contribute in mediating anxiety and changes in the glutamatergic, and GABAergic, mediated transmission in the mesolimbic, mesocortical and nigrostriatal dopaminergic system may influence anxiety-like behavior (Zarrindast, 2015).

Norepinephrine is an excitatory neurotransmitter and stress hormone associated with the "flight or fight" response. It increases alertness, attention, blood pressure, heart rate, increased energy and anxiousness. Scientists hypothesize that GAD emerges from excessive brain activation of the "flight or fight" response producing behavioral, physical, and psychosocial consequences. Sensitivity in the amygdala from anxiety disorders can cause an overreaction to non-threatening situations and evoke stress response (Harvard Health, 2019). Evidence indicates individuals with anxiety disorders have increased norepinephrine reactivity (Blier et al., 2007).

Epinephrine acts as a neurotransmitter and hormone that releases at noxious environmental or internal stimuli threatening homeostasis, activating the adrenal gland to

release epinephrine and the sympathetic nervous system (Goldstein, 2011). Activation causes elevated heart rate, muscle strength, blood pressure, and sugar metabolism. One study demonstrated associations between epinephrine and anxiety symptoms through a 24 hour epinephrine excretion and a positive correlation between scores (Paine et al., 2016).

Catecholamine levels are obtained through blood or urine tests. High levels of catecholamines are identified with pheochromocytoma, paraganglioma, and neuroblastoma tumors (Medline, 2021). Catecholamine testing is often done when a patient is showing symptoms of headaches, unusual heartbeat patterns, bone pain, weight loss, sweating, walking impairment, or unidentified lumps in the stomach (Beckerman, 2020). Urine testing is more commonly applied, since blood testing can raise levels of stress resulting in higher amounts of catecholamines produced (UCLA Health, 2021). Urine testing measures the total amount of catecholamines released through a 24-hour period. Since catecholamine levels fluctuate, a urine test can detect excess episodic production that a blood test might miss (Lab Tests, 2020). Blood catecholamine testing can be most useful in individuals with persistent hypertension or are experiencing paroxysm of hypertension (Lab Tests, 2020). Normal catecholamine levels within children and adolescents vary in dopamine, norepinephrine, and epinephrine. Dopamine levels for ages 4 and older are 65.0 to 400.0 mcg/24 hours. Norepinephrine levels in 4 to 6 years are 8.0 to 45.0 mcg/24 hours, 7 to 9 years 13.0 to 65.0 mcg/24 hours, and 10 years and older are 15.0 to 80.0 mcg/24 hours. Epinephrine levels in 4 to 9 years are 0.2 to 10.0 mcg/24 hours, 10 to 15 years are 0.5 to 20.0 mcg/24 hours, and 16 years and older are 0.0 to 20.0 mcg/24 hours (Carey, 2017; URMC, 2021). Abnormal results may indicate acute anxiety or severe stress along with some rare forms of tumor (UCLA Health, 2021).

Meta analysis of almost 50 years of catecholamine research

There have been a number of studies on the effects of catecholamines on anxiety related behavior. I will briefly summarize the following studies spanning from the 1970s to 2010s. It is my objective to provide a brief relevant literature review before summarizing the topic as a whole.

In 1976, Mount Sinai School of Medicine conducted a study injecting saline (positive control), epinephrine, and dopamine + norepinephrine into male adult albino rats in an attempt to quantitate the effects on aggression and anxiety (Torda, 1976). To establish a negative control, the researchers in this study subjected the rats to a series of 50 pulse-sets in foot-shocks through a wire grid floor by a Grason-Stadler 700 shock-generator and solid state programming apparatus in order to determine the base-line attack-responses. Extinction of avoidance response tested for anxious behaviors in which the rats could avoid shock through climbing on a safely ledge. Thereafter, the rats were injected either with treatment and reshocked. Dopamine and norepinephrine rats as well as epinephrine injected rats displayed a

statistical significance between the number of responses with aggressive behaviors and responses made in extinction of avoidance response. Combined injections of dopamine and norepinephrine increased aggressive behaviors within the rats displaying an average amount of 34.5 ± 2.9 responses and an average of 69% of the shock period spent fighting as compared to the control group with an average amount of 23.0 ± 1.4 responses and an average of 46% spent fighting. Conversely, multiple injections of epinephrine reduced the attack-behavior with an average amount of 9.3 ± 0.9 responses and the rats spending an average of 18.6% of the shock period fighting. During measures made in extinction of avoidance response, the dopamine-norepinephrine injection group displayed an average amount of 27.2 ± 2.8 responses compared to the control group with an average amount of 40.3 ± 2.6 responses, while the epinephrine group displayed an average amount of 93.2 ± 4.3 responses. Varying levels of epinephrine production may affect anxiety-type elements of aggressive behavior and anxiety-type behavior. One may conclude that dopamine, norepinephrine, and epinephrine concentrations can determine the relative amounts of aggression or anxiety type behavior.

A previous study by the Texas Research Institute of Mental Sciences in 1981 found a correlation between biofeedback relaxation and lower heart rate and anxiety levels (Mathew et al., 1981). Researchers hypothesized that relaxation training with GAD patients would lower monoamine oxidase activity in anxiety. Participants included twenty diagnosed GAD patients by the Research Diagnostic Criteria, and twenty control volunteers. Each subject underwent a blood test before and after relaxation training to determine levels of biochemical assays including epinephrine and norepinephrine. Participants then completed a State Anxiety Scale of State Trait Anxiety Inventory (STAI). The control group's pretreatment levels showed a 33.3 ± 6.8 mean for state anxiety, 26.9 ± 14.2 mean for epinephrine, and 232.2 ± 81.5 mean for norepinephrine. The GAD group's pretreatment levels showed a 44.9 ± 11.6 mean for state anxiety, 56.4 ± 33.5 mean for epinephrine, and 514.5 ± 299.4 mean for norepinephrine. The control group's post treatment levels showed a 34.5 ± 12.2 mean for state anxiety, 32.1 ± 24.8 mean for epinephrine, and 232.9 ± 50.9 mean for norepinephrine. The GAD group's post treatment levels showed a 32.2 ± 6.6 mean for state anxiety, 39.0 ± 20.3 mean for epinephrine, and 402.7 ± 210.5 mean for norepinephrine. The results indicate a reduction in levels of anxiety following biofeedback assisted relaxation. The patients were found to have significantly higher levels of state anxiety, epinephrine, and norepinephrine levels as compared with the controls.

In 1982, researchers at the Texas Research Institute of Mental Sciences gave epinephrine injections to humans to study the effects on anxiety behaviors (Mathew et al., 1982). Researchers hypothesized that anxiety might be controlled through catecholamine output. Testing included thirteen individuals with a diagnosis of generalized anxiety disorder using the DSM III questionnaire, and seven non-anxious participants. The test subjects selected had no statistically significant age difference. Blood samples were taken from the study group before and after an injection of 0.10mg/kg body weight of 1/1000 epinephrine. Levels of anxiety

post-injection were quantified via the STAI questionnaire. Results indicated the anxious subjects scored significantly higher neuroticism epinephrine scores as compared to the control group (patients, mean 11.69, standard deviation 5.87; controls, mean 4.17, standard deviation 2.93; t = 2.95,*P* <0.009). The two groups revealed significant differences in post injection heart rate and state anxiety (heart rate responders, heart rate: mean 86.27, standard deviation 5.76, non-responders, mean 73.07, standard deviation 6.18, t = 3.98, P <0.002; heart rate responders, state anxiety: mean 67.86, standard deviation 6.87, non-responders, mean 56.67, standard deviation 6.19,t =3.06, P*C*0.01). The scores indicate an association between epinephrine-induced increase in heart rate and anxiety.

In 1984, researchers from the University of Michigan Medical Center measured urinary catecholamines and Mitral Valve Prolapse (MVP) in panic-anxiety patients (Nesse et al., 1984). Two consecutive 12-hour urine catecholamine collections were gathered during normal activity and sleep. Tests were given to 23 panic-anxiety patients in which 7 had MVP, and 9 control subjects. Diagnoses were made according to the DSM-III criteria. Panic-anxiety patients without MVP excreted significantly higher nighttime epinephrine compared to both controls (F=6.19, p<0.019) and patients with MVP (F=4.76, p<0.038). Panic-anxiety patients without MVP excreted significantly higher nighttime norepinephrine compared to both controls (F=12.27, p<0.002) and patients with MVP (F=7.43, p<0.011). Elevated catecholamine levels were seen in panic disorder patients as panic patients without MVP had significantly greater catecholamine excretion rates compared to control subjects and panic patients with MVP.

From the Departments of Pediatrics and Child Psychiatry, Children's Hospital and Medical Center and University of Washington School of Medicine, researchers measured catecholamines, anxiety, and biofeedback in children and adolescents with symptomatic mitral valve prolapse (MVP) (Smith et al., 1989). STAI scores and a 24-hour urine catecholamine collection were gathered in 11 patients without MVP, 6 with asymptomatic MVP, and 14 with chest pain. Ten symptomatic patients randomly received either the treatment group with skin temperature biofeedback and relaxation-mental imagery or the attention-placebo condition. Patients without MVP excreted higher epinephrine values but lower STAI values compared to patients with MVP. In the treatment group and attention-placebo group, there were trends of increased epinephrine and decreased norepinephrine while STAI scores showed a trend towards reduction.

At the University of Michigan Medical School, researchers studied the correlation between plasma and urinary catecholamine levels and the symptoms of anxiety within patients with and without pheochromocytoma (PCC), and patients with panic disorder (Starkman et al., 1989). Patients were tested through structured interview, SCL-90R Anxiety and Phobic Anxiety scales, STAI criteria, and DSM-III criteria. Of the subjects, 17 were PCC-positive, 25 were PCC-negative, 23 had panic disorder, and 9 were control. Four of those patients who were also

diagnosed with GAD had mean plasma epinephrine levels significantly higher than the control group (Kruskal Wallis ANOVA for nonparametric data: 2983 ± 4493 pg/ ml versus 102 ± 90 pg/ml, $p < 0.02$), and a trend toward higher mean norepinephrine levels as well. In the PCC-negative group, plasma norepinephrine was significantly correlated with anxiety scores on all anxiety scales used. In the panic disorder group, plasma norepinephrine was significantly correlated with anxiety symptoms on the SCL-90R Anxiety scale, whereas in the PCC-negative group, plasma norepinephrine was significantly correlated with four of five cognitive items of anxiety and one of five noncognitive items. In the PCC-positive group, plasma epinephrine was significantly correlated with three of five somatic or mixed items (nervous, shaky $r = +0.48$, $p < 0.05$; tense, keyed up $r = +0.57$, $p < 0.05$; trembling $r = +0.56$, $p < 0.05$). In the PCC-negative group, urinary epinephrine displayed a correlation with three of five cognitive items of anxiety (fearful $r = -0.40$, $p < 0.05$; suddenly scared for no reason r =—0.40, $p < 0.05$; frightening thoughts $r = -0.51$, $p < 0.05$). Plasma epinephrine was positively correlated with somatization scale scores in PCC-positive patients ($r=+0.51$, $p<0.05$) and PCC-negative patients ($r=+0.41$, $p<0.05$). Both urinary epinephrine and norepinephrine showed significant correlations with the cognitive experience of anxiety.

In 1990, a study published in the Society of Biological Psychiatry explored adrenergic status in anxiety disorders and plasma catecholamines in panic and GAD patients as compared to control subjects (Cameron et al., 1990). DIagnoses were determined through DSM-III criteria and the SCID-UP (Upjohn version of the Structured Clinical Interview for DSM-III). There were 24 panic patients in which 5 had MVP, 8 GAD patients in which 1 had MVP, and 32 control subjects. Blood was drawn after each subject assumed supine position for a set amount of time. The GAD patients' lower systolic blood pressure prompted a trend toward significance for standing systolic blood pressure ($F=3.21$, $df=2,35$, $p<0.06$) and the transition from supine to standing systolic blood pressure ($F=2.72$, $df=2,35$, $p<0.08$). There was lower blood pressure in MVP-positive panic and GAD patients compared to MVP-negative patients. Panic and GAD patients both showed higher epinephrine values than control subjects.

A study published in the Journal of the American Academy of Child & Adolescent Psychiatry Home in 1994 tested urinary catecholamines in individuals with attention-deficit hyperactivity disorder (ADHD) with and without comorbid overanxious (ANX) disorder (Pliszka et al., 1994). Fifty-seven subjects ranging from 6-12 years old were tested through parent and child interviews, IOWA Conners Teacher Rating Scale, DSM-III-R criteria for ADHD and ANX, and the Revised Children's Manifest Anxiety Scale. There were 20 ADHD, 15 ADHD/ANX, and 22 control subjects. A 2-hour urinary test was administered to determine epinephrine and norepinephrine levels. The subjects underwent a fixed series of mentally stressing tasks. Results indicated subjects with ADHD/ANX had a significantly higher number of overanxious disorder symptoms. While children with ADHD alone had lower epinephrine and norepinephrine

ratios than the controls, the ADHD/ANX group was significantly higher in epinephrine excretion than the ADHD group.

At the Research Unit of the Ness Ziona Mental Health Center, researchers assessed levels of platelet-poor plasma norepinephrine, and 24-hour urinary norepinephrine and dopamine (Spivak, 1999). PTSD was considered a type of anxiety disorder until revisions in the DSM-V; PTSD is now considered a "trauma and stressor-related disorder" (Zoellner, 2012). Chronic symptoms of PTSD include elevated anxiety levels. Seventeen male outpatients with untreated chronic combat-related posttraumatic stress disorder (CR-PTSD) and 10 control subjects were tested though DSM-III-R criteria, Impact of Events Scale (IES), Hamilton Depression Rating Scale (HDRS), and Hamilton Anxiety Rating Scale (HARS). Blood samples and 24-hour urine samples were collected. The HDRS score was significantly higher in the CR-PTSD patients (18.7 ± 7.7) than in control subjects (1.7 ± 1.4)($t=2.1$, $df=25$, $p=.0001$). CR-PTSD patients (12.2 ± 17) also scored higher in HARS scores than control subjects (1.0 ± 1.2)($p=.0001$). Mean 24-hour urinary excretion of norepinephrine and dopamine were significantly higher in the CR-PTSD patients than control subjects (NE, $t=2.1$, $df=25$, $p=.05$; DA, $t=2.1$, $df=25$, $p<.05$). Urinary norepinephrine and dopamine measures showed a significant inter-correlation in the PTSD group and not in control subjects.

In 1999, the School of Dental Medicine, University of Athens, Greece tested emotionally stressful states measured by urinary catecholamine levels and its effects on bruxism in children (Vanderas et al., 1999). Bruxism is considered one physical manifestation of anxiety and individuals with bruxism tend to report more symptoms of anxiety and depression than non-bruxers (Sutin et al., 2010). In this study, bruxism was recorded through clinical examination and interview. Of the 273 children aged 6-8 years old that had a complete 24-hour urine test, bruxism was present in 129 subjects and absent in 38 subjects. The logistic multiple regression analysis showed that epinephrine, norepinephrine, and dopamine had a significant influence on the probability of developing bruxism. Catecholamine mean levels were higher in children with bruxism than without bruxism. Epinephrine and dopamine had a significant and strong association to bruxism.

A study by the Sherwood lab at Duke University Medical Center in 2004 evaluated the relationship between depression and anxiety scores and 24-hour urinary catecholamine excretion (Hughes et al., 2004). The study involved ninety-one women between the ages of 47 and 55 years. Each was assessed by the Beck Depression Inventory (BDI) and the STAI questionnaire. Twenty-four hour urine collections were assayed for epinephrine and norepinephrine levels. The study concluded that higher levels of depression symptoms were associated with increased 24-hour norepinephrine excretion ($r = .27$, $P = .009$), with depressed women ($n = 17$, BDI scores z10) exhibiting an approximately 25% higher rate of urinary norepinephrine excretion than women with BDI scores <10 ($n = 74$), $P = .007$. Higher levels of

state anxiety were also related to greater norepinephrine excretion (r = .28, P = .01). These findings displayed statistical significance that higher levels of depression and state anxiety are both related to increased 24-hour urinary norepinephrine excretion among middle-aged women.

In 2008, a study published in Springer measured urinary catecholamine levels in subjects with and without sleep bruxism (SB) (Seraidarian et al., 2008). Anxiety and stress have been linked as SB trigger factors. Subjects aged 30-35 years old were evaluated through medical history and dental examination. Twenty individuals were selected as the control group and twenty other individuals presented with sleep bruxism. The subjects went through a 24-hour urine test. A statistical difference was found in subjects with SB (adrenaline = 111.4 µg/24 h; noradrenaline = 261,5 µg/24 h; dopamine = 479.5 µg/24 h) compared to control subjects (adrenaline = 35,0 µg/24 h; noradrenaline = 148,7 µg/24 h; dopamine = 201,7 µg/24 h). Individuals with SB presented with higher urinary catecholamines levels than those without SB.

At the University of Miami School of Medicine, researchers studied the effects of comorbid depression and anxiety on pregnancy mood states within a large multi-ethnic sample (Field, 2010). Nine hundred eleven women at their second trimester of pregnancy were assigned to 4 groups based on DSM-IV criteria as follows: 1) Control (n=345); 2) Anxiety Disorder (n=77); 3) Depressive Disorder (n=181); and 4) Comorbid Anxiety-Depressive Disorder (n=308). Subjects were given the SCID, the Center for Epidemiological Studies-Depression scale (CES-D), STAI, as well as the Behavioral Inhibition Scale (BIS). Subjects then provided a urinary catecholamine sample of norepinephrine, epinephrine, and dopamine. During the prenatal early gestation (20 weeks), both comorbid and depressive groups scored higher on depression measures compared to anxiety or control groups. The comorbid group scored higher anxiety and lower dopamine levels. The depressive group, comorbid group, and anxiety group scored high on sleep disturbance and behavioral inhibition scales. During prenatal late gestation (32 weeks), separate ANOVAs suggested the comorbid group had higher depressive scores, and both comorbid group and anxiety group scored higher on anxiety scales than other groups. All groups showed elevated levels in norepinephrine and epinephrine compared to control, allowing these catecholamines to be a possible indicator of anxiety, depressive or comorbid anxiety-depressive disorders.

In 2012, the Journal of Jahrom University of Medical Sciences compared the effectiveness of drug therapy, relaxation therapy, and compound therapy on epinephrine and norepinephrine levels within GAD patients (Hosseini et al., 2012). There were thirty GAD subjects, split evenly into three groups: relaxation therapy, drug therapy, and combination therapy. Ten healthy subjects formed the control group. Each subject was tested under the Beck Anxiety and Depression Inventory and Hamilton's Rating Scale. A 24-hour urine test was used to analyze norepinephrine and epinephrine levels. Results indicated a significant difference between pre-test and post-test anxiety, epinephrine, and norepinephrine scores between the

three GAD groups, all showing a similar decreasing trend. There was no significant difference among the control group. For the non-control groups, anxiety scores had a significant relationship with epinephrine ($r=0.85$, $P<0.05$) and norepinephrine ($r=0.88$, $P<0.05$). All three treatments had the desired effect of anxiety reduction.

The Sherwood lab conducted a follow up study in 2016 examined the relationship between anxiety and depression within untreated high blood pressure individuals (Paine et al., 2016). The study tested one hundred and forty participants (mean age ± SD: 45.5±8.55 years) and collected three norepinephrine and epinephrine urine samples over a 24-hour period, each one week apart. Depressive symptoms were assessed using the BDI, and anxiety symptoms were assessed by the STAI. BDI scores ranged from 0 to 33 with a mean score of 5.7 (SD = 6.4) and trait anxiety scores ranged from 21 to 67 with a mean score of 34.7 (SD = 9.0). Depressive symptoms were associated with trait anxiety ($r(134) = .76$, $p < .001$). The 24 hour epinephrine excretion and anxiety scores ($r(133) = .20$, $p = .022$) were positively correlated indicating an association between epinephrine and anxiety symptoms.

Results

Through publicly accessible data, a meta-analysis was performed by analyzing the correlation between catecholamine levels and anxiety within the general population. The data found in each paper's figures and results included any pre-experiment baseline measurements of epinephrine, norepinephrine, and dopamine of both control and anxiety patients. These papers found these catecholamine levels using urinary and plasma enzyme linked immunosorbent assay (ELISA) analysis. Graphs and tables are separated based on urine or blood analysis. These papers reported means, standard deviations (SD), and sample sizes (n).

By using GraphPad software, a cross-paper analysis analyzes each paper's provided data in parallel. By selecting specific data that compared anxiety patients with a control group, data from these papers used subjects that had not undergone experimental treatment (pre-experiment data). This was done in order to ensure there were no contributing factors that could negatively impact the results.

In Tables 1-5, papers were gathered from 1989-2012 and directly compared the means and the standard deviations of the control subjects with the means and standard deviations of the anxiety subjects. A two-tailed unpaired t-test analyzes the given data. When given multiple data sets for anxiety subjects in the same paper, data was summarized by taking the mean of all the anxiety subjects and combining them into one overarching group. Unsummarized data is included in the supplementary tables and figures.

Significance was found through GraphPad analysis comparing control and anxiety groups' mean, SD, and n. Two-tailed unpaired t-tests assumed Gaussian distribution with both populations sharing the same SD. Two-tailed paired t-tests assumed Gaussian distribution with consistent differences between paired values. An ordinary one-way Anova with a post-hoc Dunnett's test compared the mean of each column with the mean of a control column.

Table 1. Pre- Experiment Urinary Epinephrine Values

Pre- Experiment Urinary Epinephrine Values (ug/ml 24h)

Author	Year Published	Control			Anxiety			p-value	Significance
		Mean	SD	n	Mean	SD	n		
Hosseini	2012	17.62	1.98	10	21.54	2.31	30	<0.0001	Y
Starkman	1989	8.00	3.00	9	35.91	54.83	65	0.1335	N
Nesse	1984	5.62	2.58	9	7.53	4.57	22	0.2507	N
Vanderas	1999	4.39	1.84	38	5.54	2.52	129	0.0098	Y
Seraidarian	2008	35.51	15.00	20	111.41	40.00	20	<0.0001	Y
Field	2010	4.25	3.17	345.00	4.19	2.40	77.00	0.8758	N

Urinary epinephrine levels are in (µg/ml 24h), Significance denoted by a Y for statistical significance and N for no statistical significance. Statistical significance was set at a value of >0.05. Statistical significance was determined by analyzing control values vs the anxiety values using an unpaired student t-test.

Summarized pre-experiment urinary epinephrine values reported an overall two-tailed unpaired t-test value of p=0.1672. A two-tailed paired t-test found a result of p=0.1144.

Table 2. Pre- Experiment Urinary Norepinephrine Values

Pre- Experiment Urinary Norepinephrine Values (ug/ml 24h)

Author	Year Published	Control			Anxiety			p-value	Significance
		Mean	SD	n	Mean	SD	n		
Hosseini	2012	49.40	6.00	10	113.63	13.36	30	<0.0001	Y
Starkman	1989	18.00	5.00	9	142.74	94.28	65	0.0002	Y
Nesse	1984	11.40	5.67	9	18.93	9.65	22	0.0367	Y
Vanderas	1999	18.71	6.19	38	22.12	8.45	129	0.0221	Y
Seraidarian	2008	148.72	15.00	20	274.45	40.00	20	<0.0001	Y
Field	2008	42.88	22.35	345	52.82	22.15	77	0.0005	Y
Spivak	1999	28.60	17.80	10	43.70	23.70	17	0.0939	N

Urinary norepinephrine levels are in (µg/ml 24h), Significance denoted by a Y for statistical significance and N for no statistical significance. Statistical significance was set at a value of >0.05. Statistical significance was determined by analyzing control values vs the anxiety values using an unpaired student t-test.

Summarized pre-experiment urinary norepinephrine values reported an overall two-tailed unpaired t-test value of p=0.0778. A two-tailed paired t-test found a result of p=0.0577.

Table 3. Pre- Experiment Urinary Dopamine Values

Pre- Experiment Urinary Dopamine Values (ug/ml 24h)

Author	Year Published	Control			Anxiety			p-value	Significance
		Mean	SD	n	Mean	SD	n		
Vanderas	1999	214.35	63.68	38	253.24	75.53	129	0.0044	Y
Seraidarian	2008	201.70	15.00	20	479.60	40.00	20	<0.0001	Y
Field	2010	241.34	104.76	345	302.64	127.66	77	<0.0001	Y
Spivak	1999	158.5	81.3	10	265.5	130	17	0.0277	Y

Urinary dopamine levels are in (µg/ml 24h), Significance denoted by a Y for statistical significance and N for no statistical significance. Statistical significance was set at a value of >0.05. Statistical significance was determined by analyzing control values vs the anxiety values using an unpaired student t-test.

Summarized pre-experiment urinary dopamine values reported an overall two-tailed unpaired t-test value of p=0.0316. A two-tailed paired t-test found a result of p=0.0426.

Table 4. Pre- Experiment Plasma Epinephrine Values

Pre- Experiment Plasma Epinephrine Values (pg/ml 24h)

Author	Year Published	Control			Anxiety			p-value	Significance
		Mean	SD	n	Mean	SD	n		
Mathew	1982	29.86	18.33	7	29.50	22.61	13	0.9716	N
Mathew	1981	26.90	14.20	12	56.40	33.50	20	0.0072	Y
Cameron	1990	32.23	32.27	58	47.38	36.59	106	0.0091	Y

Plasma epinephrine levels are in (pg/ml 24h), Significance denoted by a Y for statistical significance and N for no statistical significance. Statistical significance was set at a value of >0.05. Statistical significance was determined by analyzing control values vs the anxiety values using an unpaired student t-test.

Summarized pre-experiment plasma epinephrine values reported an overall two-tailed unpaired t-test value of p=0.0100. A two-tailed paired t-test found a result of p=0.0082.

Table 5. Pre- Experiment Plasma Norepinephrine Values

Pre- Experiment Plasma Norepinephrine Values (pg/ml 24h)

Author	Year Published	Control			Anxiety			p-value	Significance
		Mean	SD	n	Mean	SD	n		
Mathew	1982	269.43	161.07	7	331.91	159.90	13	0.4166	N
Mathew	1981	232.20	81.50	12	514.50	299.40	20	0.0034	Y
Cameron	1990	292.72	109.69	58	195.94	60.80	106	<0.0001	Y

Plasma norepinephrine levels are in (pg/ml 24h), Significance denoted by a Y for statistical significance and N for no statistical significance. Statistical significance was set at a value of >0.05. Statistical significance was determined by analyzing control values vs the anxiety values using an unpaired student t-test.

Summarized pre-experiment plasma norepinephrine values reported an overall two-tailed unpaired t-test value of p=0.5673. A two-tailed paired t-test found a result of p=0.3123.

Figure 1. Pre- Experiment Epinephrine (EPI) Values

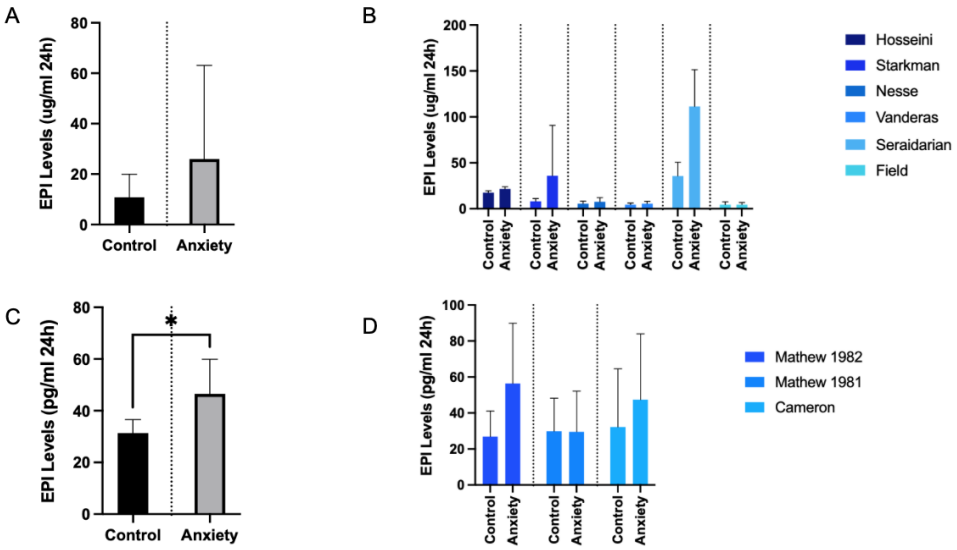

Figure 1. Summarized results from epinephrine in urine (A, B) and blood (C, D). Data is represented as mean plus or minus SD.

Two-tailed unpaired t-test of urinary epinephrine summarizing seven studies produced no significance (p=0.1672) when analyzed (A, B). Two-tailed unpaired t-test of plasma epinephrine summarizing three studies produced statistical significance (p=0.0100) when analyzed (C, D).

Figure 2. Pre- Experiment Norepinephrine (NE) Values

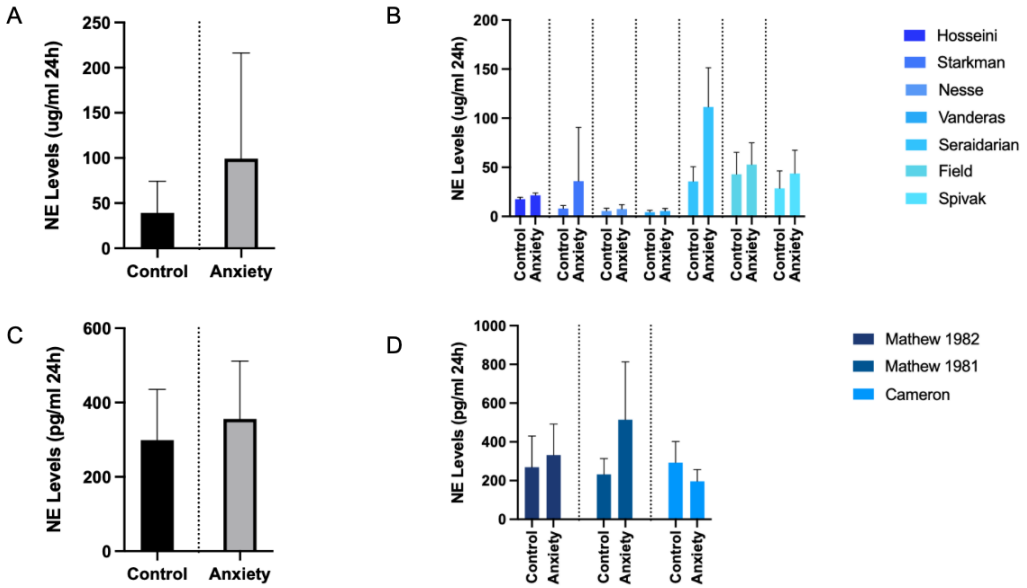

Figure 2. Summarized results from norepinephrine in urine (A, B) and blood (C, D). Data is represented as mean plus or minus SD.

Two-tailed unpaired t-test of urinary norepinephrine summarizing seven studies produced no significance (p=0.0778) when analyzed (A, B). Two-tailed unpaired t-test of plasma epinephrine summarizing three studies produced no significance (p=0.5673) when analyzed (C, D).

Figure 3. Pre- Experiment Dopamine (DA) Values

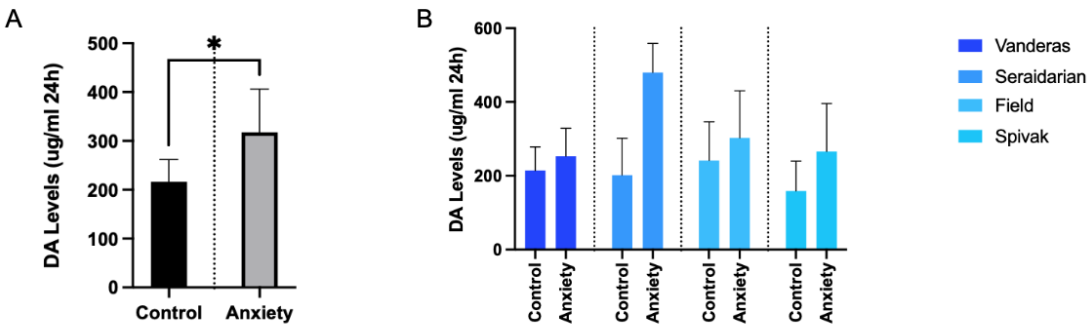

Figure 3. Summarized results from dopamine in urine (A, B). Data is represented as mean plus or minus SD.

Two-tailed unpaired t-test of urinary dopamine summarizing four studies produced statistical significance (p=0.0316) when analyzed (A, B).

Supplementary Figures and Tables

Table 6. Pre- Experiment Unsummarized Urinary Epinephrine Values

Pre- Experiment Unsummarized Urinary Epinephrine Values (ug/ml 24h)

Author	Year Published	Control			Anxiety			p-value	Significance
		Mean	SD	n	Mean	SD	n		
Hosseini (GAD: Relaxation Therapy)	2012	17.62	1.98	10	21.70	2.18	10	0.0007	Y
Hosseini (GAD: Drug Therapy)	2012	17.62	1.98	10	20.98	2.21	10	0.0053	Y
Hosseini (GAD: Combined Therapy)	2012	17.62	1.98	10	21.93	2.55	10	0.0004	Y
Starkman (PCC-Positive)	1989	8.00	3.00	9	105.00	191.00	17	0.0289	Y
Starkman (PCC-Negative)	1989	8.00	3.00	9	10.00	9.00	25	0.9999	N
Starkman (Panic Disorder)	1989	8.00	3.00	9	13.00	4.00	23	0.9971	N
Nesse (Panic Anxiety: Day)	1984	14.18	2.80	9	17.08	5.32	22	0.4476	N
Nesse (Panic Anxiety: Night)	1984	8.28	2.35	9	13.04	3.81	22	0.0936	N
Vanderas (Bruxism)	1999	4.39	1.84	38	5.54	2.52	129	0.0098	Y
Seraidarian (Bruxism)	2008	35.51	15.00	20	111.41	40.00	20	<0.0001	Y
Field (Anxiety at Labor: 20 weeks)	2010	4.74	3.18	345.00	5.90	2.83	77.00	0.0034	Y
Field (Anxiety at Labor: 32 weeks)	2010	3.35	3.41	345.00	4.08	3.20	77.00	0.0867	N
Field (Anxiety at Labor: 2 days)	2010	4.67	2.93	345.00	2.60	1.17	77.00	<0.0001	Y

Urinary epinephrine levels are in (µg/ml 24h), Significance denoted by a Y for statistical significance and N for no statistical significance. Statistical significance was set at a value of >0.05. For Vanderas and Seraidarian, statistical significance was determined by analyzing control values vs the anxiety values using an unpaired student t-test. For Hosseini, Starkman, Nesse, and Field, an ordinary one-way ANOVA with a post-hoc Dunnett's test compared the mean of each column with the mean of a control column.

Table 7. Pre- Experiment Unsummarized Urinary Norepinephrine Values

Pre- Experiment Unsummarized Urinary Norepinephrine Values (ug/ml 24h)

Author	Year Published	Control			Anxiety			p-value	Significance
		Mean	SD	n	Mean	SD	n		
Hosseini (GAD: Relaxation Therapy)	2012	49.40	6.00	10	115.50	15.56	10	<0.0001	Y
Hosseini (GAD: Drug Therapy)	2012	49.40	6.00	10	111.70	12.99	10	<0.0001	Y
Hosseini (GAD: Combined Therapy)	2012	49.40	6.00	10	113.70	11.54	10	<0.0001	Y
Starkman (PCC-Positive)	1989	18.00	5.00	9	432.00	307.00	17	<0.0001	Y
Starkman (PCC-Negative)	1989	18.00	5.00	9	47.00	29.00	25	0.893	N
Starkman (Panic Disorder)	1989	18.00	5.00	9	33.00	8.00	23	0.9823	N
Nesse (Panic Anxiety: Day)	1984	27.68	6.19	9	42.96	11.43	22	0.0698	N
Nesse (Panic Anxiety: Night)	1984	17.92	5.12	9	32.76	7.86	22	0.0145	Y
Vanderas (Bruxism)	1999	18.71	6.19	38	22.12	8.45	129	0.0221	Y
Seraidarian (Bruxism)	2008	148.72	15.00	20	274.45	40.00	20	<0.0001	Y
Field (Anxiety at Labor: 20 weeks)	2010	52.00	23.10	345	63.95	27.44	77	<0.0001	Y
Field (Anxiety at Labor: 32 weeks)	2010	45.32	30.24	345	63.06	18.00	77	<0.0001	Y
Field (Anxiety at Labor: 2 days)	2010	4.67	2.93	345	2.60	1.17	77	0.9297	N
Spivak (PTSD)	1999	28.60	17.80	10	43.70	23.70	17	0.0939	N

Urinary norepinephrine levels are in (µg/ml 24h), Significance denoted by a Y for statistical significance and N for no statistical significance. Statistical significance was set at a value of >0.05. For Vanderas, Seraidarian, and Spivak, statistical significance was determined by analyzing control values vs the anxiety values using an unpaired student t-test. For Hosseini, Starkman, Nesse, and Field, an ordinary one-way ANOVA with a post-hoc Dunnett's test compared the mean of each column with the mean of a control column.

Table 8. Pre- Experiment Unsummarized Urinary Dopamine Values

Pre- Experiment Unsummarized Urinary Dopamine Values (ug/ml 24h)

Author	Year Published	Control			Anxiety			p-value	Significance
		Mean	SD	n	Mean	SD	n		
Vanderas (Bruxism)	1999	214.35	63.68	38	253.24	75.53	129	0.0044	Y
Seraidarian (Bruxism)	2008	201.70	15.00	20	479.60	40.00	20	<0.0001	Y
Field (Anxiety at Labor: 20 weeks)	2010	287.49	114.93	345	361.91	176.73	77	<0.0001	Y
Field (Anxiety at Labor: 32 weeks)	2010	189.69	109.52	345	275.64	99.37	77	<0.0001	Y
Field (Anxiety at Labor: 2 days)	2010	246.85	89.84	345	270.37	106.87	77	0.0458	Y
Spivak (PTSD)	1999	158.50	81.30	10	265.50	130.00	17	0.0277	Y

Urinary dopamine levels are in (µg/ml 24h), Significance denoted by a Y for statistical significance and N for no statistical significance. Statistical significance was set at a value of >0.05. For Vanderas, Seraidarian, and Spivak, statistical significance was determined by analyzing control values vs the anxiety values using an unpaired student t-test. For Field, an ordinary one-way Anova with a post-hoc Dunnett's test compared the mean of each column with the mean of a control column.

Table 9. Pre- Experiment Unsummarized Plasma Epinephrine Values

Pre- Experiment Unsummarized Plasma Epinephrine Values (pg/ml 24h)

Author	Year Published	Control			Anxiety			p-value	Significance
		Mean	SD	n	Mean	SD	n		
Mathew (GAD)	1982	29.86	18.33	7	29.50	22.61	13	0.0072	Y
Mathew (GAD)	1981	26.90	14.20	12	56.40	33.50	20	0.9716	N
Cameron (Panic Anxiety: 20 min supine)	1990	25.00	24.00	9	43.00	34.00	14	0.0274	N
Cameron (Panic Anxiety: 30 min supine)	1990	35.00	43.00	8	39.00	33.00	14	0.9498	N
Cameron (Panic Anxiety: 15 min stand)	1990	37.00	31.00	9	57.00	49.00	13	0.4708	N
Cameron (GAD: 20 min supine)	1990	25.00	24.00	9	33.00	25.00	7	0.8110	N
Cameron (GAD: 30 min supine)	1990	35.00	43.00	8	45.00	28.00	8	0.7828	N
Cameron (GAD: 15 min stand)	1990	37.00	31.00	9	69.00	46.00	8	0.2400	N

Plasma epinephrine levels are in (pg/ml 24h), Significance denoted by a Y for statistical significance and N for no statistical significance. Statistical significance was set at a value of >0.05. For the Mathew papers, statistical significance was determined by analyzing control values vs the anxiety values using an unpaired student t-test. For Cameron, an ordinary one-way Anova with a post-hoc Dunnett's test compared the mean of each column with the mean of a control column.

Table 10. Pre- Experiment Unsummarized Plasma Norepinephrine Values (pg/mL 24h)

Pre- Experiment Unsummarized Plasma Norepinephrine Values (pg/ml 24h)

Author	Year Published	Control			Anxiety			p-value	Significance
		Mean	SD	n	Mean	SD	n		
Mathew (GAD)	1982	269.43	161.07	7	331.91	159.90	13	0.4166	N
Mathew (GAD)	1981	232.20	81.50	12	514.50	299.40	20	0.0034	Y
Cameron (Panic Anxiety: 20 min supine)	1990	189.00	68.00	10	216.00	76.00	16	0.5073	N
Cameron (Panic Anxiety: 30 min supine)	1990	218.00	98.00	10	223.00	76.00	15	0.9822	N
Cameron (Panic Anxiety: 15 min stand)	1990	491.00	169.00	9	479.00	167.00	15	0.957	N
Cameron (GAD: 20 min supine)	1990	189.00	68.00	10	174.00	40.00	8	0.8504	N
Cameron (GAD: 30 min supine)	1990	218.00	98.00	10	210.00	51.00	8	0.9666	N
Cameron (GAD: 15 min stand)	1990	491.00	169.00	9	464.00	107.00	8	0.9089	N

Plasma norepinephrine levels are in (pg/ml 24h), Significance denoted by a Y for statistical significance and N for no statistical significance. Statistical significance was set at a value of >0.05. For the Mathew papers, statistical significance was determined by analyzing control values vs the anxiety values using an unpaired student t-test. For Cameron, an ordinary one-way Anova with a post-hoc Dunnett's test compared the mean of each column with the mean of a control column.

Discussion

A strong correlation was found between catecholamine levels and anxiety scores. According to figure 1C, there was a statistical significance (p=0.0100, two-tailed unpaired t-test) when comparing plasma epinephrine levels between control patients and anxiety patients. This data reflects the findings of a recent Duke University Medical Center paper (Paine et al., 2016) that claims a positive correlation between anxiety and EPI24 excretion. From this data, there is a strong confidence that epinephrine levels can be measured through plasma testing to determine a candidate for anxiety diagnosis.

This trend was not as strong in norepinephrine values although there was a strong indicator (p=0.0778, two-tailed unpaired t-test) in the urinary norepinephrine data. According to figure 1B, in each of the seven studies analyzed, the anxiety patients consistently had higher norepinephrine levels than their respective controls. This confirms findings from the Institute of Mental Health Research at the University of Ottawa (Blier et al., 2007) that claimed individuals with anxiety disorders experience increased norepinephrine reactivity, leading to increased basals of norepinephrine. From the data, urinary analysis of norepinephrine can be suspected to be a possible indicator for anxiety disorders.

Statistical significance was found in urinary dopamine values (p=0.0316, two-tailed unpaired t-test). Previous findings (Berry et al., 2019) indicate that low dopamine levels are an indicator of anxiety. This is due to dopamine being known as the neurotransmitter responsible for pleasure and delight. However, an overabundance of dopamine is also associated with anxiety as shown in figure 3A. Elevated dopamine levels are associated with addictive behavior and are parallel channels of mesocorticolimbic signals, which can produce anxiety (Faure et al., 2008). An abnormal amount of dopamine can be a gauge of anxiety. The data strongly suggests that elevated expression of dopamine may be a sign of anxiety disorder.

Throughout this analysis, some publications were excluded from the data. The values from the 1976 paper from Mount Sinai School of Medicine were derived from catecholamine levels in rats and can not be directly compared to the other papers referenced in the study due to the difference in experimental subjects. This analysis focuses strictly on data found in anxiety in human patients. Furthermore, papers that used inconsistent values were also excluded from the analysis due to their incompatibility. For instance, the Pliszka, Smith, and Sherwood papers had values that could not be transformed to be appropriately comparative with the other uniformed data. Nevertheless, these papers showed similar trends which helps strengthen the hypothesis that catecholamines could be a quantitative indicator for diagnosing anxiety.

While these studies show a general trend, there are not enough publications with these specific catecholamine measurements; a greater data pool is needed for statistical significance. The studies thus far have been productive, however, the number of publications are limited. Plasma dopamine values were excluded due to this factor. Another limitation is the inherent biases that exist due to the methods of testing, including the possibility of under or over reporting of symptoms by the parent or individual. Also, the individual's interpretation of the language used in the questionnaire or individual report bias could potentially influence the overall results. In order to address these inconsistencies in DSM-5 anxiety diagnoses, a more quantitative method would be beneficial to help reduce misdiagnosis of anxiety disorders. A potential biomarker may provide insight into early detection.

Further testing can allow for more individuals to receive a diagnosis as the prevalence of anxiety disorders have increased over time (Goodwin et al., 2020). Among young adults aged 18-25, 14.66% reported anxiety in 2018 compared to 7.97% in 2008 (Goodwin et al., 2020). Anxiety appears more frequently in young adults; however, an overall increase in anxiety is present among the United States population (Walters et al., 2012). Studies have found that anxiety can lead to a higher risk of subsequent onset of anxiety disorders, depression, physical health problems, as well as an increase in poor sleep and stress (Goodwin et al., 2020). This can potentially affect brain development among children and young adults and lead to potential complications in psychological and social growth. These findings reflect the need for recognition and treatment early on. By identifying early indicators of anxiety disorder, patients can be more efficiently and accurately identified for diagnosis and given appropriate treatment to address their condition. Utilizing non-invasive assays such as urinary and plasma catecholamine analyses can give insight into early diagnosis and treatment for a multitude of anxiety disorders.

Current therapy and medicine often involves either or both psychological therapy and pharmacotherapy, or first-line medications such as selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors (Bandelow et al., 2017). In the United States, 54.4% of individuals with panic disorder and 27.3% of individuals with specific phobias contacted health services over a year; in a European study, a mere 20.6% of individuals with an

anxiety disorder sought professional help (Bandelow et al., 2017). With current treatments for anxiety often reducing the risk of subsequent disorders and anxiety symptoms (Goodwin et al., 2020), a higher incidence of patients with anxiety disorders are in need of some treatment method. By using tests that can designate a specific numerical value, a diagnosis is better facilitated and the patient is more apt to accept the diagnosis. Quantitative testing removes the subjectivity and reporter bias.

Additional research can be conducted in order to further supplement the data. An experiment that would further confirm the hypothesis that catecholamine levels are strong indicators of anxiety would include the following steps: 1) a significant population would be gathered, 2) the subjects would then be given the DSM-V anxiety criteria, 3) the subjects would be placed into the anxiety group or control group depending on their anxiety scores, 4) both urinary and plasma catecholamine tests would be administered (both urinary and plasma testing would be used to test for the most effective values), 5) the data values would be compared to determine if the catecholamine levels had a significant difference between groups.

With the proper resources and infrastructure, there should be further reinforcement for the findings in this study. In order to complete the proposed experiment, a large population of anxiety patients as well as suspected anxiety patients and control group would need to be gathered. Due to the current poor economic situation and unique social environment, there may be a good position to identify these potential study groups. Moreover, carrying out both qualitative and quantitative tests with these experimental groups at the same time would address potential concerns regarding the limitations of this study. With increasing anxiety rates, further research is imperative to allowing more to receive diagnosis and specialist care. Being able to diagnose anxiety disorders sooner and with greater specificity could significantly improve the health of those with anxiety disorders. Furthermore, other indicators that may be measured in a non-invasive manner can also be studied to further confirm these disorders. Catecholamine physiology and the study of their biochemical pathways are important targets for early intervention and the ultimate treatment for these anxiety symptoms. Through a deeper understanding of these biomarkers and other potential comorbidities, there is hope to reduce the risk of suicidal ideation through early recognition and treatment of this crippling condition.

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