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Sexual functioning in patients with anxiety disorders: an investigation of the potential influence of neuroinflammatory and endocrine factors

by

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Abstract

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Previous studies have revealed complex associations between sexual dysfunction, depressive symptoms, and treatment with antidepressant drugs, and provide evidence linking depression, neuroinflammation and hypothalamo-pituitary-axis (HPA) dysregulation. However, little is known about the prevalence of sexual dysfunction or incidence of treatment-emergent sexual dysfunction in patients with anxiety disorders. Published studies have found contrasting evidence of the association between anxiety symptoms and disrupted levels of inflammatory markers, and investigations of HPA function in anxiety disorders have produced inconsistent findings. Augmentation with COX-2 inhibitors in patients with depression can reduce depressive symptoms and improve quality of life, but the potential therapeutic benefit of COX-2 inhibitors in patients with anxiety disorders is uncertain.

This thesis includes a systematic review of the utility of the Arizona Sexual Experiences scale (ASEX) and a series of investigations in patients with anxiety disorders (n=35), with exploration of sexual function, anxiety symptoms, neuroinflammation and HPA dysregulation, at baseline, after six weeks of treatment, and after six weeks of augmentation with the COX-2 inhibitor celecoxib.

The ASEX appears reliable, valid, and sensitive to change, and acceptable in a broad range of clinical settings.

Cross-sectional findings indicate a point prevalence of sexual dysfunction of 57.1% at Baseline, 75.1% at Week 6 and 39.3% at Week 12. Sexual dysfunction was significantly positively correlated with the severity of anxiety symptoms, and significantly negatively correlated with mental wellbeing at Baseline, Week 6 and Week 12. There were low levels of IL-12p70 and low IL-2 but a high level of TNF-α at Week 6. At Week 12, there were low levels of IL-1β, low IL-12p70 and IL-13, a high level of TNF-α (regardless of augmentation with celecoxib) but low IL-2 levels in the non-augmentation group. At Baseline, patients with panic disorders with agoraphobia had a high hair cortisol concentration (HCC).

Longitudinal analysis found worsening of sexual function at Week 6, but significant improvement in anxiety symptoms, wellbeing and sexual function at Week 12 in the celecoxib augmentation group. There was a significant reduction in IL-2 level from Week 6 to Week 12 in the augmentation group, a reduction of HCC from Baseline to Week 6, and a slight elevation at Week 12, although changes in HCC were not statistically significant.

Investigating sexual dysfunction as part of the clinical assessment of patients with anxiety disorders, is important to facilitate better management and well-being. Augmentation with celecoxib can improve clinical outcomes, yet further research is needed to retest this. More research is needed to explore HCC in anxiety disorders in larger clinical samples.

Table of Contents

Table of Tables

Table of Tables

Table of Figures

List of Accompanying Materials

Research Thesis: Declaration of Authorship

Print name:	Hesham Yousry Elnazer

Title of thesis:	Sexual functioning in patients with anxiety disorders: an investigation of the potential influence of neuroinflammatory and endocrine factors

I declare that this thesis and the work presented in it are my own and has been generated by me as the result of my own original research.

I confirm that:

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3. Where I have consulted the published work of others, this is always clearly attributed;
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7. None of this work has been published before

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Definitions and Abbreviations

3α,5α-THDOC	3α,5α-tetrahydrodesoxycorticosterone
3α,5α-THDOC	3α,5α-tetrahydrodesoxycorticosterone
5’GMP	5'-guanidylic acid
5-HT	5-hydroxytryptamine
5-HTP	5-hydroxytryptophan
ACC	anterior cingulate cortex
ACh	acetylcholine
ACTH	adrenocorticotrophic hormone
AMP	adenosine monophosphate
Ang II	angiotensin II
Ang-(1-7)	angiotensin 1-7
ANP	atrial natriuretic peptide
APC	antigen-presenting cells
API	acute panic inventory
ASES	acute sexual experience scale
ASEX	Arizona sexual experiences scale
AT1receptor	angiotensin II receptor type 1
AUC	area under the curve

Definitions and Abbreviations

BAI	Beck anxiety inventory
BAT	behavioural approach test
BDNF	brain-derived neurotrophic factor
BISF	brief index of sexual functioning
BSA	bovine serum albumin
cAMP	cyclic adenosine monophosphate
CBT	cognitive behaviour therapy
CCK-4	cholecystokinin tetrapeptide
CECA-Q	care and abuse-questionnaire
CGI	clinical global impression
cGKI	cyclic guanosine monophosphate dependent protein kinase I
cGMP	cyclic guanosine monophosphate
Cis	confidence interval
CNS	central nervous system
CO2	carbon dioxide
COA	certificate of analysis
CoP	copeptin
COX-2	cyclo-oxygenase-2
CRH	corticotrophin releasing hormone
CRHR1	corticotropin-releasing hormone receptor

CRP	C-reactive protein
CSA	childhood sexual abuse
CV	coefficient of variation
CYP2D6	cytochrome P2D6
DAG	1,2-diacylglycerol
DAMPs	damage-associated molecular patterns
DASS-2	depression anxiety stress scales
DFFS	depression and family functioning scale
DHEA	dihydroepiandrosterone
DS	digit span
DSM-5	diagnostic and statistical manual of mental disorders, 5th edition
ED	erectile dysfunction
EGF	epidermal growth factor
eNOS	endothelial nitric oxide synthase
EQR	emotional quality of the relationship scale
EQRS	emotional quality of the relationship Scale
ET-1	endothelin-1
ETA	endothelin-A
ETB	endothelin-B
FMD	flow-mediated dilation of the brachial artery

FSQ	fear of spiders questionnaire
GAD	generalized anxiety disorder
GAD–7	generalised anxiety disorder–7 item scale
GAS	Goldberg anxiety scale
GC	guanylyl cyclase
GDP	guanosine diphosphate
GGT	gamma glutamyl transpeptidase
GH-SFQ	general hospital sexual function questionnaire
Glx/Cr	glutamate+glutamine/creatine
GM-CSF	granulocyte-macrophage colony-stimulating factor
GRISS	Golombok Rust sexual satisfaction scale
GS	guanylate cyclase
GSR	gold standard clinician rating scale
GTP	guanosine trisphosphate
HADS	hospital anxiety and depression scale
HAM-A	Hamilton rating scale for anxiety
HDAC2	histone deacetylase 2
HONOS	health of the nation outcomes scales
HPA	hypothalamo-pituitary-adrenal axis
HPETE	hydro-peroxy-eicosate-traenoic acid

hsCRP	high sensitivity C-reactive protein
IDS	inventory of depressive symptomatology
IDS-SR	inventory of depressive symptomology, self-report version
IFN-γ	interferon-γ
IIEF	international index of erectile function
IL-10	interleukin 10
IL-13	interleukin 13
IL-17	interleukin 17
IL-18	interleukin 18
IL-1b	interleukin 1b
IL1R2	interleukin receptor 2
IL-5	interleukin 5
IL-6	interleukin 6
IL-6	interleukin 6
IL-8	interleukin 8
iNOS	inducible nitric oxide synthase
IP3	inositol 1,4,5-trisphosphate
IP3R	inositol 1,4,5-trisphosphate specific receptors
LAK cells	lymphokine-activated killer cell
LC-MS/MS	liquid-chromatography coupled to tandem-mass spectrometry

LCN2	lipocalin-2
LNG-SI	levonorgestrel subcutaneous implant
LNS	letter number sequencing
LPS	lipopolysaccharide
LTA4	leukotriene A4
LTC4	leukotriene C4
LTD4	leukotriene D4
LTE4	leukotriene E4
MADRS	Montgomery-Åsberg depression rating scale
MAMPs	microbe-associated molecular patterns
MAQ	multidimensional anxiety questionnaire
mCPP	metachlorophenylpiperazine
MDD	major depressive disorder
MHPG	3-methoxy-4-hydroxyphenethyleneglycol
MHQ	Michigan hand outcomes questionnaire
MI	Mobility Inventory
MINI	mini international neuropsychiatric interview
MIST	Montreal imaging stress task
MLCK	myosin light-chain kinase
MLCP	myosin light-chain phosphatase

mRNA	messenger ribonucleic acid
MSISQ-19	multiple sclerosis intimacy and sexuality questionnaire-19
NAcc	nucleus accumbens
NADPH	nicotinamide adenine dinucleotide phosphate
NE	norepinephrine
NFKB2	nuclear factor kappa beta 2
NK cells	natural killer cells
nNOS	neuronal nitric oxide synthase
NO	nitric oxide
NT-3	neurotrophin-3
OCD	obsessive-compulsive disorder
OQuESA	Oxford questionnaire of emotional side effects of antidepressants
PAI-1	plasminogen activator inhibitor-1
PANSS	positive and negative syndrome scale
PD	panic disorder
PDE	phosphodiesterase
PDE-5	phosphodisterase-5
PDSS	panic disorder severity scale
PGE1	prostaglandin E1
PGE2	prostaglandin E2

PGF2α	prostaglandin-F2-alpha
PGI	patient global impression
PGWBI	psychological General Well-Being Index
PHQ-9	patient health questionnaire-9
PIP2	phosphatidylinositol 4,5-biphosphate
PKA	protein kinase A
PKG	cyclic guanosine monophosphate-dependent protein kinase
PLC	phospholipase C
PMA	phorbol 12-myristate 13-acetate
PRRs	pattern recognition receptors
PSS	panic symptom scale
PSS	perceived stress scale
PTSD	post-traumatic stress disorder
QLS	quality of life questionnaire
QMI	quality of marriage index
RhoA	Ras homolog gene family, member A
RIPK2	receptor-interacting serine/threonine-protein kinase 2
RLS	restless legs syndrome
ROC	receiver operating characteristic
ROS	reactive oxygen species

RPM	revolutions per minute
RSES	Rosenberg self-esteem scale
sAA	serum alpha-amylase
SALES	stressful life events scale
SCL-90	symptoms check list 90
SDS	Sheehan disability scale
SECPT	socially evaluated cold pressor test
SFQ-V1	sexual function questionnaire
SNRI	serotonin-noradrenaline reuptake inhibitor
SPST	simulated public speaking test
SSRI	selective serotonin reuptake inhibitor
SST	serum separator tube
STAI	state-trait anxiety inventory
STAI-S	Spielberger state inventory
STAI-T	Spielberger trait anxiety inventory
Th1	type 1 T helper cells
Th2	type 2 T helper cells
TNF	tumour necrosis factor
TPQ	temperament and personality questionnaire
TSST	Trier Social Stress Test

TSST	Trier social stress test
UFC	urinary free cortisol
WEMWEBS	Warwick-Edinburgh mental well-being scale
WPAI	work productivity and activity impairment questionnaire
xMAP	luminex multi-analyte profiling
Y-BOCS	Yale-Brown obsessive compulsive scale

Chapter 1 Introduction

1.1 General Introduction

Stress is a common unpleasant experience most often triggered by external stressors. At certain levels, stress can have a functional role in optimizing performance, exerting this effect via complex and multiple pathways, including the central and autonomic nervous systems, and cardiovascular and endocrine systems, with optimal performance seen at 60-70% of maximal arousal (Arent et al., 2003). Anxiety symptoms and anxiety disorders can develop when the physiological response to actual or perceived stress becomes impaired leading to reduced levels of functioning. This process can be conceptualised as arising due to high levels of stressors beyond the optimal level, to a deficit in acquired coping mechanisms, or to impaired tolerance to stress due to subtle alterations in stress response mechanisms (Kandel et al., 2012).

The hypothalamo-pituitary-adrenal (HPA) axis is known to be particularly involved in stress responses. 'Recognition' of a stressor activates the hypothalamus, which in turn stimulates the pituitary gland. The pituitary secretes adrenocorticotrophic hormone (ACTH) which stimulates the cortex of the adrenal gland to produce cortisol. Cortisol stimulates gluconeogenesis and glycogenolysis, and also suppresses inflammation. A bio-feedback mechanism usually serves to maintain physiological levels of activity within this system (Barrett et al., 2016).

Anxiety symptoms are associated with reported sexual difficulties and poor satisfaction. Antidepressant drugs are widely used in the treatment of patients with anxiety disorders, but treatment is commonly associated with adverse effects on sexual function and satisfaction, the prevalence of which has not been determined accurately. Addition of COX-2 inhibitors may boost the response to antidepressants in patients with depressive disorders (Abbasi et al., 2012) but it is currently uncertain whether they are also potentially beneficial in reducing anxiety symptoms in patients with anxiety disorders, and whether they might have a role in diminishing 'treatment-emergent' sexual dysfunction.

1.2 Anxiety Disorders

Anxiety is a normal emotion with psychological and physical features. Intervention is usually required if symptoms are severe, persist, and interfere with everyday function. A mixture of symptoms are shared by most anxiety and anxiety-related disorders, which are distinguished by the presences of certain characteristic symptoms (Table 1.1).

Table 1.1 **Anxiety disorders** (**Diagnostic and Statistical Manual of Mental Disorders, 5th Edition)**

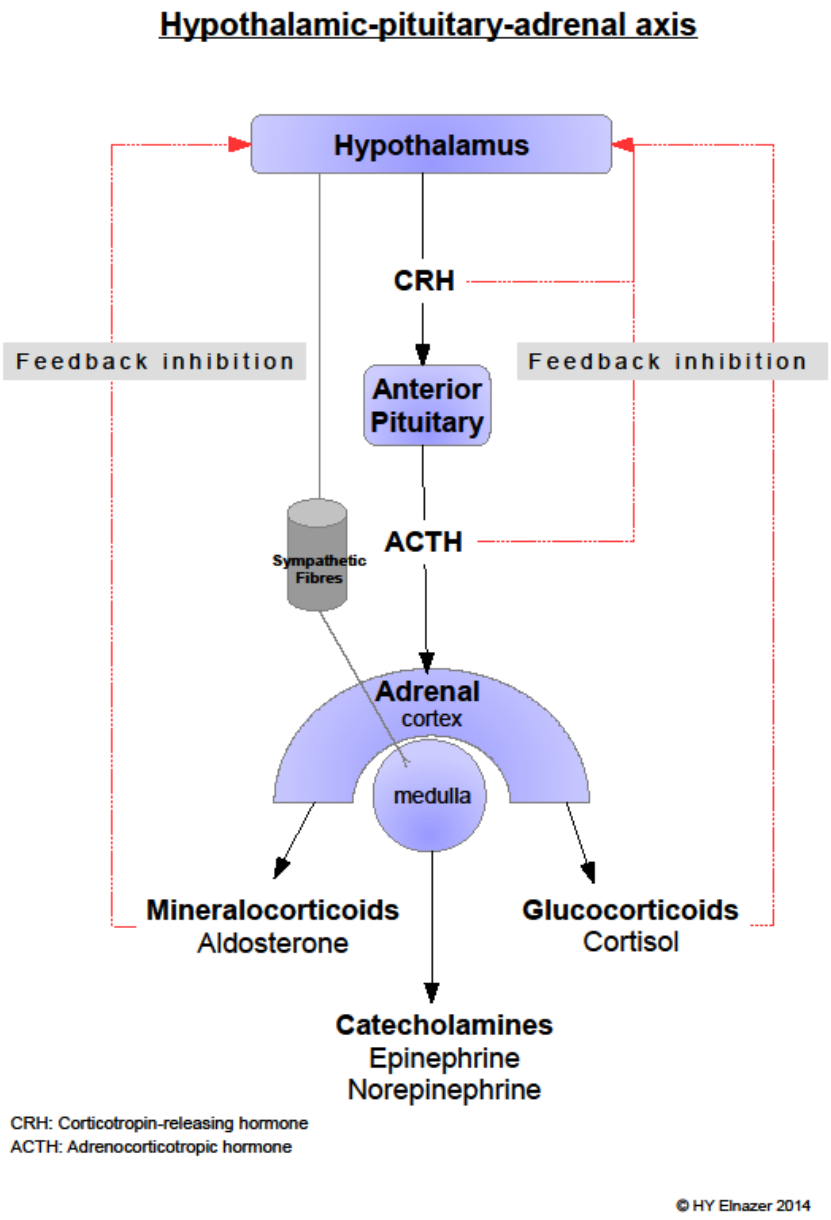
Separation Anxiety Disorder
Selective Mutism
Specific Phobia
Social Anxiety Disorder (Social Phobia)
Panic Disorder
Agoraphobia
Generalized Anxiety Disorder
Substance/Medication-Induced Anxiety Disorder
Anxiety Disorder Due to Another Medical Condition
Other Specified Anxiety Disorder
Unspecified Anxiety Disorder

Anxiety disorders are common, usually have an early onset, typically run a chronic or relapsing course, cause substantial distress, impair social and occupational function, reduce quality of life and impose a substantial personal and societal burden. Unfortunately, the effectiveness of pharmacological and psychological treatment interventions for patients with anxiety disorders in real-world clinical practice is often disappointing. Advances in genetics, genetics, psychoneuroimmunology and psychophysiology have all deepened understanding of the causes of anxiety disorders, but it remains hard to attribute particular psychopathological states to specific neuropsychobiological substrates. Furthermore, despite advances in investigation of the biological, environmental and temperamental mediators of resilience to traumatic adversity, on an individual level it is difficult to predict who will become troubled by anxiety symptoms (Baldwin et al., 2010).

1.3 Hypothalamic-pituitary-adrenal (HPA) axis

The HPA axis is a complex endocrine system consisting of the hypothalamus, the pituitary gland and the adrenal glands, which 'communicate' via feedback systems to facilitate multiple functions (Figure 1.1). The HPA axis influences many body processes and haemostatic systems (immune, metabolic, cardiovascular, reproductive and central nervous systems). The HPA axis also plays a major role in stress regulation and the sleep-wake cycle (Barrett et al., 2016). Cytokines can activate the HPA axis and the HPA axis modulates the immune response via cortisol secretion (Besedovsky et al., 2008).

Figure 1.1 **HPA axis**



Steadily growing awareness of the importance of disturbances of the HPA axis in the pathophysiology, and potentially in the treatment, of mood disorders and psychosis (Pariante et al., 2009) has naturally encouraged parallel investigations into the role of neuroendocrine disturbances in the origin, investigation and treatment of anxiety disorders. Hair cortisol is a helpful biological index which reflects long term cortisol levels (Kirschbaum et al., 2007): elevated hair cortisol is a recognised reliable measure for chronically raised cortisol associated with prolonged

stressful procedures in primates (Davenport et al., 2006), and elevated hair cortisol levels are detectable in patients with depression, when compared to controls (Dettenborn et al., 2011).

1.4 Cortisol Levels in Patients with Anxiety Disorders

1.4.1 Method for the Literature Review

I searched all titles listed in MEDLINE via Pub Med and EMBASE up to December 2017 for all anxiety disorders, excluding obsessive-compulsive disorder (OCD) and post-traumatic stress disorder (PTSD), being mindful of changes in the categorization of the latter two conditions within DSM-5 (American Psychiatric Association 2013); however, papers which examined cortisol and in which OCD or PTSD were co-morbid with an anxiety disorder were included in the review. For generalized anxiety disorder (GAD) I included the terms, generalised/generalized anxiety and GAD; for phobic disorders, I used the terms phobia, social phobia, simple phobia and specific phobia. A combined list was generated and duplications were eliminated; all letters, and papers that were not available in English, were eliminated. The search terms were as follows: agoraphobia (with or without a history of panic disorder) with glucocorticoids, cortisol, hypercortisolism; generalized/generalised anxiety disorder or GAD with glucocorticoids, cortisol, hypercortisolism; panic disorder with glucocorticoids, cortisol, hypercortisolism; phobic disorders, phobia, social phobia, simple phobia, specific phobia, with glucocorticoids, cortisol and hypercortisolism.

1.4.2 Panic Disorder and Agoraphobia

Evaluation of cortisol levels has encompassed investigations of urinary, salivary and plasma cortisol levels, non-suppression following dexamethasone administration, and cortisol response to psychological and pharmacological challenges (Table 1.2). In an early investigation, no significant differences in mean urinary free cortisol or plasma 3-methoxy-4-hydroxyphenethyleneglycol (MHPG) (a metabolite of noradrenaline) were found between patients with panic disorder (n=12) or healthy controls (Uhde et al., 1988). Significant group differences in urinary free cortisol between patients with panic disorder (n=65) and healthy controls were reported in a larger investigation,

but only in the sub-group of patients with more marked depressive symptoms or agoraphobic avoidance (Kathol et al., 1988); an extension of this study demonstrated that elevated urinary cortisol was less marked than that in depressed patients (Kathol et al., 1989). In patients with panic disorder (n=66), coexisting depression and agoraphobia were found to be associated with significantly elevated urinary free cortisol levels when compared to healthy controls; these levels decreased during treatment with alprazolam or diazepam (Lopez et al., 1990).

Nocturnal levels of urinary cortisol, epinephrine and norepinephrine were found to be persistently elevated in patients with panic disorder (n=16) (Bandelow et al., 1997), though not to decline following successful treatment with the selective serotonin reuptake inhibitor (SSRI) paroxetine, exercise or relaxation (Wedekind et al., 2008).

Plasma cortisol (and growth hormone) levels were found to be elevated in patients with 'panic anxiety' compared to levels in healthy controls (Nesse et al., 1984). However, another comparative study found that plasma cortisol levels were not significantly different between patients with panic disorder (n=10) and healthy controls (Villacres et al., 1987). Both total and free plasma levels and salivary levels of cortisol were found to be elevated in patients with panic disorder (n=47) compared to healthy controls (Wedekind et al., 2000). In further investigations, salivary cortisol levels taken during a panic attack were found to decrease 24 hours later in patients with panic disorder (n=25) (Bandelow et al., 2000a) and daytime salivary cortisol levels were correlated with symptom severity (Bandelow et al., 2000b).

Salivary cortisol levels were found to be significantly lower in an experimental group performing high-level endurance training in combination with cognitive behaviour therapy (CBT) at a 7-month follow-up (n=27) compared to a control group (n=31) who received CBT only (there were no between-group differences in salivary alpha-amylase levels). These results suggest a decelerated effect of endurance-training on HPA functioning in panic disorder (Plag et al., 2014).

Adolescent female offspring (n=476) of mothers with panic disorder or agoraphobia had elevated levels of both 30-minute cortisol and total cortisol produced throughout the day. Levels of cortisol were highest among offspring of mothers with multiple anxiety diagnoses (Goldstein et al., 2017). Another study found elevated salivary cortisol and panic symptoms (but not salivary alpha-amylase) in children with temporomandibular (n=76) disorders, when compared to controls (n=38), (Kobayashi et al., 2017).

A novel study investigated patients with agoraphobia (n=23) and their therapists (n=23). Therapists reported similar levels of perceived stress as patients before exposure. Both groups displayed significantly elevated salivary cortisol levels during in vivo exposure compared to the control sessions. Therapists reached peak concentrations of salivary cortisol before the start of the intervention followed by a decline during exposure, while patients displayed peak levels of cortisol secretion after 60 minutes of exposure (Schumacher et al., 2014).

In an early investigation, levels of cortisol and ACTH were elevated in patients with panic disorder (n=30), but the ACTH and cortisol response following challenge with corticotrophin releasing hormone (CRH) was diminished compared to healthy controls (Roy-Byrne et al., 1986).

Another study found that baseline plasma ACTH levels were elevated, and the ACTH response to stimulation with CRH was disturbed in patients with panic disorder (n=17), when compared to healthy controls (Brambilla et al., 1992). However, another investigation found no significant difference between patients with panic disorder and healthy controls in the ACTH and cortisol response to CRH challenge (Curtis et al., 1997). A third investigation involving CRH challenge with dexamethasone administration found no difference between patients with panic disorder (n=30) and depressed patients (Erhardt et al., 2006); a fourth suggested that the plasma cortisol response, but not the ACTH response, to CRH stimulation was decreased (Petrowski et al., 2012). Administration of the cortisol synthesis inhibitor metyrapone reduced ACTH and cortisol both in patients with panic disorder (n=14) and healthy controls, but with no difference between groups (Kellner et al., 2004).

A genetic study found that reduced corticotropin-releasing hormone receptor (CRHR1) expression, is associated with increased risk for panic disorder in females (n=54) compared to matched controls. Risk allele carriers of rs17689918 showed aberrant differential conditioning predominantly in the bilateral prefrontal cortex and safety signal processing in the amygdalae, arguing for predominant generalization of fear and hence anxious apprehension. Additionally, the risk allele of rs17689918 led to less flight behaviour during fear-provoking situations but rather increased anxious apprehension and went along with increased anxiety sensitivity. These results highlights the role of CRHR1 in panic disorder and suggests the mechanisms by which genetic variation in cortisol function is linked to this condition (Weber at al. 2016).The ratio of dihydroepiandrosterone (DHEA) to cortisol, which is considered a measure of adrenal cortical activity, was found to be significantly higher in patients with panic disorder (n=24) than in depressed patients or healthy controls and, in female patients, decreased during treatment with alprazolam, clonazepam or placebo (Fava et al., 1989). An early investigation found that successful treatment of patients with panic disorder with the SSRI fluvoxamine was not associated with a reduction in plasma levels of cortisol (Den Boer and Westenberg 1990); however, a reduction in cortisol levels has been reported to be associated with successful treatment with other SSRIs (Herran et al., 2005).

In an early study, non-suppression following dexamethasone administration was found in 11.8 % of patients experiencing panic attacks (Sheehan et al., 1983); in a second study, none of ten patients with panic disorder showed non-suppression, compared to 9 of 22 patients with depressive disorders (Lieberman et al., 1983). In a third investigation, non-suppression was found in 29% of patients with agoraphobia, compared to 64 % of depressed patients, and 12% of healthy controls (Whiteford and Evans 1984). A similar proportion of patients with panic disorder showing non-suppression (29%) was seen in another early study, but non-suppression was not significantly more prevalent in patients than in healthy controls (9.5 %) (Judd et al., 1987).

Another investigation found that 20 % of patients with agoraphobia and panic attacks were ‘non-suppressors’, the likelihood being greater in patients with co-morbid depression or a family history

of depressive disorders (Cottraux et al., 1984). In another study, non-suppression following dexamethasone administration was found in 12.4 % of patients with agoraphobia (n=97), independent of depressive symptom severity (Peterson et al., 1985). In a comparative study, non-suppression was significantly less common (16.7 %) among patients with panic disorder (n=30) than in patients with major depressive episodes (56.7 %) (Faludi et al., 1986). Similar findings were reported in another comparative study involving patients with panic disorder (n=24), depressed patients and healthy controls (Goldstein et al., 1987). Dexamethasone non-suppression was similarly prevalent in depressed patients with or without co-morbid panic disorder (Grunhaus et al., 1987). Non-suppression was more common in panic disorder patients with agoraphobia (28 %) than in those without agoraphobia (Westberg et al., 1991). It should be noted that the distribution of dexamethasone itself may be altered in patients with panic disorder, with significantly lower levels being achieved following administration of a standard dose (Carson et al., 1988).

Successful treatment of patients with agoraphobia with panic attacks was associated with 'escape' from dexamethasone non-suppression (Coryell et al., 1985). Another study found the response to treatment with benzodiazepine anxiolytics or placebo was not associated with a change in response to dexamethasone challenge: but persistent non-suppression despite successful treatment was predictive of a relapse in symptoms, following withdrawal of treatment (Bridges et al., 1986). A further investigation found that dexamethasone non-suppression at baseline was not predictive of response to treatment with alprazolam (Coryell et al., 1988), but in another investigation baseline dexamethasone non-suppression was predictive of relapse following successful treatment of patients with panic disorder (n=82) with alprazolam, diazepam or placebo (Coryell et al., 1989; Coryell et al., 1991). In a series of studies in which patients with panic disorder (n=20) were found to have evidence of increased nocturnal cortisol levels compared to healthy controls (Abelson and Curtis 1996a), subsequent successful treatment with alprazolam was associated with a reduction in hypercortisolaemia (Abelson et al., 1996), and at 2-year follow-up, mean 24-hour cortisol levels at baseline, prior to alprazolam treatment, were predictive of greater symptom-related disability (Abelson et al., 1996b).

There have been many investigations of the cortisol response to psychological and pharmacological challenge. An early investigation found that exposure to feared situations was associated with increased reported fear, but not with increases in plasma cortisol or MHPG in patients with agoraphobia (n=18) (Woods et al., 1987). Detailed psychometric and physiological assessment of patients with panic disorder (n=24) was associated with a failure of salivary cortisol levels to decline, in contrast to the diminution seen in healthy controls (Stones et al., 1999). A more recent study involving repeated in vivo exposure to phobic situations ('flooding') found this therapeutic challenge was not associated with increases in plasma cortisol or ACTH levels; patients with lower responses had the least benefit from treatment (Siegmund et al., 2011). A simulated public speaking task engendered anxiety but did not increase salivary cortisol levels in either remitted (n=16) or symptomatic (n=18) patients with panic disorder (Garcia-Leal et al., 2005). Challenge through the Trier Social Stress Test (TSST) was associated with significantly lower increases in plasma and salivary cortisol in patients with panic disorder (n=27) than in healthy controls (Petrowski et al., 2013), regardless of the presence of depressive symptoms and a normal cortisol awakening response (Petrowski et al., 2010).

Another study found decreased cortisol concentrations in patients with panic disorder (n=28), compared to healthy controls (n=32), in response to TSST. The study also found a significant inverse association of the TSST-induced cortisol stress response with the Mobility Inventory (MI) total score. Results indicate attenuated TSST-induced cortisol stress response is associated with the no response to psychotherapy (Wichmann et al., 2016).

A 3 weekly in vivo psychotherapy exposure sessions in patients with panic disorder with agoraphobia (n=24) found that early sessions had better outcomes compared to later-day sessions. The difference was found to be associated with higher pre-exposure cortisol levels, which in turn were related to greater clinical improvement (Meuret et al., 2016).

There have been many investigations on the effects of cortisol on experimental alterations of 5-hydroxytryptamine (5-HT); serotonin levels and receptor function. Patients with panic disorder

(n=7) did not differ markedly from healthy controls in either the cortisol or beta-endorphin response, following administration of the 5-HT precursor 5-hydroxytryptophan (5-HTP) (Westenberg et al., 1989); an enhanced cortisol response being seen only transiently at the highest 5-HTP dosage (van Vliet et al., 1996). The lack of an enhanced cortisol response (assessed with salivary cortisol levels) to 5-HTP challenge was confirmed in a subsequent investigation (n=24) (Schruers et al., 2002). Challenge with the 5-HT releasing agent fenfluramine elicited both a significantly greater panic response, and greater increases in prolactin and cortisol levels in patients with panic disorder than in depressed patients or healthy controls (Targum et al., 1989 [n=9]; Targum 1990 [n=17]). However, in another investigation involving fenfluramine challenge, there were no significant differences in cortisol response between patients with panic disorder (n=16) and healthy controls (Judd et al., 1994).

Administration of the non-selective 5-HT2B and 5-HT2C agonist metachlorophenylpiperazine (mCPP) appeared no more likely to cause panic attacks in patients with panic disorder than in healthy controls, with no significant differences between groups in cortisol, growth hormone or prolactin responses (Charney et al., 1987a). No significant differences between patients with panic disorder (n=27) and controls in the cortisol response were seen in another study involving intravenous mCPP infusion (Germine et al., 1994). Another study found evidence of an exaggerated response to mCPP challenge when patients with panic disorder (n=15) were compared to depressed patients and healthy controls, with a positive correlation between cortisol response and anxiety level (Kahn et al., 1988); but a further investigation found no differences between patients and controls in the cortisol response to mCPP challenge (Wetzler et al., 1996).

Administration of the 5-HT1A agonist ipsapirone was found to result in a diminution of the hypothermic and ACTH/cortisol response in patients with panic disorder (n=14) compared to healthy controls, suggesting that 5-HT1A receptor-related serotonergic dysfunction may be a factor in the pathophysiology of panic disorder (Lesch et al., 1992). A diminution of the cortisol response and hypothermic response was also seen following ipsapirone challenge in patients with panic

disorder (n=40) compared to healthy controls, in a study in which administration of mCPP was associated with a trend towards a greater increase in cortisol levels, together suggesting opposite changes in the responsiveness of 5-HT1A and 5-HT2C receptors (Broocks et al., 2000). However, in another investigation in patients with panic disorder (n=39), plasma cortisol levels rose significantly in response to challenge with ipsapirone, this increase being particularly marked in cigarette smokers (Broocks et al., 2002), and the hypothermic response to ipsapirone challenge was reduced with successful treatment with clomipramine (Broocks et al., 2003). However, although rapid intravenous administration of mCPP induced panic attacks significantly more frequently in patients with panic disorder (n=10) than in healthy controls, there were no differences between groups in the neuroendocrine response (van der Wee et al., 2004).

Cortisol levels have been found to increase during challenge of healthy volunteers with air 'enriched' with 35 % carbon dioxide (CO2), a common challenge test for inducing panic attacks in patients with panic disorder (Sasaki et al., 1996; van Duinen et al., 2005; Hood et al., 2006). However, patients may not differ from controls in the cortisol response to CO2 challenge, despite marked differences between groups in the induction of anxiety symptoms (van Duinen et al., 2004; van Duinen et al., 2007); indeed, in one investigation, cortisol levels decreased significantly following CO2 challenge (Sinha et al., 1999). Another more recent study on healthy volunteers (n=59) found no correlation between panic symptoms (at baseline, during or after CO2 induction) and neuroactive steroids 3α,5α-tetrahydrodesoxycorticosterone (3α,5α-THDOC); DHEA or cortisol levels (Brambilla et al., 2013). Furthermore, administration of the cortisol synthesis inhibitor metyrapone prior to CO2 challenge reduces cortisol levels prior to challenge, but does not affect the anxiety response (Belgorodsky et al., 2005).

Caffeine administration was associated with a significantly greater increase in anxiety and nervousness in patients with panic disorder and agoraphobia (n=21) compared to healthy controls, but with no difference between groups in change in plasma levels of cortisol or MHPG (Charney et al., 1985). Challenge with the alpha-2-adrenergic receptor agonist clonidine has been used as an

investigational tool for evaluating norepinephrine function in panic disorder. The cortisol response to challenge with clonidine differed between patients with panic disorder (n=12) and controls (Brambilla et al., 1995). However in another study, the decline in cortisol levels following clonidine challenge did not differ significantly between patients with panic disorder (n=10), patients with mood disorders or healthy controls (Stein et al., 1988). In another investigation involving clonidine challenge before and after treatment with the SSRI fluoxetine, which demonstrated significantly increased 'volatility' (i.e. within-subject oscillatory activity) of plasma MHPG levels in patients with panic disorder (n=17) compared to healthy controls at baseline, successful treatment was accompanied by a reduction in 'volatility' to levels seen in controls (Coplan et al., 1997). By contrast, induction of panic attacks through challenge with yohimbine, an alpha-2-adrenergic receptor antagonist, was characterized by increases in both cortisol and MHPG levels (Charney et al., 1987b).

A significant but moderate increase in plasma cortisol after the Simulated Public Speaking Test (SPST) in healthy volunteers (n=36) has been reported, this response being independent of treatment with sumatriptan. Treatment post-SPST was associated with increased speech-induced fear, enhanced vigilance, and decreased plasma prolactin levels (de Rezende et al., 2013).

Hyperventilation, a common feature of panic attacks, can lead to an increase in serum lactate levels (Maddock et al., 1991) and infusion of sodium lactate is often used as an anxiogenic challenge, both in healthy volunteers and in patients with anxiety disorders. Induction of panic through intravenous sodium lactate infusion in a mixed sample of patients with panic disorder or agoraphobia with panic (n=43) was not consistently associated with increases in plasma cortisol or adrenaline (epinephrine) levels (Liebowitz et al., 1985). In addition, neither ACTH nor cortisol increased with lactate-induced panic attacks in patients with panic disorder and agoraphobia (Levin et al., 1987). However, in another study the presence of elevated plasma cortisol level at baseline was found to be predictive of late panic attacks following lactate infusion, in a mixed sample of patients with panic disorder or agoraphobia with panic attacks (n=103) (Hollander et al., 1989).

Elevated cortisol levels (along with higher reported fear and evidence of hyperventilation) at baseline were predictive of a greater likelihood of experiencing panic during placebo with placebo-controlled lactate infusion studies (Coplan et al., 1998). In another study, lactate infusion was accompanied by an increase in cortisol levels in patients with panic disorder (n=17) and in patients with major depression and panic attacks (n=12), but not in depressed patients without panic attacks (n=27) or healthy controls (Targum 1990). A further investigation found no evidence that lactate infusion enhanced the cortisol response in either patients or healthy controls (Seier et al., 1997), nor did infusion of lactate or the GABAA receptor antagonist flumazenil in patients with panic disorder (n=10) (Ströhle et al., 1998). The lack of consistent evidence for an enhanced cortisol response following lactate infusion has led to speculations that panic attacks may simply result from the infusion of hypertonic solutions (being seen with hypertonic saline, as well as with sodium lactate) (Peskind et al., 1998), with enhanced release of atrial natriuretic peptide (ANP) exerting an inhibitory role on ACTH and cortisol release (Kellner et al., 1998). Furthermore, ANP may have anxiolytic effects, as prior administration of ANP reduces the likelihood of experiencing panic following administration of cholecystokinin tetrapeptide (CCK-4) (Wiedemann et al., 2001).

Intravenous infusion with CCK-4 can induce panic attacks in patients with panic disorder in a dose-dependent manner (van Megen et al., 1996). Early investigations suggested that neuroendocrine responses to induction of panic through intravenous infusion of pentagastrin (a cholecystokinin-B receptor agonist) did not differ between patients with panic disorder (n=10) and healthy controls (Abelson et al., 1991; 1994). However, in another investigation of patients with panic disorder (n=24), ACTH levels were significantly higher in patients experiencing panic attacks than in those without attacks; and even patients without attacks had brief but mild increases in ACTH levels (Ströhle et al., 2000). CCK-4 infusion induced a vasopressinergic activation in health subjects (n=30), which was found to be correlated positively with panic symptoms and pituitary-adrenocortical release: there was a positive correlation between plasma ACTH and cortisol levels, and Copeptin (CoP) levels were correlated positively with ACTH and cortisol concentrations throughout the CCK-4 challenge (Demiralay et al., 2016).

Another study (n=18) found an increase in CCK-4-related cortisol release accompanied with increased panic scores on the Acute Panic Inventory (API) and Panic Symptom Scale (PSS), and a significant increase of brain glutamate+glutamine/creatine (Glx/Cr) levels in the anterior cingulate cortex (ACC). Significant positive correlations were found between baseline Glx/Cr and both API maximum maximum heart rate during the challenge. CCK-4-induced panic was also accompanied by significant glutamate increase in bilateral ACC (Zwanzger et al., 2013).

The ACTH and cortisol response to pentagastrin challenge can be reduced by prior cognitive intervention, both in patients with panic disorder and healthy controls (Abelson et al., 2005); and can be enhanced through prior administration of clonidine (Kellner et al., 1997). Successful treatment of patients (n=8) with the SSRI citalopram has been found to reduce the panic response, but not the cortisol, prolactin or growth responses, to challenge with CCK-4 delivered as a bolus injection (Shlik et al., 1997). Other intravenous challenge tests include infusion of physostigmine and insulin. A small study of intravenous infusion of physostigmine found that patients with panic disorder (n=9) did not differ from controls in anxiety symptoms or cortisol response (Rapaport et al., 1991), whereas administration of an intravenous insulin bolus was associated with an attenuated cortisol (and growth hormone and prolactin) response in patients with panic disorder compared to healthy controls (Jezova et al., 2010).

Table 1.2 **Investigations of cortisol in panic disorder**

study	**findings**
Urinary cortisol levels	
Uhde et al., 1988	No significant differences in mean urinary cortisol or plasma MHPG
Kathol et al., 1988	Elevation of urinary free cortisol in patients with more marked depression or agoraphobia
Kathol et al., 1989	Elevation of urinary cortisol less marked than in depressed patients
Lopez et al., 1990	Elevated urinary free cortisol levels decline during benzodiazepine treatment
Bandelow et al., 1997	Elevation of nocturnal cortisol levels, persisting SSRI treatment, exercise or relaxation
Plasma, salivary and hair cortisol levels	
Nesse et al., 1984	Elevation of cortisol and growth hormone levels
Nesse et al., 1984	Elevation of cortisol and growth hormone levels
Wedekind et al., 2000	Elevation of total and free plasma (and salivary) cortisol levels
Bandelow et al., 2000a	Decline in salivary cortisol levels following a panic attack
Bandelow et al., 2000b	Daytime salivary cortisol levels correlated to symptom severity
Staufenbiel et al., 2013	Evidence of low levels of cortisol in panic disorder and GAD
Plag et al., 2014	Significantly lower salivary cortisol levels in the experimental group performing high-level endurance training in combination with CBT. A decelerated effect of endurance-training on HPA-system's functioning in PD.
Goldstein et al., 2017	Female offspring of mothers with panic disorder or agoraphobia had elevated cortisol. Levels of cortisol were highest among offspring of mothers with multiple anxiety diagnoses.
Kobayashi et al., 2017	Elevated salivary cortisol and panic symptoms (but not salivary alpha-amylase) in children with temporomandibular disorders compared to controls.
ACTH and cortisol levels	
Roy-Byrne et al., 1986	Elevation of cortisol and ACTH, diminished response to CRH
Brambilla et al., 1992	Elevation of ACTH levels, ACTH response to CRH disturbed
Curtis et al., 1997	No significant difference in ACTH and cortisol response to CRH challenge
Erhardt et al., 2006	No significant difference in CRH challenge following dexamethasone administration
Petrowski et al., 2012	Diminished cortisol (but not ACTH) response to CRH challenge
Kellner et al., 2004	No significant difference in reduction of cortisol levels following metyrapone administration
Fava et al., 1989	Higher ratio of DHEA to cortisol, declining during benzodiazepine and placebo treatment
Den Boer and	No reduction in plasma cortisol levels with successful SSRI treatment

Westenberg 1990	
Abelson and Curtis 1996a	Increased nocturnal cortisol levels
Abelson et al., 1996	Reduction in hypercortisolaemia with successful alprazolam treatment
Abelson and Curtis 1996b	Baseline cortisol levels predictive of symptom-related disability 2 years later
Herran et al., 2005	Decline in cortisol levels with successful SSRI treatment
Weber et al., 2016	Reduced gene expression driven by Corticotropin-Releasing Hormone Receptor (CRHR1) risk allele leads to a phenotype characterized by fear sensitization and sustained fear. Four single-nucleotide polymorphisms SNPs were found to be associated with panic disorder.
Dexamethasone non-suppression	
Sheehan et al., 1983	Non-suppression in 11.8 % of patients
Lieberman et al., 1983	Non-suppression in none of 10 patients
Whiteford and Evans 1984	Less non-suppression in panic patients (29 %) than depressed patients (64 %)
Judd et al., 1987	Non-suppression in 29 % of patients (not significantly greater than in controls)
Cottraux et al., 1984	Greater non-suppression with co-morbid depression or family history of depressive disorders
Peterson et al., 1985	Non-suppression independent of depressive symptom severity
Faludi et al., 1986	Non-suppression significantly less frequent (16.7 %) than in depressed patients (56.7 %)
Goldstein et al., 1987	Non-suppression significantly less frequent than in depressed patients
Grunhaus et al., 1987	Co-morbid panic disorder does not affect chance of non-suppression in depressed patients
Westberg et al., 1991	Non-suppression more common in patients with co-morbid agoraphobia
Carson et al., 1988	Dexamethasone distribution may be altered in panic disorder
Coryell et al., 1985	Reduction in non-suppression with successful treatment
Bridges et al., 1986	Persistent non-suppression predictive of relapse following withdrawal of treatment
Coryell and Noyes 1988	Baseline non-suppression not predictive of response to alprazolam
Coryell et al., 1989, 1991	Baseline non-suppression predictive of relapse following response to benzodiazepines
Vreeburg et al., 2010	No significant difference in non-suppression compared to controls
Psychological challenge	
Woods et al., 1987	No decrease in cortisol or MHPG levels with exposure to feared situations
Stones et al., 1999	No decline in salivary cortisol levels following detailed personal assessment

Siegmund et al., 2011	No increase in plasma cortisol or ACTH during in vivo exposure
Garcia-Leal et al., 2005	No increase in salivary cortisol levels during simulated public speaking task
Petrowski et al., 2010	Cortisol response in TSST not influenced by depression or cortisol awakening response
Petrowski et al., 2013	Reduced cortisol response following TSST.
Schumacher et al., 2014	In patients with agoraphobia and their simultaneous therapists; therapists reported similar levels of perceived stress as patients before exposure. Both groups displayed significantly elevated salivary cortisol levels during in vivo exposure compared to the control sessions. Patients displayed peak levels of cortisol secretion after 60 min of exposure.
Wichmann et al., 2016	Significant inverse association of the TSST cortisol stress response with the MI (Mobility Inventory) total score when accompanied.
Meuret et al., 2016	Early-day extinction-based therapy sessions were associated with higher pre-exposure cortisol levels, which in turn were related to greater clinical improvement.
Relationship between cortisol and 5-HT	
Westenberg et al., 1989	No significant difference in response to 5-HTP
Van Vliet et al., 1996	Enhanced cortisol response following 5-HTP administration is only transient
Schruers et al., 2002	No evidence of enhanced cortisol response following 5-HTP administration
Targum et al., 1989	Significantly greater increase in cortisol and prolactin levels following fenfluramine challenge
Targum 1990	Significantly greater increase in cortisol and prolactin levels following fenfluramine challenge
Judd et al., 1994	No significant difference in cortisol response to fenfluramine challenge
Charney et al., 1987b	No significant difference in cortisol, growth hormone or prolactin response to mCPP challenge
Germine et al., 1994	No significant difference in cortisol response to mCPP challenge
Kahn et al., 1988	Exaggerated response to mCPP challenge, compared to controls and depressed patients
Wetzler et al., 1996	No significant difference in cortisol response to mCPP challenge
Van der Wee et al., 2004	No difference in cortisol response to mCPP challenge
Lesch et al., 1992	Reduction in hypothermic and ACTH/cortisol to ipsapirone challenge
Broocks et al., 2000	Reduction in hypothermic and ACTH/cortisol to ipsapirone challenge
Broocks et al., 2002	Enhanced response to ipsapirone challenge, particularly in smokers
Broocks et al., 2003	Hypothermic response to ipsapirone challenge corrected with clomipramine treatment
de Rezende et al., 2013	A significant but moderate increase in plasma cortisol after Simulated Public Speaking Test (SPST), occurred, independent of treatment with sumatriptan

	treatment post SPST increased speech-induced fear, enhanced vigilance and decreased plasma levels of prolactin.
Cortisol and adrenergic function	
Stein et al., 1988	No difference in decline in cortisol level after clonidine (alpha-2 adrenergic agonist) challenge
Brambilla et al., 1992	Altered cortisol response following clonidine challenge
Coplan et al., 1997	Increased MHPG volatility following clonidine challenge, lessening with SSRI treatment
Charney et al., 1987a	Increased cortisol and MHGP following yohimbine (alpha-2 adrenergic antagonist) challenge
Lactate infusion	
Liebowitz et al., 1985	No consistent increase in cortisol or epinephrine levels
Levin et al., 1987	No increase in ACTH or cortisol in association with panic attacks
Hollander et al., 1989	Elevated cortisol at baseline predictive of panic attacks following lactate infusion
Coplan et al., 1998	Elevated cortisol at baseline predictive of panic attacks following infusion of saline
Targum 1990	Infusion accompanied by increase in cortisol in panic disorder and depression plus panic
Seier et al., 1997	No increase in cortisol levels
Ströhle et al., 1998	No increase in cortisol levels with either lactate or flumazenil
Peskind et al., 1998	Panic attacks induced by hypertonic solutions
Kellner et al., 1998	Enhanced release of ANP exerts inhibitory role on ACTH and cortisol release
Cholecystokinin challenge	
Abelson et al., 1991, 1994	No difference in neuroendocrine response to pentagastrin challenge
Kellner et al., 1997	Prior administration of clonidine enhances response to CCK challenge
Shlik et al., 1997	Successful SSRI treatment reduces anxiety but not endocrine response to CCK-4 challenge
Ströhle et al., 2000	ACTH levels following challenge greater in those experiencing panic attacks
Wiedemann et al., 2001	ANP reduces likelihood of panic following administration of CCK-4
Abelson et al., 2005	Cognitive intervention diminishes ACTH and cortisol response to pentagastrin challenge
Zwanzger et al., 2013	Increase in CCK-4-related cortisol release accompanied with increased panic scores on symptoms and significant increase of (Glx/Cr) levels in (ACC) and positive correlations were found between baseline Glx/Cr and both API max maximum heart rate during the challenge. CCK-4-induced panic is accompanied by glutamate increase in the bilateral ACC.
Demiralay et al., 2016	CCK-4 induced a vasopressinergic activation in health subjects (n=30), which was correlated positively to panic symptoms and pituitary-adrenocortical release. Positive correlation between plasma ACTH and cortisol levels. Copeptin (CoP)

	levels correlated also positively with ACTH and cortisol concentrations throughout the CCK-4 challenge.
Carbon dioxide challenge	
Sinha et al., 1999	Reduction in cortisol levels following CO2 challenge
Van Duinen et al., 2004	No difference in cortisol response to CO2 challenge
Belgorodsky et al., 2005	Pre-challenge metyrapone reduces cortisol levels but does not affect anxiety response
Brambilla et al., 2013	No correlation between baseline, during or after CO2 induced panic symptoms and neuroactive steroids (3α,5α-tetrahydrodesoxycorticosterone (3α,5α-THDOC), dehydroepiandrosterone (DHEA), and cortisol in healthy individuals.

1.4.3 Generalised Anxiety Disorder (GAD)

Similar to endeavours in panic disorder, evaluation of the influence of cortisol in GAD has included investigations of plasma and salivary cortisol, dexamethasone non-suppression, and cortisol response to psychological and pharmacological challenge (Table 1.3). As with major depression, GAD appears common among patients with a primary diagnosis of Cushing's disease, defined as Cushing's syndrome associated with an ACTH-secreting pituitary microadenoma, and characterized by hypercortisolism (Loosen et al., 1992). Chronic exposure to excess cortisol can result in structural abnormalities and persistent anxiety symptoms which persist beyond normalised cortisol levels (Valassi et al., 2017), and long term treatment of the hypercortisolic state cannot prevent the persistence of anxiety symptoms (Dimopoulou et al., 2015).

Patients with Cushing's disease (n=17) continued to report high scores on the Hospital Anxiety and Depression Scale, despite the normalisation of urinary free cortisol excretion with medical treatment (van der Pas et al., 2013). In patients with Cushing's disease (n=25), in long term symptom remission, with normal values in the dexamethasone suppression test, urinary cortisol excretion rates, and midnight salivary cortisol levels, continued to have high scores on the Beck Anxiety Inventory (BAI), smaller grey matter volumes of areas in the ACC and a greater volume of the left posterior lobe of the cerebellum, when compared with healthy controls (n=25) (Andela et al., 2013). Patients in remission from Cushing's disease (n=36) had worse scores on the State-Trait Anxiety Inventory (STAI) and Perceived Stress Scale (PSS) and low brain-derived neurotrophic factor

(BDNF), which was associated with more anxiety and stress and affective balance disturbance. The study also found that morning salivary cortisol was inversely associated with trait anxiety in patients with Cushing's disease (Valassi et al., 2017). A cross-sectional observational study of patients with Cushing's disease (n=80), who received surgical treatment, irradiation therapy and/or medical treatment, found that patients continued to show increased anxiety-associated personality traits, as measured by the STAI, Cloninger Temperament and Personality Questionnaire (TPQ), and Eysenck Personality Questionnaire (EPQ-RK) (Dimopoulou et al., 2015).

These more recent findings contrast with previously reported suggestions that successful treatment of Cushing's syndrome through correction of hypercortisolism is associated with a gradual reduction in the presence of mood and anxiety disorders (Dorn et al., 1997).

Investigations of HPA axis function among patients with GAD have produced variable findings, with no consistent evidence of hypercortisolism. In an early study, significant diurnal changes in plasma cortisol levels were reported in a small sample (n=13) of patients with GAD (Hoehn-Saric et al., 1991). A current or lifetime history of GAD or phobic disorder (but not post-traumatic syndromes) was found to be associated with a pattern of up-regulated diurnal cortisol secretion in a large population study in elderly individuals (Chaudieu et al., 2008). Both GAD (n=12) and major depression (n=8) were characterized by a failure of the pattern of cortisol-induced serotonin uptake in lymphocytes, seen in matched healthy controls (n=8) (Tafet et al., 2001). However, a comparison of morning plasma cortisol and DHEA sulphate levels in Vietnam-era US army veterans with GAD, major depression or co-morbid depression and GAD, found that depressed and co-morbid patients, but not patients with GAD alone, had evidence of hypocortisolism (Phillips et al., 2011).

Investigations have more recently focused on salivary cortisol levels and concentrations of cortisol in hair. An investigation involving serial saliva sampling found the cortisol awakening response to be less elevated in patients with GAD than in patients with panic disorder, with neither group showing more dexamethasone non-suppression than in matched controls (Vreeburg et al., 2010). A lower cortisol awakening response was seen in individuals with GAD, drawn from a large

population-based study of older people (aged 65 years and above) (Hek et al., 2013). A small case–control study in pre-pubescent children found no difference in bedtime salivary cortisol levels between 'anxious patients' (with a primary diagnosis of GAD) and healthy controls (Alfano et al., 2013). In a case–control study of cortisol concentrations in hair, there were significantly lower levels among patients with GAD (n=15) than in age- and gender-matched controls (Steudte et al., 2011). This observation accords with findings of a meta-analysis of hair cortisol and stress exposure, indicating hypocortisolism in both GAD and panic disorder (Staufenbiel et al., 2013).

An early investigation involving the dexamethasone suppression test (using a minimum cortisol value of 5 mcg/dl to indicate non-suppression) found no significant group differences between medication-free patients with GAD (n=26), panic disorder (n=22), agoraphobia with panic attacks (n=13), or 'primary affective disorder' (n=60) (Avery et al., 1985). A subsequent investigation in 79 patients with GAD found a non-suppression rate of 27 %, similar to that reported in patients with major depression, but greater than the previously reported rate in panic disorder, the presence of non-suppression being independent of depressive symptom severity (Schweizer et al., 1986). Non-suppression in the dexamethasone test was found to have little value in distinguishing between patients with GAD (n=15) or major depression (n=15), in an investigation of the suppression of rapid eye movement sleep by clonidine administration in depressed patients and healthy controls (Schittecatte et al., 1995).

It is uncertain whether change in cortisol levels, or dexamethasone non-suppression, is predictive of the response to experimental pharmacological or psychological challenge. In a mixed group of patients with GAD (n=8) or panic disorder (n=13), challenge by intravenous diazepam administration was associated with a reduction in cortisol levels (but increase in levels of growth hormone and ACTH) (Roy-Byrne et al., 1991). A case–control study involving psychological challenge in adolescents with GAD (n=20) found no significant changes in cortisol or ACTH during challenge in either cases or controls, in contrast to increases seen in norepinephrine, growth hormone and testosterone (Gerra et al., 2000). A case–control study in older individuals with GAD

(n=69) found that their participation in detailed neuropsychological assessment was associated with a lowering of salivary cortisol levels (Rosnick et al., 2013). In a small study (n=12) inhalation of air enriched with 7.5 % carbon dioxide was associated with increased subjective anxiety and with autonomic responses seen in heightened anxiety, but not with a change in cortisol levels (Seddon et al., 2011).

Despite early contrary findings, it seems possible that changes in cortisol levels and in other indices of HPA function are altered during the response to pharmacological or psychological treatment. A placebo-controlled study of the 5-HT1A partial agonist buspirone in 23 patients with GAD, which found that buspirone was effective in reducing anxiety symptom severity, found no association with change in plasma levels of cortisol (or prolactin or growth hormone) (Cohn et al., 1986). In a mixed group of patients with GAD (n=35) or panic disorder (n=36), treatment with alprazolam was associated with a reduction in plasma cortisol levels in only the panic disorder group, the group with GAD having a reduction in plasma epinephrine levels (Klein et al., 1995). However, a case–control study of the effects of acute challenge and subsequent prolonged administration of diazepam in individuals with GAD found it was associated with a reduction in plasma cortisol levels, particularly in elderly patients, in both cases and controls (Pomara et al., 2005). In addition, in a placebo-controlled study of treatment with the SSRI escitalopram in elderly patients with GAD, reduction in previously elevated cortisol levels was associated with a more marked reduction in symptom severity (Lenze et al., 2011), and with improvements in measures of immediate and delayed memory (Lenze et al., 2012). Furthermore, in an investigation which found a 27% rate of non-suppression among 30 patients with GAD, successful psychological treatment was associated with 'conversion' to suppression, though post-treatment concentrations remained significantly lower in the initial non-suppressors (Tiller et al., 1988). A controlled investigation of cognitive therapy in 24 patients with GAD found that successful treatment was accompanied by a significant decline in plasma cortisol levels (Tafet et al., 2005). Another study found that employment of 'expressive writing' in patients with Parkinson's disease (n=15) and their healthy carers (n=8), was associated with reduced elevated salivary cortisol awakening response and reduction in anxiety

(measured by Multidimensional Anxiety Questionnaire, MAQ): this was associated with significant improvements in tests of learning and memory scores (Trail making Tests A), auditory attention and working memory (Digit Span: DS), and Letter Number Sequencing (LNS) in both groups (Cash et al., 2015).

Table 1.3 **Investigations of cortisol in generalized anxiety disorder**

study	**findings**
Plasma, salivary and hair cortisol levels	
Hoehn-Saric et al., 1991	Significant diurnal changes in plasma cortisol levels
Chaudieu et al., 2008	Up-regulated diurnal cortisol secretion in elderly individuals with current or past GAD
Tafet et al., 2001	Abnormal cortisol-induced lymphocyte serotonin uptake similar to that seen in depression
Phillips et al., 2011	Co-morbid depression and GAD associated with hypocortisolism
Vreeburg et al., 2010	Lesser elevation of cortisol awakening response than in depressed patients
Hek et al., 2013	Lower cortisol awakening response in older individuals with GAD
Alfano et al., 2013	No significant difference in bedtime salivary cortisol levels in pre-pubescent children
Steudte et al., 2011	Lower cortisol levels in hair than in controls
Staufenbiel et al., 2013	Evidence of low levels of cortisol in GAD and panic disorder
Andela et a. 2013	Cushing's disease patients with long term remission continues to manifest with high anxiety smaller grey matter volumes of areas in the anterior cingulate cortex and greater volume of the left posterior lobe of the cerebellum.
van der Pas et al., 2013	Cushing's disease patients with normalised cortisol level with medical treatment continued have high scores of anxiety
Dimopoulou et al., 2015	Treated Cushing's patients in remission has increased anxiety-associated personality traits.
Valassi et al., 2017	Cushing's patients in remission has worse state-trait anxiety and perceived stress trait anxiety is inversely associated to cortisol levels.
Dexamethasone non-suppression	
Avery et al., 1985	No evidence of increased non-suppression compared to controls
Schweizer et al., 1986	Non-suppression rate of 27 %, presence independent of depressive symptom severity
Schittecatte et al., 1995	Non-suppression rate similar in GAD and major depression
Vreeburg et al., 2010	No significant difference in non-suppression compared to controls

Psychological and pharmacological challenge	
Roy-Byrne et al., 1991	Reduction in cortisol levels following IV diazepam administration
Gerra et al., 2000	No differences in cortisol or ACTH levels in adolescents in GAD after psychological challenge
Rosnick et al., 2013	Lowering of salivary cortisol levels following detailed psychological assessment
Seddon et al., 2011	No change in cortisol levels after inhalation of 7.5 % CO2
Cohn et al., 1986	Buspirone administration lowers anxiety but has no effect on cortisol levels
Klein et al., 1995	No reduction in plasma cortisol levels with alprazolam treatment
Pomara et al., 2005	Diazepam administration reduces cortisol levels in GAD and healthy controls
Lenze et al., 2011	Reduction in elevated cortisol levels associated with greater reduction in symptom severity
Lenze et al., 2012	Reduction in elevated cortisol levels associated with greater improvement in memory
Tiller et al., 1988	Successful psychological treatment converts previous dexamethasone nonsuppression
Tafet et al., 2005	Successful cognitive therapy accompanied by decline in plasma cortisol levels
Cash et al., 2015	Expressive writing reduces cortisol awakening response in anxiety

1.4.4 Specific (Simple) Phobia

There have been comparatively few investigations of cortisol levels in individuals with specific phobia 'at rest' (Table 1.4). In children and adolescents with major depressive disorder, co-morbidity with phobic disorders or panic disorder was associated with an absence of the elevated cortisol levels that were seen in depressed patients without co-morbidity (Herbert et al., 1996). Another investigation in children and adolescents with varying anxiety disorders (n=99) found no difference between the disorders in salivary cortisol or diurnal cortisol rhythm (Kallen et al., 2008). Compared to pregnant but healthy controls, pregnant women with blood-injection phobia (n=110) showed evidence of higher cortisol output, but no difference in diurnal cortisol rhythm (Lilliecruz et al., 2011).

A series of investigations have suggested that experimental exposure of individuals with specific phobia to a feared object or situation is associated with an enhanced cortisol response, but again not all evidence is consistent. An early investigation of cortisol, electrodermal activity and subjective distress in a mixed sample (n=12) of individuals with blood-injection phobia or animal phobia found that experimental exposure to pictorial images of feared objects (but not exposure to neutral objects) elicited cortisol excretion (Fredrikson et al., 1985). A study of patients with spider phobia (n=60) found that administration of exposure therapy during peak time for endogenous cortisol (08:00 am), led to significantly reduced fear of spiders in the behavioural approach test (BAT) and a trend for lower scores on the Fear of Spiders Questionnaire (FSQ) than patients who were treated in the evening. This effect continued to be present at post-treatment and follow-up. These results indicate that exposure therapy is more effective in the morning than in the evening due to higher endogenous cortisol levels in the morning group that enhance extinction memory (Lass-Hennemann et al., 2014).

Cortisol levels (and levels of epinephrine, norepinephrine, growth hormone and insulin) were also found to rise during therapeutic in vivo exposure to feared animals in a small sample (n=10) of women with various animal phobias (Nesse et al., 1985). Cortisol levels were found to increase during exposure therapy in two patients with height phobia (Abelson and Curtis 1989). Although baseline cortisol levels did not differ between groups, a significantly greater increase in cortisol levels was reported immediately before, during and immediately after a driving task in individuals with driving phobia, when compared to healthy controls (Alpers et al., 2003). But not all evidence is supportive: an investigation in women with spider phobia (n=46) and healthy control women found few differences in cortisol response when challenged with neutral or feared images (Knopf and Possel 2009); and cortisol levels did not increase following presentation of the feared stimulus, despite increases in self-reported fear, in an investigation in spider phobia (n=16) (Van Duinen et al., 2010).

Investigations of the interaction between cortisol exposure and the effectiveness of exposure therapy have produced intriguing findings. In a placebo-controlled study, cortisol administration one hour prior to experimental exposure to feared social situations or animals was found to significantly reduce stimulus-induced self-reported fear (but not to reduce more general non-phobic anxiety) (Soravia et al., 2006). In patients with specific phobia, social phobia and PTSD, prior cortisol administration was also associated with reduced stimulus-induced fear, both immediately after exposure and two days later (de Quervain and Margraf 2008). In a placebo-controlled study in individuals (n=40) with height phobia, cortisol administration prior to virtual reality therapeutic exposure was found to significantly reduce both reported fear and the degree of exposure-induced increased skin conductance (de Quervain et al., 2011). Intensive therapeutic in vivo exposure in military personnel (n=46) with protective mask phobia (a form of simple phobia) was associated with a reduction in salivary cortisol levels, this reduction not being seen in controls from emergency responder services (Brand et al., 2011). Another study found that administration of oral cortisol (20 mg) one hour before each exposure therapy session to patients with spider phobia (n=22) led to increased salivary cortisol concentrations and a significantly greater reduction in fear of spiders (measured by FSQ) when compared to placebo administration at follow-up, but not immediately post-treatment. Cortisol-treated patients reported significantly less anxiety during standardized exposure to living spiders at follow-up than did placebo-treated subjects. These findings suggest that adding cortisol to in vivo exposure-based group therapy might enhance treatment outcomes in patients with simple phobia (Soravia et al., 2013).

Table 1.4 **Investigations of cortisol in specific (simple) phobia**

study	**findings**
Herbert et al., 1996	Co-morbid phobic disorders associated with lower likelihood of hypercortisolism
Kellner et al., 1998	No difference from other anxiety disorders in salivary cortisol or diurnal cortisol rhythm
Lilliecreutz et al., 2011	Blood-injection phobia in pregnant women associated with hypercortisolism
Fredrikson et al., 1985	Exposure to pictorial images of feared objects elicits rise in cortisol levels
Nesse et al., 1985	Cortisol levels rise during in vivo exposure to feared animals
Abelson et al., 1989	Cortisol levels rise during exposure therapy for height phobia
Alpers et al., 2003	Greater increase in cortisol levels before, during and after driving task in driving phobia
Knopf and Possel 2009	No differences in cortisol levels following exposure to feared or neutral images
Van Duinen et al., 2010	Increased fear following presentation of feared stimuli not accompanied by increase in cortisol
Soravia et al., 2006	Cortisol administration prior to exposure to feared situations reduces stimulus-induced fear
De Quervain et al., 2008	Cortisol administration associated with reduction in stimulus-induced fear
De Quervain et al., 2011	Cortisol administration reduces fear and exposure-induced increased skin conductance
Brand et al., 2011	Reduction in cortisol levels with in vivo exposure in protective mask phobia
Soravia et al., 2013	Oral Cortisol (20 mg) 1 hour before each exposure therapy session to patients with spider phobia lead to increased salivary cortisol concentrations and a significantly greater reduction in fear of spiders. Cortisol-reduced anxiety during exposure.
Lass-Hennemann et al., 2014	Exposure therapy during peak time for endogenous cortisol exhibited significantly less fear of spiders than patients treated in the evening.

1.4.5 Obsessive Compulsive Disorder (OCD)

A total of 17 case-control studies have investigated the HPA axis in OCD patients (Table 1.5). Ten studies found an elevation of cortisol levels in patients with OCD (total n=128) compared to controls (total n=167) (Gehris et al., 1990; Morgado et al., 2013; Wang et al., 2013; Fluitman et al., 2009; Brambilla et al., 2000; Monteleone et al., 1998; Monteleone et al., 1997; Monteleone et al., 1995; Monteleone et al., 1994; Catapano et al., 1992). By contrast, five studies found no difference between OCD (total n=68) and healthy controls (total n=91) (Millet et al., 1998; Brambilla et al., 1997; Maes et al., 1994; Benkelfat et al., 1991; Weizman et al., 1990).

A total of 13 studies have investigated dexamethasone suppression in patients with OCD, using variable methodological approaches. Five studies found an increase in dexamethasone suppression in OCD patients, when compared to controls (Reimlod et al., 2013; Vallejo et al., 1992; Catapano et al., 1990; Insel et al., 1984; Insel et al., 1982), but three studies found no significant difference between patients and controls (Lucey et al., 1992; Coryell et al., 1989; Lieberman et al., 1985).

Four studies found a high proportion of non-suppression in OCD patients with co-existing depressive symptoms (Kuloglu et al., 2009; Vallejo et al., 1988; Jenike et al., 1987; Monteiro et al., 1986). However, another study reported that the increased rate of dexamethasone non-suppression in OCD was independent of coexisting depressive symptoms (Cottraux et al., 1984).

A total of 8 studies have employed differing behavioural tasks to measure cortisol response in patients with OCD. Of these, three found elevated cortisol responses to the Montreal Imaging Stress Task (MIST) (Lord et al., 2012), exposure to aversive stimuli (Kasvikis et al., 1988), or Cold Pressor Test (Lord et al., 2010). By contrast, three studies found no elevation in cortisol levels, following exposure to a behaviour therapy session which was rated as stressful by participant patients (Kellner et al., 2012), after a standardised provocation paradigm (Fluitman et al., 2009), or electrical stimulation test (Kawano et al., 2012). By contrast, cortisol levels were reduced with 'attribution retraining group therapy' (Wang et al., 2013), and with exposure therapy (Gustafsson et al., 2008). A more recent study in 'treatment refractory' OCD patients (n=16) who underwent deep brain

stimulation targeted at the nucleus accumbens found increased median urinary free cortisol levels with 53% in the 'OFF' condition which was strongly correlated with an increase in Yale-Brown Obsessive Compulsive Scale (Y-BOCS) (39%), and HAM-D (78%) scores. These findings indicate that symptom changes following DBS for OCD patients are associated with changes in UFC levels (de Koning et al., 2013).

Table 1.5 **Investigations of cortisol in Obsessive Compulsive Disorder (OCD)**

study	**findings**
Gehris et al., 1990, Morgado et al., 2013, Wang et al., 2013, Fluitman et al., 2009, Brambilla et al., 2000, Monteleone et al., 1998, Monteleone et al., 1997, Monteleone et al., 1995, Monteleone et al., 1994, Catapano et al., 1992)	elevation of cortisol levels in patients with OCD (total n=128) compared to controls (total n=167)
Millet et al., 1998, Brambilla et al., 1997, Maes et al., 1994, Benkelfat et al., 1991, Weizman et al., 1990	found no difference between OCD (total n=68) and healthy controls (total n=91)
Reimlod et al., 2013, Vallejo et al., 1992, Catapano et al., 1990, Insel et al., 1984, Insel et al., 1982)	increase in dexamethasone suppression in OCD patients, when compared to controls
Lucey et al., 1992, Coryell et al., 1989, Lieberman et al., 1985	no significant difference between patients and controls
Kuloglu et al., 2009, Vallejo et al., 1988, Jenike et al., 1987, Monteiro et al., 1986	high proportion of non-suppression in OCD patients with co-existing depressive symptoms
Cottraux et al., 1984	increased rate of dexamethasone non-suppression in OCD was independent of coexisting depressive symptoms
(Lord et al., 2012	elevated cortisol responses to the Montreal Imaging Stress Task (MIST)
Kasvikis et al., 1988	elevated cortisol responses to exposure to aversive stimuli
Lord et al., 2010	elevated cortisol responses to Cold Pressor Test
Kellner et al., 2012	no elevation in cortisol levels following exposure to a behaviour therapy session which was rated as stressful by participant patients
Fluitman et al., 2009	no elevation in cortisol after a standardised provocation paradigm
Kawano et al., 2012	no elevation in cortisol with electrical stimulation test
Wang et al., 2013	cortisol levels were reduced with 'attribution retraining group therapy
Gustafsson et al., 2008	cortisol levels were reduced with exposure therapy
de Koning et al., 2013	refractory OCD treated with Deep brain stimulation; showed increased Median UFC levels increased with 53% in the OFF condition which was strongly correlated with increase in Y-BOCS (39%), and HAM-D (78%) scores.

1.4.6 Social Anxiety Disorder (Social Phobia)

Compared to panic disorder and GAD, there have been relatively few investigations of cortisol in patients with social phobia. I included studies that investigated different behavioural, hormonal and cognitive changes associated reactive cortisol levels and response to experimental social stress paradigm (Table 1.6).

Although a prospective study in a community sample (n=238) found that elevated afternoon salivary cortisol levels in early childhood were predictive of subsequent social phobia in adolescence (Essex et al., 2010), a series of investigations have suggested cortisol levels are not elevated in patients with social phobia in the 'resting' or unchallenged state.

An early investigation found no significant differences in urinary cortisol levels between patients with social phobia (n=10) and healthy controls (Potts et al., 1991): this finding being replicated in an analysis of 24-hour urinary cortisol levels, which also found no evidence of dexamethasone non-suppression in a larger group (n=64) of patients with social phobia (Uhde et al., 1994). No significant differences were found between patients with social phobia (n=26) and healthy controls in plasma levels of cortisol, pregnenalone or DHEA (Laufer et al., 2005). Although patients with social phobia (n=43) differed from healthy controls in salivary alpha-amylase (a marker of sympathetic autonomic nervous system activity), there were no differences in salivary cortisol levels (van Veen et al., 2008). A case–control study of men with social phobia (n=12) found that salivary cortisol levels were significantly lower than in healthy controls, with strong negative correlations between cortisol levels and 5-HT1A binding in the amygdala, hippocampus and retrosplenial cortex (Lanzenberger et al., 2010).

Investigations of the response to psychological challenge have produced reasonably consistent findings. An early study found that challenge through the Trier Social Stress Test (TSST) was associated with a significant elevation in salivary cortisol levels in adolescent girls with social phobia (n=27), but no more so than in healthy controls (Martel et al., 1999). By contrast, a public speaking task (but not physical exercise) was associated with a significantly greater increase in salivary

cortisol in patients with social phobia (n=18) compared to healthy controls (Furlan et al., 2001). Performance of a public speaking task was associated with a significantly greater increase in salivary cortisol in children with social phobia (n=25) compared to healthy controls (van West et al., 2008). In addition, performance in a social approach-avoidance task and challenge through the TSST was associated with a significantly greater increase in salivary cortisol in patients with social phobia (n=18) compared to healthy controls and patients with PTSD (Roelofs et al., 2009). However, in children with social phobia (n=41) undergoing challenge with the TSST, the increase in salivary cortisol was not significantly greater than in healthy controls (Krämer et al., 2012). In a functional imaging study involving a public speaking task in patients with social phobia (n=12), the increase in salivary cortisol levels was associated with increased regional cerebral blood flow in the hypothalamus (especially the mamillary bodies) but with decreased flow in the medial prefrontal cortex (Ahs et al., 2006).

Table 1.6 **Investigations of cortisol in social anxiety disorder (social phobia)**

study	**findings**
Essex et al., 2010	Elevated afternoon salivary cortisol level in childhood predicts social phobia in adolescence.
Potts et al., 1991	No difference in urinary cortisol levels.
Uhde et al., 1994	No difference in 24-h cortisol levels and no evidence of dexamethasone non-suppression.
Laufer et al., 2005	No difference in levels of cortisol, pregnenalone or DHEA.
Van Veen et al., 2008	No difference in salivary cortisol levels despite difference in salivary alpha-amylase.
Lanzenberger et al., 2010	Significantly lower cortisol levels and negative correlations with 5-HT1A binding.
Martel et al., 1999	No significant difference in elevation of cortisol levels following TSST.
Furlan et al., 2001	Enhancement of increase in salivary cortisol levels following public speaking task.
Van West et al., 2008	Enhancement of increase in salivary cortisol levels following public speaking task.
Roelofs et al., 2009	Greater increase in salivary cortisol levels with psychological task following TSST challenge.
Ahs et al., 2006	Increase in salivary cortisol levels associated with increased blood flow in hypothalamus.
Krämer et al., 2012	No significant difference in rise in salivary cortisol level following TSST.
DeVane et al., 1994	No correlation between cortisol level and degree of improvement with SSRI treatment.
Tancer et al., 1994	Augmentation of cortisol response following fenfluramine challenge.
Hollander et al., 1998	Trend towards enhancement of cortisol response following mCPP challenge.
Van Veen et al., 2007	No significant difference in cortisol response following mCPP challenge.
Shlik et al., 2004	No significant difference in cortisol response to citalopram challenge.
Van Veen et al., 2009	No increase in cortisol level following acute tryptophan depletion and public speaking task.
Soravia et al., 2006	Cortisol administration reduces fear before, during and after social evaluative stress task.
Van Peer et al., 2009, 2010	Cortisol administration enhances processing of social stimuli and event related amplitudes.
Katzman et al., 2004	No difference in cortisol response following CCK-4 challenge.

More recent studies have investigated pathophysiological reactions to laboratory-induced social stress paradigms in healthy volunteers (Table 1.7). These studies investigated different behavioural, hormonal and cognitive changes associated with reactive cortisol levels and reactivity to experimental social stress challenge. Social stressors can lead to behavioural changes that might be conferred via HPA changes/disturbances. TSST cortisol responders (but not non-responders) have increased rates of excessively discounting the subjective value of future rewards i.e. delay discounting (measured by questionnaire version with inter-temporal choice). This suggests a possible influence of the pathway from the HPA axis to the dopaminergic systems under acute stress (Kimura et al., 2013).

The number of people in the 'social space' of an individual might play a role. In an investigation involving 60 healthy students, randomised to three clinically identical simulation-based scenarios designed to elicit varying levels of social-evaluation anxiety (by manipulating the number of other people also present during the simulation [1, 2 or 3 others], anxiety levels and salivary cortisol measurements were significantly different within the first minute of the simulation according to the number of other people in the room. This suggests that a socially evaluated and more challenging encounter, influenced by a greater number of observing individuals during simulation, can lead to measurably greater anxiety, higher salivary cortisol and measurably poorer performance (Mills et al., 2016).

The type of social surrounding and interaction might contribute to differing patterns of psychological and hormonal response. A study of participants with 'anxiety distress symptoms' found that exposure to an urban natural outdoor environment was associated with elevated salivary cortisol and anxiety, when compared to exposure to a rural green environment or blue sea (Triguero-Mas et al., 2017). The content of social interaction may also have a role: an investigation in healthy female volunteers (n=22) which examined salivary cortisol in response to three different conditions of social interactions ('gossip', 'emotional non-gossip', 'neutral') found no significant differences in cortisol level and response across the three conditions, but the 'gossip' condition was

associated with raised oxytocin levels (Brondino et al., 2017). Increased cortisol was found to be associated with increased attentional performance in the post-stress condition in healthy individuals (n=48) who underwent the Socially Evaluated Cold Pressor Test. However, there were neither stress or responder main effects, nor an interaction effect on reasoning abilities (Plieger et al., 2016). Salivary cortisol was elevated following experimental exposure to social stress (n=39), and this was associated with significantly increased charitable donation frequency and positively associated with cortisol in male participants, but only in subjects with low baseline pro-environmental orientation (Sollberger et al., 2016).

Some studies have investigated the potential role of gender differences in response to experimental social stressors. For example, in healthy adults (n=204; 60 males, 144 females) who underwent the TSST, increased salivary cortisol levels were more frequent among men than women. Male participants had higher reactive cortisol than women in an unadjusted analysis, but this difference was attenuated after adjusting for sex hormones. While diurnal cortisol showed no sex differences in unadjusted models, adjusting for sex hormones revealed that women had higher morning cortisol. Correlations using 'area under the curve' formulae showed sex-specific associations with progesterone in men and testosterone in women (Juster et al., 2016). A TSST-based investigation in healthy women (n=40) at different stages of the menstrual cycle found that the follicular phase, but not the luteal phase, demonstrated a significant cortisol response to the TSST. There was a stress-induced decrease in emotional retrieval following the TSST, but this effect was not modified by the menstrual phase. Regression and correlational analyses showed that individual differences in stress-induced cortisol levels were associated with impaired emotional retrieval in the follicular phase only. These findings indicate that cortisol responsivity, and the impairing effects of cortisol on emotional memory, are lower when levels of oestradiol and progesterone are relatively high, compared to when levels are low (Maki et al., 2015).

Some studies have investigated the effect of a past history of demanding social encounters and prolonged/chronic social stressors on HPA functioning in healthy individuals. A history of a

prolonged psychosocial stressor was found to be associated with lower levels of self-reported emotional attentional control in association with elevated salivary cortisol (n=90), and with slower decline in cortisol throughout the day (n=71). It is plausible therefore, that difficulty controlling attention during socially-driven emotional experiences may be due to chronic HPA-axis hyperactivity after prolonged exposure to stress (Lenaert et al., 2016).

Another study investigated the strength of 'affiliation motive' (assessed using the Operant Motive Test) in school students (n=59) in response to acute social stress (publishing the results of an intelligence test) versus physical stress: affiliation motive outcomes negatively predicted salivary cortisol reactions to acute social stress but not to physical stress when compared to a control group, suggests that association motive might have a buffering effect on the response to social stress (Wegner et al., 2014).

TSST-induced elevated salivary cortisol levels with HPA hyper-activation in 'chronically stressed' but otherwise healthy male subjects (n=75) were found to be normalised with an oral supplementation of phosphatidylserine and phosphatidylserine/ phosphatidic acid complex (PAS 400, MemreePlus) (Hellhammer et al., 2014).

Another study investigated the effect of stigma-related social anxiety in lesbian, gay, and bisexual young adults (n=70): a greater level of family support, but not peer support or overall support satisfaction, was associated with reduced salivary cortisol activity following the TSST, thereby indicating that differing sources of social support may have varying effects on neuroendocrine functioning (Burton et al., 2014).

A randomized controlled trial that investigated the offspring of divorced mothers (n=161), found that higher externalizing symptoms were associated with lower salivary cortisol reactivity to a social stress task. Older offspring in the control group had higher cortisol reactivity, when compared to those who underwent a family-focused group preventive intervention for mothers and children in newly-divorced families (Luecken et al., 2015).

In an investigation of the influence of trait-anxiety on the response to social anxiety challenge, male subjects with elevated levels of trait anxiety received either no treatment (n=24), a placebo pill (n=24), or St. John's wort (n=6) before the TSST: when compared to baseline, subjects had increased levels of subjective stress and anxiety (measured using the state sub-scale of SSTAI and Multidimensional Mood State Questionnaire), elevated salivary cortisol, elevated alpha-amylase, and decreased heart rate variability, with no significant differences between groups on all test parameters (Zimmermann-Viehoff et al., 2016). Another study highlighted the behavioural changes associated with TSST-elevated cortisol, finding that TSST increased salivary cortisol and led to an associated, but uncorrelated, increase in chewing frequency in healthy females (n=31), associated with reduced appetite (Petrowski et al., 2014).

Some studies have investigated the effect of psychological interventions on the behavioural, hormonal and cognitive manifestations associated with cortisol changes in experimental social stress paradigms. A double-blind within-subject experiment (n=56), found higher TSST-salivary cortisol response following supraliminal training (pictures shown with full conscious awareness), masked training and stimuli presented with limited conscious awareness. The effect of attention training on the cortisol response to stress was more robust in those with high attentional control than those with low attentional control. Supraliminal training was also associated with enhanced serum Alpha-Amylase (sAA) reactivity and a more hostile mood response (Pilgrim et al., 2014).

An investigation in healthy participants (n=54) who underwent the TSST found that shifted goal orientation from self-promotion to helping others reduced the ACTH and cortisol responses, when compared to control subjects' response to TSST. Compassionate goals reduced hormonal responses without reducing subjective anxiety, stress or fear, while increasing the expression of pro-social intentions and a focus on helping others. These results suggest that brief interventions might potentially reduce the impact of predictable social stressors through compassion and altruistic goals (Ableson et al., 2014).

Another study randomly assigned healthy participants (n=66) to brief mindfulness meditation training or cognitive training comparison program. The mindfulness group had reduced self-reported psychological stress reactivity but increased salivary cortisol reactivity to the TSST, relative to the cognitive training comparison program. Participants low in pre-existing levels of dispositional mindfulness who received mindfulness meditation training showed the greatest cortisol reactivity to the TSST, suggesting that brief mindfulness meditation training appears to buffer self-reported psychological stress reactivity, but also increases cortisol reactivity to social evaluative stress (Creswell et al., 2014).

In another controlled study in women (n=105), brief compassionate training was associated with reduced salivary cortisol and reduced subjective anxiety and serum alpha amylase response to TSST, these findings persisting even after adjusting for baseline trait anxiety (Arch et al., 2014). A randomised control study found that two weeks of high endurance training (n=96) led to a reduced cortisol response to TSST, when compared to relaxation program or control group (Klapersk et al., 2014). An investigation of the effects of aroma-massage on TSST challenge in healthy adults (n=118) found that rhythmic message compared to a sham massage was not associated with a significant change in salivary cortisol or heart rate, even though the procedure was described as ‘relaxing’ by 84% in the massage group, compared to the sham group (Kanitz et al., 2015).

The effect of physiological hormonal diurnal variation may be an important influence on the relationship between anxiety and HPA response. A study found TSST-elevated salivary cortisol levels and higher pre-sleep salivary cortisol levels and perceived tension in premenopausal females, with and without insomnia (n=40). The study also found that vagal tone recovered 4-6 h into the stress night in controls (n=18) but not in the insomnia group (n=22) (de Zambotti et al., 2016). A randomized controlled study of acute stress deprivation versus control condition in healthy subjects (n=40), found that acute sleep deprivation was associated with a greater salivary cortisol pre-stress baseline but a blunted 'ceiling effect' on the amount of cortisol in response to TSST (Vargas et al., 2017).

Some studies have investigated the response to pharmacological interventions on behavioural, hormonal and cognitive outcomes associated with HPA changes in an experimental social stress paradigm. In a placebo controlled study in healthy men (n=24), the Stroop task and TSST led to an elevation in plasma cortisol and ACTH levels, this response being attenuated by consuming 660 mL, ~26 g of alcohol. This suggests that alcohol ingestion after a mental stressor may facilitate the endocrine stress response, as reflected by decreasing plasma ACTH and cortisol levels (Schrieks et al., 2016). A double- blind placebo-controlled, 2-arm investigation in healthy individuals (n=64) who had elevated cortisol levels following the TSST found that administration of '*Neurexan*' (comprising *Avena sativa*, *Coffea arabica*, *Passiflora incarnate*, zincum isovalerianicum, lactose monohydrate, and magnesium stearate) did not affect subjective stress ratings but significantly diminished stress-induced increases in salivary cortisol and plasma adrenaline (Doering et al., 2016).

In a further investigation, administration of *bifidobacterium longum* 1714 (but not placebo) attenuated elevated salivary cortisol levels in healthy volunteers (n=22) in response to socially evaluated cold pressor test (SECPT), which represents a combined psychological and physiological stressor procedure (Allen et al., 2016). In another, intranasal insulin (compared to placebo) increased circulating cortisol levels and reduced nicotine cravings in abstinent smokers (n=37) who underwent the TSST (Hamidovic et al., 2017).

An investigation in healthy male subjects (n=32) involving induced psychosocial stress (through the Montreal Imaging Stress Task; MIST), found attenuated salivary cortisol reactivity (and significantly reduced limbic deactivation), when compared to placebo after intra-nasal oxytocin administration in subjects without a history of early life stress (assessed with the Childhood Trauma Questionnaire). Subjects who had experienced early life stress had both blunted cortisol stress reactivity and limbic deactivation during stress: furthermore, in these participants, oxytocin administration had the opposite effect, with increased hormonal reactivity and increased limbic deactivation (Grimm et al., 2014).

By contrast, another placebo-controlled study of the effects of intranasal oxytocin administration in cocaine-dependent individuals (n=32) subject to challenge with the TSST found no significant increase in either cortisol or DHEA from the pre-TSST time point: oxytocin had no modifying effect on either cortisol or DHEA response levels immediately following the TSST (Flanagan et al., 2015). Furthermore, administration of intranasal oxytocin to healthy individuals (n=60) did not alter TSST-elevated cortisol levels but led to an increment in perceived social stress (Eckstein et al., 2014).

A double blind, placebo controlled between group study, investigated the response to exposure to non-stressful social interaction (through the Friendly Tier Social Stress Test) after administration of oral hydrocortisone (20mg). The study found elevated salivary cortisol levels associated with enhanced memory for peripheral objects of the situation in men but not in women. Memory for central objects was not affected by the hormone. sAA increased in response to the test in both groups (Wiemers et al., 2015). By contrast, another study found that oral administration of hydrocortisone in healthy subjects (n=40) had no main neurocircuitry effect in either the response to exposure to composite pictures of faces and places, or in reflectively appraising the participant's own emotional response (Ma et al., 2017).

Some studies have examined cortisol parameters alongside other potential biomarkers in response to experimental social stress. An investigation found that copeptin was significantly increased along with TSST-elevated cortisol levels in healthy volunteers (n=20): patients with diabetes insipidus had lower baseline copeptin (n=8) and a blunted copeptin TSST-response, but no blunting of the cortisol TSST-response: elevated copeptin and cortisol levels were associated with reported feelings of tension and avoidance (Siegenthaler et al., 2014). Another investigation of the TSST-response in healthy volunteers (n=100) found a significant positive association between the percent change in copeptin and the percent change in log-transformed salivary cortisol (Spanakis et al., 2016). A study of testosterone levels in healthy men (n=85) found lower baseline cortisol predicted higher elevation of testosterone levels following TSST, suggesting lower cortisol levels may mobilize a larger testosterone response in situations involving social-evaluative stress (Bedgood et al., 2014).

A functional imaging study found that TSST-elevated cortisol in healthy male volunteers (n=37) was related to stronger nucleus accumbens activation (NAcc), when compared to neutral conditions: cortisol acted as a suppressor variable in the negative relation between stress and NAcc activation, suggesting that cortisol is crucially involved in the relation between stress and the responsiveness of the reward system (Oei et al., 2014).

A genetic study found that expression of RIPK2 (receptor-interacting serine/threonine-protein kinase 2) and HDAC2 (histone deacetylase 2) genes were associated with faster salivary cortisol recovery following TSST, in a day of intensive practice of mindfulness meditation in experienced subjects (n=19), when compared to a control group of subjects engaged in leisure activities in the same environment (n=21) (Kaliman et al., 2014).

Table 1.7 **Investigations of cortisol in experimentally induced social anxiety**

study	findings
Allen et al., 2016	Attenuated SECPT elevated cortisol levels with *B. longum* 1714 and not placebo.
Mills et al., 2016	Elevated stress and cortisol in socially evaluated encounter is influenced by greater numbers of observants.
Triguero-Mas et al., 2017	Urban natural outdoor environment was associated with elevated salivary cortisol and anxiety compared to exposure to green; park or beach).
Hamidovic et al., 2017	Intranasal insulin increased cortisol elevation response to TSST.
Vargas et al., 2017	Acute sleep deprivation caused elevated pre-TSST cortisol but ceiling effect on post-TSST cortisol levels.
Brondino et al., 2017	No difference in decreased salivary cortisol across gossip, emotional non-gossip, neutral social conditions. Elevated oxytocin with gossip condition.
Ma et al., 2017	Oral hydrocortisone does not affect response to experimental exposure to composite pictures of faces and places and reflectively appraising own emotional response.
Schrieks et al., 2016	TSST, stroop test associated elevated cortisol is attenuated by moderate dose of alcohol.
Plieger et al., 2016	Increased cortisol and attentional performance in response to Socially Evaluated Cold Pressor Test.
Doering et al., 2016	Neurexan diminished TSST cortisol elevation in health subjects.
de Zambotti et al., 2016	TSST elevated cortisol level in women with or without insomnia.
Sollberger et al., 2016	Social stress increased salivary cortisol associated with increased donation frequency in participants with poor environmental orientation.
Lenaert et al., 2016	Prolonged history of social stressors is associated with lower levels of self-reported emotional attentional control associated with elevated levels and slower decline in cortisol throughout the day.
Juster et al., 2016	Higher cortisol in male vs female with TSST. Effect is attenuated after adjusting for sex hormones.
Spanakis et al., 2016	TSST significantly increased copepetin along with cortisol.
Kanitz et al., 2015	TSST elevated cortisol not affected by RA, RM or SM.
Flanagan et al., 2015	No significant increase in cortisol following TSST in cocaine-dependant patients and no modifying effect of intranasal oxytocin.
Maki et al., 2015	Significant cortisol response to TSST in women during follicular phase and not luteal phase.
Zimmermann-Viehoff et al., 2016	Increased cortisol, alpha amylase and perceived anxiety in participants with trait-anxiety. Placebo, herbal medicine did not alter response.
Wiemers et al., 2015	Oral hydrocortisone increased salivary cortisol and sAA.
Luecken et al., 2015	Offsprings of divorced mothers has lower cortisol reactivity with social stress task.
Siegenthaler et al., 2014	Elevated cortisol and copeptin with TSST. DI patients has lower copeptin and blunted copeptin response but not cortisol response.
Hellhammer et al., 2014	TSST caused cortisol elevation in healthy subjects with chronic socials stressors. Response is normalized with (PAS 400, MemreePlus).

Wegner et al., 2014	Affiliation motive can predict negative cortisol reaction to acute social stress.
Bedgood et al., 2014	TSST induced higher testosterone level in men with low baseline cortisol.
Petrowski et al., 2014	TSST elevated cortisol associated with increased chewing frequency and reduced appetite.
Burton et al., 2014	TSST cortisol reduction in candidates suffering stigma-related social anxiety in presence of greater family but not peer support.
Pilgrim et al., 2014	Supraliminal training is associated with elevated salivary cortisol and sAA reactivity. Attention training has more robust effect on cortisol response following TSST.
Ableson et al., 2014	Shifted goal orientation from self-promotion to helping others attenuates cortisol response to TSST.
Creswell et al., 2014	Mindfulness increases cortisol reactivity in heathy individual's response to TSST.
Eckstein et al., 2014	Intranasal oxytocin did not alter elevated cortisol levels but led to increment in perceived social stress.
Klapersk et al., 2014	High endurance 2 weeks training reduces cortisol response to TSST compared to relaxation program or control group.
Arch et al., 2014	Brief compassionate training –compared to control- reduced salivary cortisol, subjective anxiety and sAA response to TSST in women
Kaliman et al., 2014	RIPK2 and HDAC2 gene expressions are associated with salivary cortisol recovery following TSST in day of intensive practice of mindfulness.
Grimm et al., 2014	Attenuated salivary MIST elevated cortisol levels with intranasal oxytocin.
Oei et al., 2014	TSST elevated cortisol related to stronger NAcc activation.
Kimura et al., 2013	Increased delay discounting in TSST cortisol responders but not non-responders.

1.4.7 Pharmacological challenge and cortisol in anxiety disorders

Pharmacological challenge tests and pharmacological treatment studies suggest a complex interaction between cortisol and serotonin in patients with social phobia. An early investigation found no correlation between plasma cortisol level and the degree of improvement during treatment with the SSRI fluvoxamine in patients with social phobia (DeVane et al., 1999). In a placebo-controlled study in generalized social phobia (n=21), single dose pharmacological challenge with fenfluramine was associated with a significantly augmented cortisol response, compared to that seen in healthy volunteers (Tancer et al., 1994). Single dose pharmacological challenge with mCPP was associated with a trend towards a greater cortisol response in patients with social phobia (n=18) than in controls or in patients with OCD (Hollander et al., 1998), but in a further investigation

involving mCPP challenge, the cortisol response was not significantly different between patients with social phobia (n=7) and healthy controls (van Veen et al., 2007). An investigation involving placebo-controlled single dose intravenous administration of the SSRI citalopram found no difference in plasma cortisol or prolactin responses, between patients with social phobia (n=18) and healthy controls (Shlik et al., 2004). Following successful SSRI treatment of patients with social phobia (n=18), dual pharmacological and psychological challenge — through placebo-controlled transient tryptophan depletion and performance in a public speaking task — was accompanied by significantly increased salivary amylase activity, but not by an increase in cortisol, suggesting hyper-responsivity of the autonomic nervous system but not of the HPA axis (van Veen et al., 2009).

As in patients with simple phobia, cortisol administration significantly reduced self-reported fear prior to, during and after a social-evaluative stress task (Soravia et al., 2006). Cortisol administration prior to a reaction time task enhanced the processing of social stimuli and enhanced event-related potential amplitudes.

Pharmacological challenge with intravenous CCK-4 found no differences in the ACTH, cortisol, growth hormone or prolactin response between patients with social anxiety disorder (n=12) or obsessive-compulsive disorder or healthy controls (Katzman et al., 2004).

1.4.8 Summary

Although published findings are inconsistent, panic disorder appears to be characterized by an elevation in urinary cortisol levels, by a decline in cortisol levels with successful pharmacological treatment, and by non-suppression following dexamethasone administration in a proportion greater than in healthy controls but less than that in depressed patients. There is much uncertainty about whether it is characterized by elevated plasma cortisol levels, whether cortisol levels fall following psychological challenge, and whether the anxiety response to panicogenic challenges is accompanied by changes in endocrine function. GAD appears to be characterized by a decline in cortisol levels with successful psychological or pharmacological treatment; it is uncertain whether

it is also characterized by elevated cortisol levels prior to treatment, or whether dexamethasone non-suppression is more common than in healthy controls. Specific phobia appears characterized by cortisol levels which rise during experimental exposure to feared objects or situations, but which decline with successful exposure therapy; social anxiety disorder is possibly characterized by cortisol levels that rise during psychological challenge.

Compared to the extensive literature on HPA axis function in patients with depressive illness, the evidence base relating to patients with the principal anxiety disorders is limited; the number of investigations in panic disorder and GAD is reasonably extensive, but there have been rather few studies in specific (simple) phobia and social anxiety disorder (social phobia). However, it is clear that there is no unifying disturbance of HPA axis function across these anxiety disorders; furthermore, within each disorder, the findings of investigations using similar methodology have often produced inconsistent findings. These apparent disparities in findings from studies of similar design are possibly influenced by the small sample size that is typical of most investigations, and by variations in the nature of the clinical sample. Achieving greater consensus on study objectives, the detailed characterization of patient groups, the methodological protocols for investigation and the preferred mode of statistical analysis would be an important step forward in further evaluations of HPA function in anxiety disorders (Baldwin et al., 2013).

1.5 Human sexual response

1.5.1 Background

The human sexual response is a complex physiological process. The widely accepted five stage sexual response model involves different neural, paracrine, autocrine and endocrine mechanisms. It is proposed that libido is stimulated by dopamine (Bocher et al., 2001), inhibited by serotonin, and threshold-adjusted by androgens (Stoleru et al., 1999). Arousal and the plateau phase are respectively triggered and maintained by parasympathetic signals. Orgasm is related to sympathetic neurons, and resolution represents a return to the base phase, during which different molecular mechanisms are involved both centrally and peripherally to facilitate detumescence (Root et al., 1947, Courtois et al., 1993).

Both central and peripheral regulation of penile erection involves several neurotransmitters and systems. Several studies have explored the relation between sexual dysfunction and anxiety disorders, and raise interest in whether these groups of symptoms might have an overlapping or interrelated pathogenesis. There is a strong clinical association between affective disorders and sexual dysfunction, and affective symptoms can reduce through use of pharmacological treatments targeted at sexual dysfunction (e.g. sildenafil, oxytocin) (Albersen et al., 2011, Yang et al., 2014). The common phenomenon of sexual dysfunction associated with SSRI treatment (Baldwin et al., 2013) suggests some overlap in mechanisms underlying response to antidepressant treatment within mechanisms underlying sexual functioning.

1.5.2 Physiological and molecular mechanisms in erection

Penile erection involves central and peripheral pathways. Tumescence is initiated after the central processing and integration of tactile, visual, olfactory and imaginative stimuli. Upon sexual stimulation, signals are generated to the peripheral tissues involved, the final response being mediated by coordinated spinal activity in autonomic pathways to the penis, and in somatic pathways to perineal striated muscles. The stage of penile erection requires relaxation of cavernosal smooth muscle, and is triggered by release of substances from parasympathetic and non-adrenergic non-cholinergic nerves, which in turn promote vascular and cavernosal relaxation, thereby leading to an increase in blood flow and intracavernosal pressure and so to erection (Nunes et al., 2012).

Nitric oxide (NO) is the main vasodilator involved in erection. In the penis, stimulation of parasympathetic nerves inhibits noradrenaline release and evokes acetylcholine (ACh) release, and binding to muscarinic receptors in endothelial cells promotes endothelial nitric oxide synthase (eNOS) activation and subsequent NO production. Cholinergic nerves have been demonstrated within the human cavernous smooth muscle and surrounding penile arteries, and ultrastructural examination has also identified terminals containing cholinergic vesicles in the same area (Leite et al., 2007; Toda et al., 2005; Steers et al., 1984). NO is formed from the precursor amino acid, L-arginine, by enzymatic action of nitric oxide synthases (NOS), which exists in three main isoforms: neuronal NOS (nNOS), inducible (iNOS), and endothelial NOS (eNOS). All three isoforms are detectable in penile tissue (Burnett et al., 1993), although nNOS and eNOS are the main constitutively active expressed NOS enzymes. activated by calcium entry into the cell, and binding to calmodulin (Bredt et al., 1990).

There are two main intracellular mechanisms for relaxing the cavernosal smooth muscle: the guanylate cyclase (GS)/cGMP and adenylate cyclase/cAMP pathways. NO is associated with GS/cGMP signalling, called the NO/cGMP pathway. After release, NO diffuses locally into adjacent smooth muscle cells of the corpus cavernosum and binds to soluble guanylyl cyclase (GC), which catalyzes the conversion of guanosine trisphosphate (GTP) to cyclic guanosine monophosphate (cGMP). This activates protein kinase G, also known as cGMP dependent protein kinase I (cGKI), which decreases cytosolic calcium by various mechanisms. cGMP also blocks Ras homolog gene family member A (RhoA) migration thereby avoiding Rho-kinase pathway activation, which is an important step in penile relaxation. The reduction in cytosolic calcium concentration facilitates relaxation of vascular and cavernosal smooth muscle cells, leading to dilation of arterial vessels, increased blood flow into the corpora cavernosa, and erection.

Substances such as prostaglandin E_1 (PGE_1) contribute to erection through binding to G-protein-coupled receptors and activation of the enzyme adenylate cyclase, which catalyzes conversion of adenosine monophosphate (AMP) to cyclic AMP (cAMP), which in turn activates protein kinase A

(PKA), which also decreases the intracellular calcium. These second messengers (cGMP and cAMP) activate protein kinases (cGMP-dependent protein kinase (PKG) and PKA respectively), which in turn phosphorylate certain proteins and ion channels, leading to increased opening of potassium channels and hyperpolarization, sequestration of intracellular calcium by the endoplasmic reticulum, and inhibition of voltage-dependent calcium channels, thereby blocking calcium influx. Both cGMP and cAMP levels are modulated by phosphodiesterase (PDE) enzymes, which cleave these signalling molecules to 5'GMP and 5'AMP, respectively. Phosphodiesterase-5 (PDE-5) is a key enzyme in the NO/cGMP signal transduction pathway and functions to restrain smooth muscle cell relaxation and the erectile process (Leite et al., 2007). Predominantly expressed in corpora cavernosa, PDE-5 catalyzes the hydrolysis of cGMP to the inactive metabolite 5'-guanidylic acid (5'GMP). PDE5 inhibitors (such as sildenafil) and papaverine are commonly recommended first-line pharmacological treatments for erectile dysfunction. Inhibition of PDE 2,3,4 by papaverine facilitates erection, and fasokolin exerts its effects through stimulation of adenyl cyclase (Nunes et al., 2012).

1.5.3 Physiological and molecular mechanisms in detumescence

Adrenergic enervation is found in penile tissue, mainly surrounding the cavernosal arteries, and norepinephrine has been suggested as the chief neurotransmitter derived from the sympathetic nervous system to control flaccidity and detumescense. The penis is also kept in the flaccid state through the actions of endothelins. Penile smooth muscle cells not only respond to, but also synthesize, endothelin-1 (ET-1) (Granchi et al., 2002). Vasoconstriction in erectile tissue induced by ET-1 appears to be predominantly mediated by the endothelin-A (ETA) receptor. In the penis, ET-1 and ETA receptor-mediated biological effects involve activation of the inositol trisphosphate (IP3)/calcium and RhoA/Rho-kinase signalling pathways (Wingard et al., 2003). However, both ETA and endothelin-B (ETB) receptors have been found in human corpus cavernosum smooth muscle membranes, and both receptor sub-types may be functional (Andersson et al., 2001). The role of

ETB receptors in the corpus cavernosum has not been clarified fully, although activation may induce a NO-mediated decrease in penile vascular tone (Ari et al., 1996).

In the absence of arousal stimuli, the intracellular mechanism starts with activation of G proteins following ligand binding to membrane receptors in order to keep cavernosal arterioles and sinuses constricted, maintaining the penis in the non-erect state. Subsequent to G protein activation, two signalling pathways are brought into play to cause smooth muscle contraction in the arterioles and cavernosum: the well characterized Ca^{2+} dependent pathway (phospholipase C) and the recently identified RhoA/Rho-kinase pathway known as Ca^{2+} sensitization. The Rho-kinase pathway is intrinsically involved with the process of smooth muscle contraction. The Ca^{2+} sensitivity of smooth muscle reflects the ratio of activities of myosin light-chain phosphatase (MLCP) to myosin light-chain kinase (MLCK), resulting in contraction or relaxation. Activation of G-protein coupled receptors by several agonists such as endothelin, angiotensin II, and noradrenaline, leads to the exchange of GDP for GTP on the small monomeric GTPase RhoA. This event activates RhoA and is catalyzed by the guanine nucleotide exchange factors, which causes dissociation of RhoA from its biding partner, Rho-guanine dissociation inhibitor. As a result, RhoA translocates from the cytosol to the membrane, allowing the downstream activation of several effectors such as Rho-kinase. Phosphorylation of the regulatory subunit of MLC phosphatase by Rho kinase causes inhibition of phosphatase activity, which increases the contractile response at a constant intracellular calcium concentration (Hirano et al., 2007).

MLCK and the RhoA/Rho-kinase pathway are two major cellular targets for regulating Ca^{2+} sensitivity of myosin light chain, and they generally operate in parallel. RhoA/Rho-kinase activity is a fundamental component to keep the penis in the non-erect state, and this pathway is upregulated in erectile dysfunction. The essential balance between contraction and relaxation in the penis, which is maintained by the RhoA/Rho-kinase and NO/cyclicGMP pathways, is modified in this condition (Andersson et al., 2003, Jin et al., 2006). It has been demonstrated that Rho-kinase antagonism stimulated rat penile erection independently of NO suggesting that this principle could

be a potential alternative target for treatment (Chitaley, Wingard et al., 2001, Chitaley Webb et al., 2001). Many studies have suggested that NO inhibits RhoA/Rho-kinase activity (Sawada et al., 2001, Sauzeau et al., 2000). Increased RhoA/Rho-kinase activity may lead to abnormal contractility of the CC and has been suggested to be involved not only in ED, but in several conditions which are risk factors for ED such as hypertension and diabetes (Nunes et al., 2010).

The phospholipase C (PLC) pathway is another mechanism involved in penile vasoconstriction in the absence of arousal stimuli. The stimulation of PLC occurs through the binding of vasoconstrictor agonists, such as norepinephrine (NE), angiotensin II (Ang II), endothelin-1 (ET-1) and others, to their respective receptors. PLC hydrolyzes phosphatidylinositol 4,5-biphosphate (PIP2) to release IP3 (inositol 1,4,5-trisphosphate) and DAG (1,2-diacylglycerol). IP3 binds to specific receptors (IP3R) on the endoplasmatic reticulum to stimulate the release of Ca^{2+} from the intracellular stores. DAG directly stimulates protein kinase C (PKC), which can regulate smooth muscle tone by controlling ion channels, allowing Ca^{2+} influx. PKC also phosphorylates multiple substrates to facilitate contraction (Nunes et al., 2012).

1.5.4 Renin angiotensin system

Several active peptides, particularly angiotensin II (Ang II), may be involved in the erectile mechanism. It has been demonstrated that Ang II activates the RhoA/Rho-kinase pathway via the angiotensin II receptor type 1 (AT1 receptor), which is dominantly expressed in the smooth muscle and endothelial cells of the blood vessel wall, leading to the inhibition of myosin light chain phosphatase (MLCP) (Ryan et al., 2004, Ying et al., 2006). Another significant function of AT1 is to activate nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, thereby increasing reactive oxygen species (ROS) production. ROS rapidly reacts with NO, reducing its bioavailability, and also stimulate RhoA/Rho-kinase activity (Jin et al., 2006, Jin et al., 2004). Additionally, both Ang II and AT1 were detected in endothelial and smooth muscle cells from CC, and comparing the different stages of penile flaccidity, tumescence, rigidity, and detumescence, Ang II levels were significantly higher during detumescence (Park et al., 1997). Human CC produces and secretes

physiological amounts of Ang II, as much as 200-fold greater than that in plasma. Furthermore, in vivo experiments demonstrated that injection of Ang II into the CC terminates spontaneous erections observed in anesthetized dogs (Kifor et al., 1997). Chronic infusion of exogenous Ang II for 4 weeks induced ED in Sprague-Dawley rats (Jin et al., 2008). It seems that RAS is crucial in ED. Results from human CC smooth muscle showed that Ang II and NO interact to modulate penile function, since an AT1 antagonist potentiated sodium nitroprusside (a NO donor), and electrical field stimulation mediated CC relaxation (Ertemi et al., 2011).

Ang II-mediated contraction contributes to maintenance of the penis in a flaccid state. However, the RAS system consists of two major arms: a vasoconstrictor/proliferative arm in which the major mediator is Ang II acting on AT1 receptors, and a vasodilator/antiproliferative arm in which the main effector is angiotensin 1-7 (Ang-(1-7)) acting via G protein-coupled receptors Mas (Santos et al., 2003). The Ang-(1-7)-Mas axis may play an important role in penile erection. This receptor has been observed in rat CC, and it has been demonstrated that Ang-(1-7) acts as a mediator of penile erection by activation of Mas and subsequent NO release. Additionally, in the absence of Mas, erectile function was severely compromised (da Costa et al., 2007).

1.5.5 Tumour Necrosis Factor (TNF)

In vivo administration of this cytokine induces impairment of endothelium-dependent relaxation in a diversity of vascular beds and decreases the release of NO (Chia et al., 2003). This cytokine not only induces inflammatory gene transcription, but also the activation of RhoA and Rho-kinase (Mong et al., 2008). In addition, TNFα leads to increased Ca^{2+} sensitivity via activation of the RhoA/ROCK pathway; TNFα-infused mice display decreased NANC-dependent relaxation and increased symphathetic mediated concentrations in vivo, which would contribute to penile detumescence. Enhanced direct adrenergic responses were also observed in CC tissue, and it was suggested that down-regulation of eNOS and nNOS may be the mechanism underlying functional modifications in CC strips from TNFα infused mice (Carneiro et al., 2009).

1.5.6 Endothelin-1 (ET-1)

Endothelin-1 not only induces vasoconstriction, but also stimulates the expression of adhesion molecules and activates transcriptional factors responsible for the coordinated increase in the expression of many cytokines and enzymes, which can in turn lead to the production of inflammatory mediators (Schiffrin 2005). Additionally, the RAS system and Ang II, the main known mediator of RAS, induces vascular injury through many mechanisms, including vasoconstriction, oxidative stress and inflammation. Both peptides have been shown to increase TNF-α levels and this pro-inflammatory cytokine also positively regulates release of these vasoactive peptides (Marsden et al., 1992, Kagawa et al., 2008). Finally, sexual activity has been negatively associated with circulating levels of endothelial inflammatory parameters (Vlachopoulos et al., 2006). Further studies are necessary to better clarify the role of TNFα in ED and its mechanism in CC dysfunction.

1.5.7 Interleukins

Astrocyte cultures stimulated with interleukin-1b (IL-1b) or the phorbol ester, phorbol 12-myristate 13-acetate (PMA), significantly increased prostaglandin E2 (PGE_2). The stimulatory action of IL-1b on PGE_2 production was totally abolished by NS-398, a specific inhibitor of cyclo-oxygenase-2 (COX-2) activity, as well as by the protein synthesis inhibitor cycloheximide, and the glucocorticoid dexamethasone. Furthermore, IL-1b induced the expression of COX-2 messenger ribonucleic acid (mRNA). This occurred early at 2 hours, with a maximum at 4 hours and declined at 12 hours. IL-1 b treatment also induced the expression of COX-2 protein as determined by immunoblot analysis. In that case the expression of the protein remained high for at least 12 hours. These findings suggest key roles for PKC as well as for ERK1/2 and p38 MAP kinase cascades in the biosynthesis of PGE_2, likely by regulating the induction of cyclo-oxygenase-2, in IL-1b- stimulated astroglial cells (Molina-Holgado et al., 2000).

1.5.8 Prostaglandins

PGE_2 and $PGF_{2\text{-}\alpha}$ are products of the arachidonic acid pathway. PGE_2 is known to have a pro-erectile function whereas $PGF_{2\text{-}\alpha}$ has the opposite effect. PGE_2 has been shown to induce erection in men with erectile dysfunction (ED) (Padma-Nathan et al., 1997). PGE_1, injected intracavernosally, alone or in combination, is a second-line treatment for ED (Padma-Nathan et al., 1997).

1.5.9 Damage-associated molecular patterns (DAMPs)

Stress exposure triggers a systemic sterile inflammatory response. Specifically, exposure to an intense acute stressor can release both Microbe-Associated Molecular Patterns (MAMPs) from the microbiota and/or Damage-Associated Molecular Patterns (DAMPs) from cells into the blood, and these signals are capable of arousing cells of the immune system; activating the inflammasome, and triggering the synthesis and release of a wide variety of both inflammasome-dependent and inflammasome-independent inflammatory proteins. Interestingly, there is evidence that the stress-associated neuroendocrine factors may also participate in innate immune arousal by upregulating pattern recognition receptors (PRRs) and directly regulating the inflammasome (Fleshner et al., 2013).

Lipocalin 2 (a DAMP) is increased in epilepsy and stroke and can be a marker for neural degeneration due to innate inflammation. Some evidence suggests activation of inflamatory mediators IL-1B and interleukin 18 (IL-18) by DAMPs (Banjara et al., 2014).

1.5.10 Modulators and potential therapeutic targets

The arachidonic acid pathway which exists both centrally, in the central nervous system (CNS), and peripherally (cavernous smooth muscle) might be affected in two different ways.

This can be demonstrated using the example of sexual dysfunction caused by lithium and treated by COX1/2 inhibition (aspirin), and the existing evidence for using PGE_2 in the treatment of erectile dysfunction.

Lithium intervenes with the step of the cascade; leukotriene C4 (LTC_4) to leukotriene D4 (LTD_4) and production of glutamate from glutathione. This takes place centrally reducing the available excitatory neurotransmitter (glutamate) and reducing stimulation of the parasympathetic neurons responsible for initiating erection.

Aspirin acts centrally by inhibiting COX1/2 and shifting the pathway towards the lipooxygenase side of the pathway, increasing hydroperoxyeicosatetraenoic acid (HPETE); leukotriene A4 (LTA_4) and LTC_4, thereby making more substrate available for the step affected by lithium which leads to correction of reduced glutamate levels centrally. Also HPETE is an omega-3 fatty acid known for its anti-inflammatory effects (this might explain the growing use in anxiety disorders and by extension interrelate to the increasing evidence of neural inflammation in anxiety disorders). Peripherally, the pathway is modulated differently. Where the production of PGE_2 plays a facilitatory effect for erection both physiologically and evidenced pharmacologically in treating erectile dysfunction.

Hence this side of the pathway continues the production of $PGF_2\alpha$, which is shown to play a role in physiological detumescence. A possible inhibition of this step would increase the level of PGE_2 and a possible target for treatment. COX-1/2 inhibition peripherally would lead to further reduction of PGE_2 production, shifting the pathway towards producing more glutamate and leukotrienes, both known for their stimulatory effect and smooth muscle constriction leading to erectile dysfunction. This supports the proposal of a central effect of COX-1/2 inhibition in treating erectile dysfunction and also supports the hypothesis of separate central and peripheral models of the pathway. The proposed module can be used to explain the effects/side effects of antileukotrienes (e.g. montelukast) inhibiting the production of leukotriene E4 (LTE_4) peripherally leading to smooth muscle relaxation (used in asthma) and centrally leading to loss of feedback inhibition (reducing LTE_4) and increasing glutamate, giving rise to known side effects such as agitation and hallucinations. This can be explored if antileukotirenes can be used to treat erectile dysfunction.

Existing evidence demonstrates reducing cortisol levels in response to glutamate inhibitors. Current evidence suggests an increase in apoptosis with increased levels of glutamate and cortisol

(Oosthuizen et al., 2005). Lithium acts as an antiglutamate centrally leading to accumulation of glutathione which is known to reduce cortisol and also inhibit cell apoptosis. This supports the presence of cell degeneration in affective disorders. Further trials of pharmacological agents acting via glutathione are yet to be explored.

Cytokines (IL-6, IL-8, TNF-α) stimulate apoptosis via G proteins, adenylate cyclase pathway centrally. This in turn stimulates the production of DAMPS (S100 and lipocalin-2 (LCN2)) which stimulates IL-1B and IL-18 and is stimulated further by IL-17 and IL-1.

The complexity of this mechanism which involves different cytokines at different stages suggests that innate inflammation is potentially associated with anxiety disorders, which are triggered by one group of cytokines and maintained by others.

Huntington's disease is known to be associated with psychiatric symptoms including irritability and anxiety. Huntington's patients showed high levels of IL-6, IL-8 and TNF-α (Björkqvist et al., 2008). This can be a reasonable explanation as a trigger for a neuroinflammatory process involving cell degeneration and developing anxiety symptoms. Increased levels of S100, LCN2 in epilepsy and stroke evidences trigger for this cycle and the further development of post stroke and inter epileptic anxiety disorders. This is yet to be tested and could provide different targets for treatment and prospective for understanding anxiety disorders.

Physiologically many modulators were found to be involved in detumescence. Noradrenaline, ET1, PGF2 alpha act via G-protein, increase DAG, IP3 and PKC. TNF-α, Angiotensin II, and ET1 via Rho A-guanosine diphosphatase (GDP) and Rho-kinase, inhibition of MLCP and regulating Ca^{2+} sensitivity in cavernous smooth muscles. Also, noradrenaline acts by inhibiting adenylate cyclase and CAMP formation (Nunes et al., 2012). These could be 'gates' in controlling the process by pharmacological agents acting on angiotensin II, TNF or noradrenaline.

Different pharmacological agents have been used to modulate the peripheral mechanisms involved in relaxation of cavernous smooth muscles. Sildenafil inhibits PDE5, the production of 5-GMP and

further activation of the cGMP-PTn Kinase 1 pathway. Papaverine has a similar (mirrored) action to sildenafil in reducing 5AMP. Faskolin and PGE_2 act by stimulating adenylate cyclase, increasing the production of cAMP (Nunes et al., 2012).

1.5.11 Summary

Knowledge of the complexity of the human sexual response is increasing. Both central and peripheral regulation of penile erection involves several neurotransmitters and systems, the full details of which are still not completely established. These systems are also involved in the development and maintenance of anxiety disorders. Further studies could not only help to develop novel pharmacological interventions for sexual dysfunction associated with anxiety disorders but also improve our understanding of the molecular mechanisms associated with the disorders and potentially new treatments for these conditions.

1.6 Sexual function and anxiety

1.6.1 Background

The most common sexual dysfunction in men are erectile dysfunction, affecting Between 10% (Nicolosi et al., 2004) and 16% (Rosen et al., 2004); and premature ejaculation, which affects 14% of men (Nicolosi et al., 2004) of men. The most common sexual dysfunction in women is hypoactive sexual desire disorder with a prevalence of 16%-46% (Dennerstein et al., 2006).

Sexual difficulties are more frequent among individuals with chronic conditions (Lewis et al., 2010). Many studies have explored the relationship between sexual dysfunction and depressive illness. Sexual problems in depressed individuals were found to be twice as prevalent as in healthy control subjects (Angst et al., 1998).

The presence of 12 months' mood disorders were found to have a significant association with poor sexual satisfaction (Vanwesenbeeck et al., 2014). Symptoms of depression commonly co-exist with symptoms of anxiety which are associated with sexual dysfunction (Lin et al., 2012; Laurent et al., 2009). The relationship between anxiety disorders, sexual dysfunction and dissatisfaction has not been explored extensively. Little is known about the prevalence of sexual dysfunction in patients with anxiety disorders, or its association with demographic and other clinical factors (Baldwin et al., 2014).

Recognition rates of sexual dysfunction in primary medical care are low (Cyranowski et al., 2004; Nazareth et al., 2003; Read et al., 1997). Lack of communication of sexual difficulties was reported in 50-73% of patients with enduring mental illnesses (Montejo et al., 2013). This was also found to be more pronounced in females (80%) (Rosenberg et al., 2003). Relying on spontaneous reporting of sexual dysfunction could-potentially- mislead the clinician to assume the lack of sexual difficulties.

The prevalence of reported sexual problems – when ascertained through direct but sensitive questioning by clinicians - is significantly higher than the rates reported by patients on questionnaires (Hirschfeld et al., 1999). The Third National Survey of Sexual Attitudes and Lifestyles (Natsal-3), of over 15,000 individuals aged between 16 and 74 years, found that 41.6 % of men and 51.2 % of women reported sexual problems, whereas self-reported distress about sexual life was much less frequent (9.9 and 10.9 %, respectively) (Mitchell et al., 2013).

Screening surveys and severity questionnaires can facilitate recognition of sexual difficulties, but cannot substitute for a comprehensive but sensitive assessment using adequate psychometrics; Arizona Sexual Experiences Scale (ASEX) (McGahuey et al., 2000), the Oxford Questionnaire of Emotional Side Effects of Antidepressants (OQuESA) (Price et al., 2012) and the Emotional Quality of the Relationship Scale (EQRS) (Kreuter et al., 1996).

1.6.2 Influence of treatment with psychotropic medications on sexual function

Determining the relationship between medication and adverse sexual effects is crucial to successful treatment. Adverse effects, understandably, can reduce the overall quality of life of patients and may impede their adherence to prescribed medication. Some studies have investigated the influence of treatment with psychotropic medications on sexual functions (Table 1.8).

Sexual difficulties are commonly reported adverse effects of antipsychotic (Montejo et al., 2010; Bobes et al., 2003) and antidepressant medications (Baldwin et al., 2013). Their estimated prevalence depends somewhat on the utilised method of data collection, with a low prevalence when relying on spontaneous reports and higher proportions when using confidential questioning or questionnaires (Pollack et al., 1992).

Sexual dysfunction has been reported with all antipsychotics, and present in up to 45% with conventional (‘first generation’) antipsychotics (Smith et al., 2002). Antipsychotics decrease dopaminergic neurotransmission, which can in itself decrease libido, but may also increase prolactin levels via negative feedback, leading to amenorrhoea in women and to lack of libido,

gynaecomastia and galactorrhoea in men and women (Anon et al., 1998). Higher prolactin levels are associated with higher rates of erectile and ejaculatory dysfunction in patients receiving antipsychotic medication (Weiden et al., 2001). Blockade of peripheral alpha-2 adrenoceptors can cause disorders in arousal, erection and ejaculation: drugs that block both peripheral alpha-2 adrenoceptors and cholinergic receptors can cause priapism (Baldwin et al., 2003).

Antidepressants can cause sexual dysfunction by disturbing cholinergic/adrenergic balance, antagonism of peripheral alpha-2 adrenoceptors, inhibition of nitric oxide and increased serotonergic availability (Clayton et al., 2006). An animal study found SSRI-mediated sexual dysfunction to be due to reduced NOS via increasing nicotinamide adenine dinucleotide phosphate oxidase activity (Kassan et al., 2013).

Other mechanisms may also be involved in erectile dysfunction associated with SSRI. Centrally, sensitisation of 5HT receptors can produce an inhibitory effect on the parasympathetic system. Peripherally, increasing available serotonin through inhibiting reuptake in the platelets can produce vasoconstriction at the cavernous bed, via 5HT1B, 5HT1D, and the non-receptor mechanism of serotonylation, therefore leading to erectile dysfunction.

Another possible implicated mechanism is through the arachidonic acid pathway. There is evidence that the SSRI citalopram attenuates the release of thromboxane A2. This would lead to a loss of negative feedback on the limb of the pathway and subsequently to decreased production of prostaglandins peripherally. This proposed model suggests a potential for identifying new targets for treating sexual dysfunction and for better understanding of different pathogenesis pathways of anxiety disorders. For example, if it is the case that erectile dysfunction associated with SSRI is due to a peripheral mechanism increasing serotonin release from platelets, a trial of metergoline (a 5-HT antagonist) could potentially reverse the process.

It is worth noting that some antidepressants can have a therapeutic effect in some patients with sexual dysfunction. Patients with persistent premature ejaculation can benefit from treatment with either clomipramine or SSRIs (Giuliano et al., 2008). A daily, or on-demand dose, of dapoxetine was

found to be beneficial (Hutchinson et al., 2012). High daily doses of paroxetine (150-200 mg), were also found beneficial in treating psychogenic erectile dysfunction (Fink et al., 2003).

It has proven difficult to accurately identify the incidence of antidepressant treatment-emergent sexual dysfunction (encompassing both the worsening of pre-existing problems and the development of new sexual difficulties in previously untroubled patients) (Montejo et al., 2018). However, studies of the prevalence of sexual dysfunction in patients who were prescribed either a selective serotonin reuptake inhibitor (SSRI) or serotonin-noradrenaline reuptake inhibitor (SNRI) indicated that between 27 and 65% of female patients and 26 and 57% of male patients experienced either a worsening of pre-existing difficulties or the emergence of new sexual difficulties in the early weeks of treatment (Williams et al., 20016; Williams et al., 2010).

A meta-analysis (of studies with different designs, n=14) found that treatment emergent sexual dysfunction was not more common than with placebo for the antidepressants agomelatine, amineptine, bupropion, moclobemide, mirtazapine or nefazodone: by contrast, other antidepressants had significantly more negative impact than placebo, affecting all phases of sexual function. The study found sexual dysfunction was associated with the following antidepressants, in decreasing order of impact: sertraline, venlafaxine, citalopram, paroxetine, fluoxetine, imipramine, phenelzine, duloxetine, escitalopram, and fluvoxamine, with sexual dysfunction rates ranging from 25.8% to 80.3% (Serretti et al., 2009). A more recent meta-analysis (n= 58 RCT and 5 observational studies) found relative disadvantages for paroxetine and venlafaxine, and relative advantages for bupropion, but there were only minor differences between antidepressants (Reichenpfader et al., 2014).

A systematic review found that the alpha-2, 5-HT2C receptors antagonist mirtazapine is less likely to cause sexual side effects than other antidepressants (Benelli et al., 2004). The predominantly noradrenergic-dopaminergic drug bupropion, has significantly fewer sexual side effect than the SSRI: escitalopram; fluoxetine; paroxetine or sertraline (Gartlehner et al., 2011). Agomelatine (with a mechanism of action involving 5-HT2C antagonism) appears to be associated with fewer sexual

side effects than SSRI antidepressants (Montejo et al., 2015, Montejo et al., 2010). The 5-HT1A partial agonist vilazodone appears no different from placebo in the improvement of sexual function during acute treatment of patients with major depressive episodes (Citrome et al., 2012; Schwartz et al., 2011). The multi-modal serotonin modulator and stimulator vortioxetine also appears associated with fewer reported sexual side effects than comparator antidepressants (Baldwin et al., 2015).

Mood-stabilising anticonvulsants are often used in patients with mood disorders. Sexual dysfunctions were found to affect 35-55% of patients taking anticonvulsants (Kuba et al., 2006). Despite a paucity of published evidence, lithium has also been linked to sexual dysfunction. Lithium negatively impacts sexual desire, erectile function and sexual satisfaction (Elnazer et al., 2015; Fountoulakis et al., 2012). Approximately one-third of males and female patients receiving lithium experience sexual dysfunction (Mazza et al., 2011). This risk was not correlated with lithium levels in an investigation which found that combination treatment of lithium and benzodiazepines treatment was associated with increased risk of sexual dysfunction (Ghadirian et al., 1992).

Table 1.8 **Investigations of sexual dysfunction associated with antidepressants**

study	findings
Williams et al., 20016; Williams et al., 2010	SSRI and SNRI caused emergence or worsening of sexual dysfunction.
Baldwin et al., 2015	Vortioxetine is associated with less sexual side effects that other antidepressants.
Elnazer et al., 2015; Fountoulakis et al., 2012	Negative impacts on desire, erection and satisfaction with lithium.
Montejo et al., 2015; Montejo et al., 2010	Agomelatine has less sexual side effects.
Citrome et al., 2012, Schwartz et al., 2011	Vilazodone is no different than placebo in improving sexual function.
Reichenpfader et al., 2014	Relative disadvantages for paroxetine; venlafaxine, and relative advantages for bupropion.
Hutchinson et al., 2012	Dapoxetine improves premature ejaculation.
Gartlehner et al., 2011	Bupropion less sexual side effects that SSRIs.
Mazza et al., 2011	One third of patients on lithium has sexual difficulties.
Serretti et al., 2009	No difference between antidepressants agomelatine, amineptine, bupropion, moclobemide, mirtazapine, nefazodone) and placebo.
Giuliano et al., 2008	TCAs, clomipramine, SSRIs can improve premature ejaculation.
Benelli et al., 2004	Mirtazapine is less likely to cause sexual side effects than other antidepressants.
Fink et al., 2003	High dose of paroxetine improves psychogenic sexual dysfunction.

1.6.3 Management of sexual dysfunction in mood disorders

There is modest evidence from published studies which have investigated the effectiveness of psychological and pharmacological interventions for sexual dysfunction in mood disorders (Taylor et al., 2005).

Dose reduction of antidepressant medication is a common first line approach (Balon et al., 2008). Nevertheless, this carries a risk of symptom relapse and should only be considered after sufficient period of complete symptomatic remission. Regular interruptions of treatment (so called “drug holidays”) can sometimes be beneficial but sexual side effects often reappear after re-instatement

of treatment. This is also associated with a greater risk of symptomatic relapse and discontinuation symptoms during the 'holiday' (Rothschild et al., 1995).

Switching to a different antidepressant is another commonly adopted approach, despite the paucity of supporting evidence (Taylor et al., 2005). This might carry a risk of forgoing a more effective treatment or the risk of discontinuation syndrome.

Adjuvant treatments have little supporting evidence from placebo-controlled investigations. Some studies have found some benefits with bupropion, olanzapine (Baldwin et al., 2004), topical testosterone gel (Amiaz et al., 2011) and aripiprazole (Fava et al., 2011).

PDE-5 inhibitors were found to be efficacious (for both males and females) in resolving sexual dysfunction with antidepressants (Nurnberg et al., 2003; Segraves et al., 2007). A small study suggested that adjunctive aspirin (240 mg/day) may improve erectile dysfunction in patients undergoing lithium treatment (Saroukhani et al., 2013).

Other lifestyle approaches were found beneficial in improving sexual function in patients taking antidepressants, such as regular exercise (Lorenz et al., 2014). Overall, no psychological or pharmacological approach can be considered 'ideal' (Clayton et al., 2006, Baldwin et al., 2013).

1.7 Neuro-inflammation and anxiety disorders

1.7.1 Background

Cytokines are a group of proteins involved in immune recognition, cell proliferation and cell differentiation. Cytokines are produced transiently and act in an autocrine/paracrine way. Each cytokine interacts with particular affinity to specific receptors. Activation of CD4+ subsets initiates distinct patterns of cytokine responses. Type 1 T helper cells (Th1) secrete IL-2 and IFN-γ; type 2 T helper cells (Th2) secretes IL-4, IL-5, IL-6, IL-10 and IL-13; and both Th1 and Th2 secrete TNF-α and granulocyte-macrophage colony-stimulating factor (GM-CSF). Antigen-presenting cells (APC) such as macrophages and dendritic cells secrete IL-12 and IL-10, which in turn influence the differentiation of Th1/Th2. The pattern of activation and availability of one cytokine or another in the early stage of inflammation leads to the preferential activation of immune cells and a distinct overall response and function (Figure 1.2).

Inflammation in the periphery is 'communicated' to the brain via humoral and neural pathways. Resident microglia are activated and in turn release pro-inflammatory cytokines which disrupt hippocampal neurogenesis. Peripheral cytokines activate the HPA axis, leading to increased circulating glucocorticoids which suppress neurogenesis. Reduced neurogenesis might underlie some of the neurobehavioral changes associated with chronic inflammatory conditions (Chesnokova et al., 2016) (Figure 1.3).

Experimental and clinical evidence shows that stress can produce a rise in circulating concentrations of pro-inflammatory cytokines. Chronic stress initiates changes in the HPA and the immune system that can act as a trigger for anxiety (Leonard et al., 2009). Cytokines can activate the HPA axis and the HPA axis modulates immune response via cortisol (Besedovsky et al., 2008).

Studies in healthy populations demonstrated a positive correlation between anxious state and inflammation markers, such as lower levels of circulating IL-1b (Zorrilla et al., 1994) and elevated levels of TNF-α, IL-6 and C-reactive protein (CRP) (Maes et al., 1998; Pitsavos et al., 2006; Arranz et al., 2007).

Chronic anxiety exerts a negative effect on immune function (Boscarino et al., 2004; Schneiderman et al., 2005; Zhou et al., 2005; Godbout et al., 2006). Anxiety is also reported to be related to defective immune response to some vaccines, such as hepatitis B virus (Jabaaij et al., 1996), rubella virus (Morag et al., 1999), meningitis virus (Burns et al., 2002), influenza virus (Vedhara et al., 1999; Vedhara et al., 2002; Miller et al., 2004) and pneumococcal bacteria (Glaser et al., 2000).

IL-1β, IL6, IL8, IP-10, MCP-1 and monocytes were found to be significantly higher in the patients with affective, anxiety, adjustment, psychotic, OCD, Tic or Tourette Disorders (n=77), than in controls (n=34). Results showed that patients had a significant correlation between stress measured by the Stressful Life Events Scales (SALES-C and SALES-P) and some inflammatory markers. SALES-C was correlated positively with IL-1β, IL-8, MCP-1, and SLES-P was correlated positively with IL-1β and monocytes absolute and relative counts (Gariup et al., 2015).

Figure 1.2 **Cytokine signalling.** Immune regulation via humoral and cellular interactions

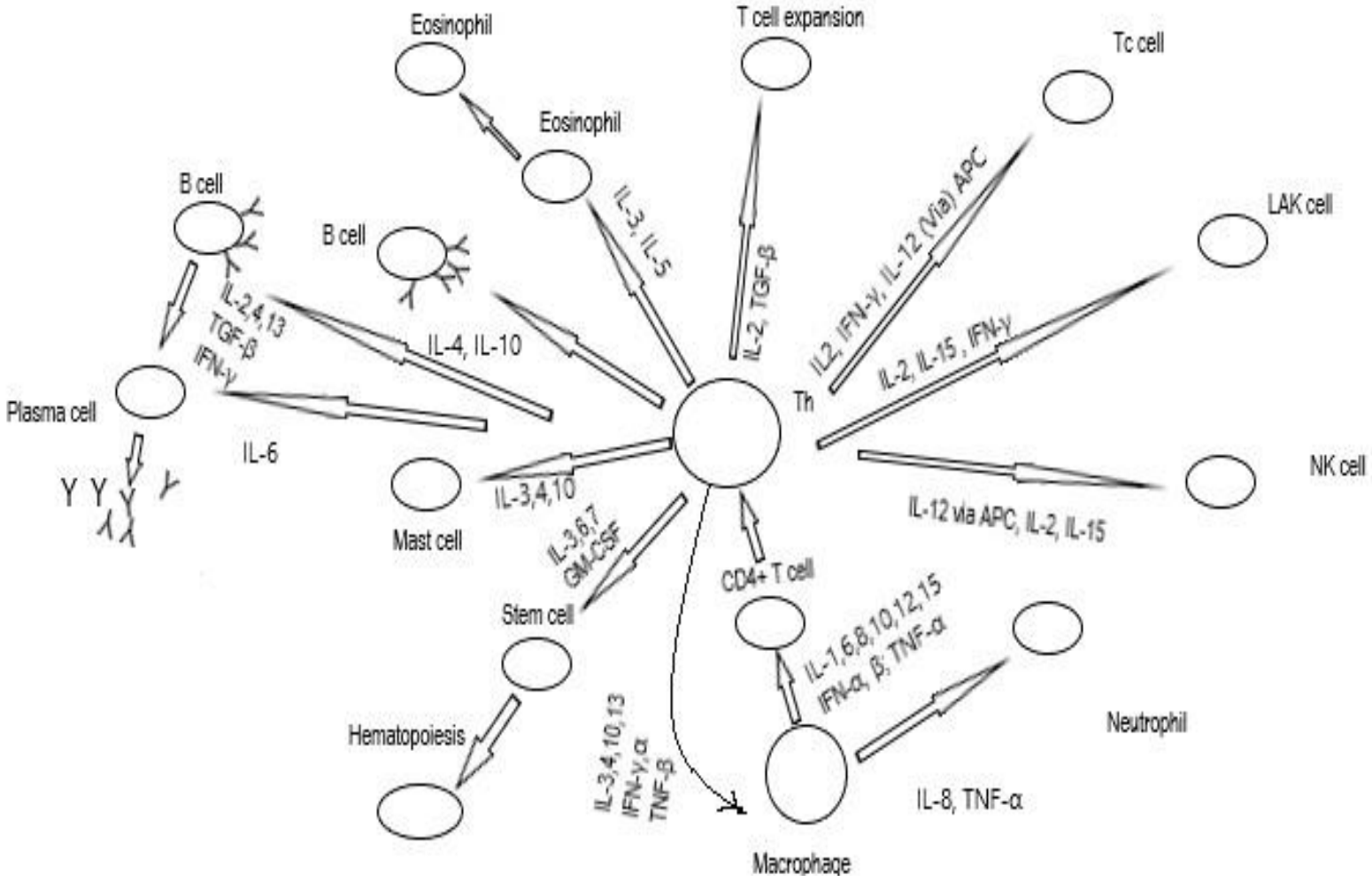
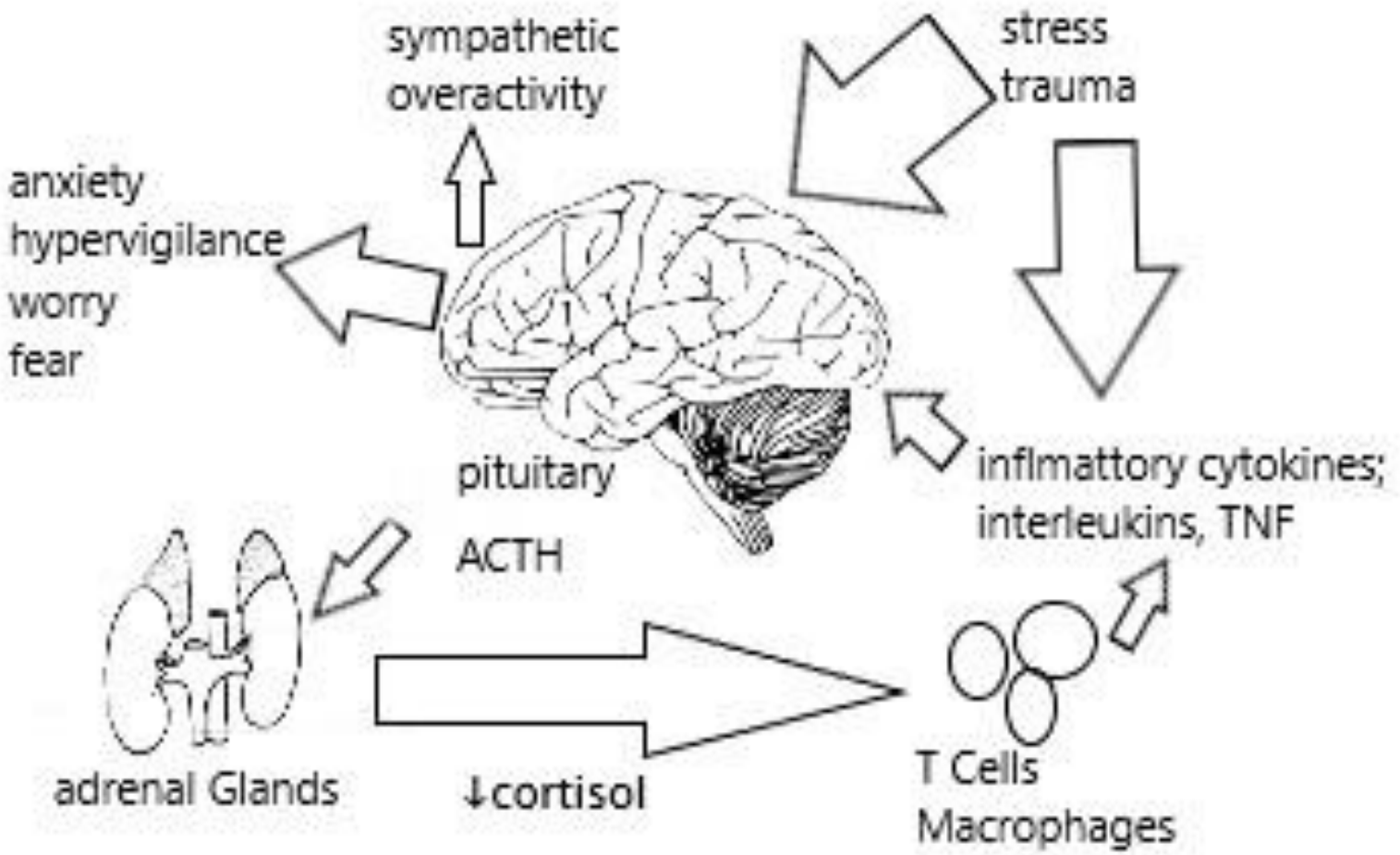


Figure 1.3 **Neuro-endocrine interactions.** Effects of stress on nervous, endocrine and immune systems.



1.7.2 Method for the Literature Review

I searched all titles listed in the electronic database MEDLINE via Pub Med and Embase up to December 2017 for all anxiety disorders, excluding obsessive-compulsive disorder (OCD) and post-traumatic stress disorder (PTSD), being mindful of changes in the categorization of the latter two conditions within DSM-5 (American Psychiatric Association 2013); however, papers which examined neuroinflammation in studies in which OCD or PTSD were co-morbid with an anxiety disorder were included.

The terms cytokine and inflammation were used, combined with each disorder to compile separate lists for each condition. For generalised anxiety disorder (GAD) I included the terms generalised/generalized anxiety and GAD; for phobic disorders, I used the terms phobia, social phobia, simple phobia and specific phobia. A combined list was generated and duplications were eliminated. All letters, and papers that were not available in English, were eliminated.

The search terms were as follows: agoraphobia (with or without a history of panic disorder) with cytokine, inflammation; generalized anxiety disorder or GAD with cytokine, inflammation; panic disorder with cytokine, inflammation; phobic disorders, phobia, social phobia, simple phobia, specific phobia, with cytokine, inflammation. As there were only few studies in this field, I expanded the search by using the term 'anxiety' with cytokine, inflammation. I included studies that investigated inflammation with anxiety symptoms as well as those which investigated inflammation in diagnosed anxiety disorders.

1.7.3 Panic disorder and Agoraphobia

Some studies investigated the interaction between inflammatory markers and panic disorder (Table 1.9).

Earlier studies found alterations in circulating levels of IL-1 (Hoge et al., 2009, Brambilla et al., 1994) and IL-2 (Vieira et al., 2010, Rapaport et al., 1994) in panic disorder. Hoge et al. also reported

Increased IL-6 and TNF-α in panic disorder and GAD, and on follow up increased TNF-α with agoraphobia. Earlier studies of agoraphobia found evidence of CRP elevation (Copeland et al., 2012, Bankier et al., 2008).

A more recent study of patients with agoraphobia (n=124) found significantly higher follow-up levels of CRP and TNF-α, as well as lower levels of the cardio-protective marker adiponectin, than their non-agoraphobic controls: however, follow-up levels of IL-1β and IL-6 did not significantly differ between the two groups (Wagner et al., 2015).

Another study investigated CRP, IL-6 and TNF-α in patients with current (n=1273) or remitted (n=459) anxiety disorders (panic disorder and/or agoraphobia, 65.4%, social phobia 51.1%, generalized anxiety disorder 35.7%). The study found that anxiety severity (measured by Beck anxiety inventory) and duration did not correlate with markers of inflammation. Pearson's correlations between inflammatory markers were modest (CRP–IL-6: r=0.31; CRP–TNF-α: r=0.13; IL-6–TNF-α.) The study found a significant sex X anxiety disorder interaction for CRP but not for IL-6. Men with current anxiety disorders had higher levels of CRP when compared with controls. In women, anxiety disorders were not significantly associated with CRP. Higher levels of CRP were found in antidepressant-treated participants in patients with current anxiety disorders. A later age of anxiety disorder onset was associated with elevated CRP levels, even after adjustment for antidepressant use. After adjustments, there were no associations between anxiety disorders and any inflammatory marker. Depression Co-morbidity status, did not differentiate anxious participants with elevated inflammation. Participants with social phobia had lower levels of CRP and IL-6, when compared with participants with other types of anxiety disorders. The association between social phobia and IL-6 appeared to be specific for women, but not men (Vogelzangs et al., 2013).

A recent study investigated IL-6, TNF-α, and high sensitivity C-reactive protein (hsCRP); in patients with GAD (n=74), social phobia (n=384), panic disorder (n=78) and agoraphobia (n=116). Baseline and follow up data were collected for patients with current or remitted disorders (mean follow up

period; 5.5 years). At baseline, all current disorders were found to be associated with a steeper increase of hsCRP levels over the follow-up period. However, the study found no significant associations between remitted anxiety disorders and inflammatory markers. After further adjustment of confounders and depression, current anxiety disorders continued to be significantly associated with hsCRP levels. Current agoraphobia was associated with a steeper increase of hsCRP levels and remitted agoraphobia was newly associated with a steeper increase of TNF-α levels over the follow-up period in the fully adjusted model. Baseline levels were not predictive of any lifetime anxiety disorder at follow-up (Glaus et al., 2017).

Experimental inhalation of 35% CO2 led to significant higher levels of anxiety in patients with panic disorder (n=18) when compared to healthy controls (n=18). However, this escalation of anxiety was not correlated with any change in cytokine levels. Baseline cytokine levels were comparable in both groups (Van Duinen et al., 2008). By contrast, reduced levels of anxiety with CBT and the anxiolytic ethyl loflazepate were associated with decreased cell-mediated immunity and increased IL-2 in panic disorder (Koh et al., 2004).

Table 1.9 **Investigations of inflammatory markers in panic disorder**

study	findings
Brambilla et al., 1994; Hoge et al., 2009	Alterations in circulating levels of IL-1 in panic disorder
Koh et al., 2004	CBT and ethyl loflazepate are associated with reduced cell-mediated immunity and increased IL-2
Van Duinen et al., 2008	CO2 35% has not effect on inflammatory markers.
Wagner et a. 2015	Elevated CRP, TNF- α. No difference in IL1, IL-6.
Bankier et al., 2008, Copeland et al., 2012	Increase CRP over time in agoraphobia.
Vogelzangs et al., 2013	Elevated inflammation is present in men with current anxiety disorders. Immune dysregulation is especially found in persons with a late-onset anxiety disorder, suggesting the existence of a specific late-onset anxiety subtype with a distinct aetiology, which could possibly benefit from alternative treatments.
Glaus et al., 2017	Increased hsCRP in current but not remitted disorders (PD, GAD, Social phobia and agoraphobia). Agoraphobia has steeper hsCRP and elevation TNF-α.
Rapaport et al., 1994; Vieira et al., 2010	Increased IL-2 in panic disorder.

1.7.4 Generalised anxiety disorder (GAD)

Several studies have assessed inflammatory markers in patients with generalised anxiety disorder (Table 1.10). Despite different methodologies, studies have reported increased CRP (Wagner et al., 2015; Copeland et al., 2012; Bankier et al., 2008), increased IL-6 (Hoge et al., 2009), decreased IL-2 (Vieira et al., 2010; Koh et al., 2004; Rapaport et al., 1994) and decreased TNF-α (Hoge et al., 2009). By contrast, Copeland et al., found that adjusting for health and environmental factors minimised the correlation between GAD and CRP, and proposed that the effect of GAD (n=146) on CRP levels was explained by the effect of GAD on health-related factors such as BMI and medication use (Copeland et al., 2012).

Examining the T cell profile - following in vitro activation in cultures - and cytokine profile in GAD (n=20) when compared with controls (n=20), found that Th1 and Th2 deficiencies were associated

with dominant Th17 phenotype, which was enhanced by substance P and T cell functional dysregulation, decreased IL-2 and increased TNF-α (Vieira et al., 2010).

More studies have investigated symptoms of generalised anxiety in non-clinical samples and anxiety symptoms across different diagnoses. For example, men reporting anxiety symptoms had elevated levels of CRP compared to those who did not report symptoms of anxiety (Liukkonen et al., 2011; Pitsavos et al., 2006).

CRP, TNF-α and soluble e-selectin were found to have significant moderating effects on the development of anxiety symptoms (measured by Generalised Anxiety Disorder – 7 scale; GAD–7) and storage lower urinary tract symptoms in otherwise healthy men (n=69) (Martin et al., 2015).

A large cohort study (n=2419; 1599 males, 820 females) involving non-clinical participants with symptoms of anxiety found that participants who had repeated low IL-6 were more likely to be symptom-free at follow-up, when compared with those with repeated high IL-6 levels (Virtanen et al., 2015).

IL-8 level was found to negatively correlate with symptoms of anxiety in suicide attempters (n=206), when compared to Il-8 levels in healthy controls (n=578) (Janelidze et al., 2015). Suicide attempters (n=42), compared to healthy controls (n=42), were found to have significantly lower concentrations of the neurotrophins, BDNF and neurotrophin-3 (NT-3), and significantly higher concentrations of CRP and IL-6. There was a significant negative correlation between levels of neurotrophins and levels of CRP, IL-6. There was also a negative correlation between neutrophin levels and anxiety scores (measured by the Hospital Anxiety and Depression Scale (HADS)) (Priya et al., 2016).

An exploratory study which investigated anxiety symptoms in patients with depression and anxiety disorders (n=2861), found significant interactions between sex and Beck Anxiety Inventory (BAI) total scores. A significant association was detected between total BAI scores and CRP levels (in men only) whereas somatic anxiety symptoms were associated with CRP levels (in men only), IL-6, and TNF-α. Cognitive anxiety symptoms were associated with CRP (in men only). These associations

diminished after lifestyle differences were considered. Markers of unhealthy lifestyle explained the significant associations and no sex-interactions were found for IL-6 or TNF-α. Adjustments for lifestyle, demographic health regression analysis, and antidepressant use rendered the associations between Inventory of Depressive Symptomatology (IDS) scores non-significant for all three markers (Duivis et al., 2013).

An investigation of epidermal growth factor (EGF) in patients with anxiety and depressive symptoms (n=166), found that baseline levels of EFG, hsCRP were significantly correlated with HAD-A scores. EGF levels were significantly decreased after both mindfulness and CBT, and were associated with treatment response of anxiety symptoms. The results were independent of the use of tranquilizers and antidepressant treatment. Levels of IL-6, IL-8 and hsCRP were not significantly associated with treatment response (measured by HADS-A). These findings suggest that improvement in symptoms of anxiety after mindfulness and CBT is associated with changes in EGF levels, but not with inflammatory markers (Memon et al., 2017).

Another study investigated the relationship between anxiety symptoms and inflammatory makers in non-demented community-dwelling elderly participants aged 70-90 years (n=1037). The study assessed inflammatory markers at baseline and after 2-years. The study found no correlation when comparing the Goldberg Anxiety Scale (GAS) scores, against markers of inflammation: CRP, IL-1β, IL-6, IL-8, IL-10, IL-12, plasminogen activator inhibitor-1 (PAI-1), serum amyloid A, TNF-α, and vascular adhesion molecule-1 (Baune et al., 2012).

Ethnicity might be play a role in variation of the associations between cytokines and anxiety. For example, higher concentrations of CRP were found among 20 week pregnant African American women (n=119), and associated with a lower risk of anxiety symptoms. Low optimism in African American women was also associated with lower IL-6 levels, but these results were only marginally significant. CRP, anxiety, and optimism were not correlated among 20 week pregnant Caucasian women (n=315) (Catov et al., 2015).

Major natural disasters are thought to be linked to persistent anxiety symptoms in non-clinical samples. Elevated salivary MCP-1 was significantly associated with anxiety symptoms in hurricane survivors (n=19) (An et al., 2015).

Prolonged stress can lead to anxiety symptoms although the presentation might not cross the diagnostic threshold for GAD. Some studies have examined the effect of prolonged stress on inflammatory makers, and in trait-anxiety rather than state-anxiety.

A 50-year prospective longitudinal study revealed that participants who had been frequently bullied in childhood had increased levels of CRP at mid-life (n=200). The study found early life emotional stress to be associated with an increased risk for age-related disease in middle adulthood, independent of co-occurring childhood and adult risks (Takizawa et al., 2015).

Another study found a significant decrease in trait anxiety (measured by the Perceived Stress Scale) and significant decreases in IL-6 levels, following mindfulness-based stress reduction sessions in participants with a history of inter-personal trauma (n=50) (Gallegos et al., 2015).

Some studies investigated the effect of chronic illness on anxiety and inflammatory markers. One study found that Hamilton Anxiety Scale (HAMA) scores were positively correlated with levels of TNF-α, hsCRP and sIL-2R in the peripheral blood of patients with Parkinson's disease (n=62) (Wang et al., 2016). In patients with acute coronary syndrome (n=216), high levels of CRP predicted elevated anxiety symptoms (measured by HADS) six months later (Steptoe et al., 2013).

In patients with metastatic breast cancer receiving chemotherapy there was some correlation between IL-6 level and symptoms of anxiety (n=23), but to a more marked extent with symptoms of depression (n=22), measured by the HADS. After adjusting for cofounding factors, tumour progression, symptoms of anxiety and IL-6 levels were independently associated with clinical depression. Anxiety symptoms were linked to tumor progression, symptoms of depression and age, but not to IL-6. These findings suggest that (unlike depression) anxiety is not associated with increased IL-6 levels, but shows a reciprocal correlation with age (Jehn et al., 2012).

In a cross-sectional sample of patients with obesity (n=100); BAI scores, but not Beck Depression Inventory-II scores, were significantly correlated with CRP levels. Results showed that BMI was also highly correlated with CRP. In multivariate models, the relation between anxiety and CRP remained significant, independent of BMI, age, and sex (Pierce et al., 2017).

Treatment of peripheral inflammation associated with chronic inflammatory illnesses did not seem to impact baseline anxiety scores. Studies found no change in anxiety scores (HADS) with TNF-α inhibitor therapy in rheumatoid arthritis involving etanercept (50 mg 1/week) plus methotrexate (Kekow et al., 2010; Machado et al., 2014). Similar results were found with etanercept (50 mg 1/week) when treating patients with ankylosing spondylitis (Packham 2012). Inversely another study found Improvement of anxiety scores (HADS) in patients with ankylosing spondylitis after treatment with TNF-α inhibitor therapy etanercept *vs*. sulphasalazine (Van der Heijde et al., 2012).

Some studies have investigated the effect of genetic polymorphism on the interaction between anxiety and inflammatory markers. A study in cancer patients (n=167) and their family caregivers (n=85) which examined trait versus state anxiety using the Spielberger State-Trait Anxiety Inventory (STAI-S; STAI-T, respectively) found that variations in IL-1 β, IL1 receptor 2 (IL1R2), and nuclear factor kappa beta 2 (NFKB2) genes, were all associated with trait anxiety, and variations in IL1R2, and TNF- α were associated with state anxiety (Miaskowski et al., 2015). Polymorphisms in TNF-α (rs1799964, rs3093662) were associated with higher anxiety (measured by SATI-S) after surgical treatment of women with breast cancer (n=398) (Miaskowski et al., 2016). Another study which examined anxiety symptoms in male subjects with chronic heart diseases (with (n=78) or without comorbid depression (n=91)) when compared with healthy subjects (n= 127) found no differences between neuroticism and anxiety scores in patients with different IL-4 -589 C/T, IL-6 -174 G/C, TNF-α -308 G/A, CRP -717A/G genotypes (Golimbet et al., 2017).

A study of Caucasian students (n=549) found that in women (but not men) possession of an IL18 haplotype (comprising both risk-related alleles) predicted increased symptoms of depression and anxiety (measured by Mood and Anxiety Symptoms Questionnaire: MASQ). This haplotype led to

increased threat-related left centromedial amygdala reactivity, relative to other haplotype groups. Path analyses revealed a significant indirect effect of IL18 risk haplotype on symptoms of depression and anxiety, through increased threat-related amygdala reactivity. These results suggest that a common functional IL18 haplotype is associated with heightened pro-inflammatory responses confers some susceptibility to stress-related depression and anxiety, possibly through effects on threat-related amygdala function, though only in women (Swartz et al., 2017).

Some studies have investigated the interaction between experimental anxiety paradigm and stimulation of inflammatory response. For example, a study in healthy subjects (n=40) found that a writing-based anxiety induction (but not a writing-based anger induction) increased mean levels of interferon-γ (IFN-γ) and IL-1β, but not IL-6 in oral mucous. Self-reported state anxiety predicted elevated levels of pro-inflammatory cytokines, but self-reported state anger did not. These findings suggest that negative emotions may differentially cause inflammatory activity (Moons et al., 2015).

A relatively large experimental study, has examined the expression of cytokines in response to *ex vivo* stimulation of blood by lipopolysaccharide (LPS) to study the innate production capacity of cytokines in symptoms of depression and anxiety (for remitted and symptomatic candidates) and possible correlation with anxiety/depression subscales across different disorders. The study compared responses in patients with a current depressive disorder (n=130) (major depressive disorder, dysthymia), pure anxiety disorder (n=219) (social phobia, generalised anxiety disorder, panic disorder, agoraphobia), mixed symptoms/comorbid disorders (n=242), participants with a history of remitted anxiety/depression symptoms (n=357), and participants without any history of anxiety or depressive symptoms (n=297). After adjustment for current smoking, alcohol intake, BMI and number of chronic diseases, IL-8 levels were still significantly associated with both remitted and current depressive/anxiety symptoms. Basal inflammation index was associated with somatic but not cognitive anxiety symptoms (measured by BAI). After adjusting for covariates, the LPS-stimulated inflammation index was still significantly associated with somatic, as well as cognitive

anxiety symptoms. LPS-stimulated IL-6, IL-8, IL-10, IL-18, MCP-1, MMP2, and TNF-β, remained significantly associated with anxiety symptoms' severity (Vogelzangs et al., 2016).

Table 1.10 **Investigations of inflammatory markers in GAD**

study	findings
Koh et al., 2004, Rapaport et al., 1994	Decreased IL-2 in patients with GAD.
Bankier et al., 2008	Significant association between CRP and GAD – but not depression- in stable coronary heart disease patients. A different inflammatory responses may occur in these two conditions.
Hoge et al., 2009	Increased IL-6 and TNF- α in GAD.
Vieira et al., 2010	In GAD: Th1 and Th2 deficiencies were associated with dominant Th17 phenotype, which was enhanced by substance P, decreased 1IL-2 and TNF-α in following in vitro activation
Copeland et al., 2012	Elevated CRP with GAD, less association with CRP elevation after adjustment for health and environmental factors.
Wagner et al., 2015	Increased CRP in GAD.
Pitsavos et al.,, 2006, Liukkonen et al., 2011	Elevated CRP associated with anxiety symptoms.
Zorrilla et al., 1994	Lower IL-1b levels with anxious state.
Maes et al., 1998, Pitsavos et al., 2006, Arranz et al., 2007	Elevated TNF- α, IL-6 and CRP with anxious state.
Baune et al., 2012	No relationship between anxiety symptoms and CRP, IL-1β, IL-6, IL-8, IL-10, IL-12, plasminogen activator inhibitor-1 (PAI-1), serum amyloid A, TNF-α, and vascular adhesion molecule-1.
Duivis et al., 2013	Somatic symptoms were associated with higher levels of CRP, IL-6 and TNF-α, whereas cognitive anxiety symptoms were associated with CRP.
Virtanen et al., 2015	Low IL-6 predicted symptoms resolution in non-clinical sample.
Janelidze et al., 2015	IL-8 level was correlated negatively with symptoms of anxiety.
An et al., 2015	Salivary level of MCP-1 is significantly associated with elevated anxiety symptoms in hurricane survivors
Catov et al., 2015	High CRP associated with lower risk of anxiety symptoms

Priya et al., 2016	Significant negative correlation bwteen neurotrophins and CRP, IL-6, anxiety.
Martin et al., 2015	CRP, TNF-α and soluble e-selectin were found to have significant moderating effects on the development of anxiety symptoms.
Memon et al., 2017	Elevated baseline EGF, hsCRP associated with anxiety symptoms. Declined EGF level with treatment response.
Gariup et al., 2015	Elevated IL-1β, IL6, IL8, IP-10, MCP-1 in symptoms of affective, anxiety, and OCD
Takizawa et al., 2015	Elevated CRP in adults with history of childhood bullying.
Gallegos et al., 2015	History of trauma is associated with Increased trait anxiety and with increased IL-6
Kekow et al., 2010 Machado et al., 2014 Packham et al., 2012	No change in anxiety scores (HADS) in tumor necrosis factor-α inhibitor therapy in rheumatoid arthritis.
Van der Heijde et al., 2012	Improved anxiety with TNF-α inhibitors in patients with ankylosing spondylitis.
Jehn et al., 2012	IL-6 not correlated with anxiety in cancer patients receiving chemotherapy.
Steptoe et al., 2013	Elevated CRP predicted elevated anxiety symptoms in acute coronary syndrome.
Wang et al., 2016	Hamilton Anxiety Scale (HAMA) scores were positively correlated with the levels of TNF- α, hsCRP and sIL-2R in the peripheral blood of Parkinson's disease patients.
Pierce et al., 2017	BAI scores correlated with elevated CRP in obesity.
Moons et al., 2015	Writing-based anger induction, increased mean levels IFN- γ and IL-1β.
Vogelzangs et al., 2016	Cytokine production capacity is positively associated with severity of anxiety symptoms, even while taking lifestyle and health factors into account. Elevated IL-8 production capacity in both previously and currently anxious persons might indicate a genetic vulnerability for these disorders
Miaskowski et al., 2016	TNF- α polymorphism (rs1799964, rs3093662) is associated with higher anxiety.
Miaskowski et al., 2015	Variations in IL1R2, NFKB2 genes is associated with trait anxiety.
Golimbet et al., 2017	No differences between neuroticism and anxiety scores in patients with different IL-4 -589 C/T, IL-6 -174 G/C, TNF-α -308 G/A, CRP -717A/G genotypes.
Swartz et al., 2017	Significant indirect effect of IL18 risk haplotype on symptoms of depression and anxiety through increased threat-related amygdala reactivity.

1.7.5 Other anxiety disorders

In other anxiety disorders inflammatory markers have been little researched (Table 1.11). One study found that patients with social phobia had lower levels of CRP and IL-6, compared to other anxiety disorders, this association being specific for women (Vogelzangs et al., 2013).

In OCD, studies have found higher levels of TNF-α and IL-6 in patients with depression comorbidity (Konuk et al., 2007), a decrease in TNF-α, and low levels of lipopolysaccharide-stimulated IL-6 (Fluitman et al., 2010, Denys et al., 2004). However, others have found no IL-6 differences in patients with OCD (Carpenter et al., 2002, Monteleone et al., 1998).

Table 1.11 **Investigations of inflammatory markers in other anxiety disorders**

study	findings
Vogelzangs et al., 2013	Among persons with a current anxiety disorder, those with social phobia had lower levels of CRP and IL-6. The association between social phobia and IL-6 appeared to be specific for women, but not men.
Monteleone et al., 1998; Carpenter et al., 2002	No IL-6 differences in patients with OCD.
Denys et al., 2004; Fluitman et al., 2010	Decreased TNF- α and low levels of lipopolysaccharide-stimulated IL-6 with OCD.
Konuk et al.,2007	Higher levels of TNF- α and IL-6 in patients with OCD with depression comorbidity.

1.7.6 Anti-inflammatory treatment and anxiety disorders

Pro-inflammatory cytokines can lead to the induction of cyclooxygenase enzymes (Harden et al., 2015). COX-1 and COX-2 catalyse the oxidation of arachidonic acid (AA) to produce prostaglandin G2 (PGG2) and the peroxidation, converting PGG2 to prostaglandin H2 (PGH2). These reactions produce reactive oxygen species (ROS), which can cause cell damage (Maes et al., 2012). Some studies investigate the potential therapeutic effect of interrupting this inflammatory process in mood disorders. A meta-analysis of clinical trials which used NSAIDs found positive results in patients with depression (n=1497) (Iyengar et al., 2013). A relatively recent, meta-analysis of studies which investigated the use of anti-inflammatory treatments in mood disorders found improvement

in depressive symptoms scores compared to placebo (6 trials, n=214) and improved manic symptoms in patients with bipolar affective disorder (3 trials, n=96). Qualitative analysis of the studies which investigated the use of celecoxib (11 RCTs) suggests that celecoxib might be associated with antidepressant effect in patients MDD without increased risk of side effects (Husain et al., 2017).

1.7.7 Summary

Most published studies have detected evidence of elevated CRP, TNF α, IL-1 and IL-2 in panic disorder. Nevertheless, some studies report evidence of low IL-2 levels in panic disorder.

Studies of GAD have found evidence of increased CRP, TNF- α and IL-6 and decreased IL-2: though after adjustment for environmental and health factors the correlation with elevated CRP levels is minimised.

Results from investigations of anxiety traits and generalised anxiety symptoms are inconsistent. Published evidence has shown that symptoms of anxiety are associated with decreased levels of CRB, IL-1β, TNF-α, IL-6, IL-8 and neurotrophins. Somatic symptoms were found to be associated with higher levels of CRP, IL-6 and TNF-α, whereas cognitive anxiety symptoms were associated with CRP. Low IL-6 levels also appeared to be a predictor for symptomatic resolution.

By contrast, a relatively large study (n=1037) found no correlation between anxiety symptoms and inflammatory markers, after adjusting for environmental and health factors.

Published studies have found consistent evidence of the elevation of inflammatory CRP, TNF-α, and anxiety symptoms in patients with chronic illnesses. Pharmacological modulation of the peripheral inflammatory process related to the physical illness is associated with improvement of anxiety symptoms in some but not all studies. This difference might be a manifestation of the involvement of different inflammatory cell signalling pathways in different illnesses and different pharmacodynamic properties of the drugs used.

Experimentally induced anxiety was associated with elevated levels of CRP, IL-1, TNF-α and IFN-γ. More recent studies provide evidence highlighting the importance of genetic variation coding for cytokines production and functions. Some variations were found to be associated with an increased risk of anxiety symptoms.

Only few studies have examined inflammatory markers in social phobia, specific phobia and comorbid anxiety disorders with OCD. Published studies found decreased CRP and IL-6 in patients with social phobia. Studies in OCD have found decreased levels of TNF- α and IL-6 whereas another found the opposite in OCD patients with co-morbid depression.

Further research work needs to include adjusting for environmental, health and genetic factors, to accurately ascertain the role of inflammation in anxiety disorders. Some studies found beneifical effect of treatment with NSAIDs in MIDD. It remains uncertain whether celecoxib can be beneficial in reducing anxiety symptoms in patients with anxiety disorders.

1.8 Hypotheses and aims

The preceding introduction emphasised the importance of neuro-inflammation and HPA modulation in anxiety disorders and the association between sexual dysfunction, anxiety disorders and treatment with SSRI.

1.8.1 Hypothesis 1

I hypothesise firstly: that there will be a correlation between sexual dysfunction psychometric scores and anxiety disorders.

H0: no statistically significant correlation between sexual dysfunction psychometrics scores and anxiety disorders psychometric scores.

H1: statistically significant correlation between sexual dysfunction psychometrics scores and anxiety disorders psychometric scores.

1.8.2 Hypothesis 2

I hypothesise secondly: that there will be a correlation between hair cortisol levels and anxiety disorders.

H0: no difference between cortisol levels in patients with symptoms of anxiety disorders and reference normal range lab values for hair cortisol.

H1: statistically significant difference between cortisol levels in patients with symptoms of anxiety disorders and reference normal range lab values of hair cortisol.

1.8.3 Hypothesis 3

I hypothesise thirdly: that there will be a correlation between inflammatory markers' levels and anxiety disorders.

H0: no statistically significant correlation between levels of inflammatory makers and anxiety disorders psychometric scores.

H1: statistically significant correlation between levels of inflammatory makers and anxiety disorders psychometric scores.

1.8.4 Hypothesis 4

I hypothesise fourthly: that augmentation with COX-2 inhibitor (celecoxib) will be associated with improvement of anxiety symptoms.

H0: no statistically significant difference/change in anxiety disorders psychometric scores after celecoxib treatment.

H1: statistically significant difference/change in anxiety disorders psychometric scores after celecoxib treatment.

Chapter 2 Systematic review of the utility of the Arizona Sexual Experiences Scale (ASEX)

2.1 Background

Sexual dysfunction and sexual dissatisfaction are not uncommon. Community surveys find that approximately 40% of women and 30% of men report troublesome sexual difficulties. Poor libido (in women) and premature ejaculation (in men), are the most commonly reported sexual difficulties (Laumann et al., 1999; Moreira et al., 2005; Moreira et al., 2008). Sexual difficulties are closely associated with mental health problems, particularly depressive symptoms, but recognition of sexual difficulties in primary care is low, possibly due to difficulties in describing sexual difficulties (Read et al., 1997; Nazareth et al., 2003; Cyranowski et al., 2004; Montejo et al., 2013). Sexual dysfunction increases the risk of depression by 130–200% (Atlantis et al., 2012; Clayton et al., 2014), and 67% of depressed men and 75% of depressed women report problems relating to sexual function (Thakurta et al., 2012). A positive outcome for patients with major depressive disorder is generally associated with a positive impact on sexual function, but antidepressant drugs are also associated with treatment-emergent sexual dysfunction in a significant proportion of patients (Clayton et al., 2007).

Assessment of sexual dysfunction can be challenging in practice, partly because differing assessment methods lead to variable results. For example, an investigation found the prevalence of sexual dysfunction in men to be 20% if reliant on spontaneous report by the patient, but 60% on direct enquiry (Segraves et al., 2014). Physicians may believe that affected patients would spontaneously report sexual difficulties (Clayton et al., 2014), but less than 20% patients who suffer from sexual dysfunction spontaneously report problems or seek help (Moreira et al., 2005): 'embarrassment' appears to be the main reason for not reporting (Nicolosi et al., 2006). The most reliable approach to assessing the prevalence and nature of sexual difficulties is a comprehensive, integrated interview that considers multiple dimensions of sexual life (individual, relational,

medical, erotic, sexual skill, and situational dimensions) (McCarthy et al., 2004), but this is time-consuming and often not feasible in practice.

Use of screening questionnaires may be valuable in busy clinical settings. Existing scales fall into different categories: general measures of sexual dysfunction, measures of sexual dysfunction in depressed populations, and female- and male- specific scales (Rizvi et al., 2011). A scale must demonstrate both reliability and validity in order to prove its acceptability for use. Tests of reliability estimate the ability of an instrument to generate consistent results under the same conditions, whereas tests of validity examine whether the instrument is actually measuring the concept in question (sexual function) and not a co-occurring construct (for example, anxiety) (Rizvi et al., 2011). Use of clinician-administered schedules may increase validity, but self-reporting scales have better reliability, possibly due to the sensitivity of the subject. Screening tools for sexual dysfunction with fewer items are more prone to false positive than false negatives, whereas questionnaires with more items have a better ability to examine specific domains of sexual function (Rizvi et al., 2011).

One of the more frequently used scales for assessing sexual functioning is the Arizona Sexual Experiences Scale (ASEX). This comprises five items, which quantify sex drive, arousal, vaginal lubrication/penile erection, ability to reach orgasm, and satisfaction from orgasm. It has well-documented reliability and validity, is concise, and easy to administer in clinical settings (McGahuey et al., 2000; Clayton et al., 2014; Baldwin et al., 2015; Khin et al., 2015; Lorenz et al., 2016; Francois et al., 2017). Possible total scores range from 5 to 30, higher scores indicating greater sexual dysfunction. ASEX designates ‘sexual dysfunction’, with a total score of 19 or more; any single item with a score of 5 or more; or any three items with a score of 4 or more (McGahuey et al., 2000). The ASEX has been used in many cross-sectional prevalence studies and in randomised controlled trials of pharmacological treatment, but there is some uncertainty about its utility in other clinical settings.

2.2 Method

I therefore conducted a computerised literature search of MEDLINE via Pub Med and EMBASE for all articles relating to use of the ASEX, published up to March 2018. The terms employed were Arizona Sexual Experiences Scale; Arizona Sexual Experience Questionnaire; ASEX. A combined list was generated and duplications were eliminated. All letters, and papers that were not available in English were eliminated.

I categorised the final dataset of publications into studies concerned with ascertaining the psychometric properties of the scale; epidemiological studies concerned with establishing the prevalence of sexual difficulties in particular populations; studies where the scale was used to determine the incidence of treatment-emergent sexual dysfunction during antidepressant drug or antipsychotic drug treatment; studies in which the scale was used to examine primary sexual dysfunction; and other studies. The studies I included in this review adopted different methodologies and parallel outcome measures. It was not possible to encompass issues such as: appropriateness of study design; risk of bias; choice of outcome measures; statistical issues; quality of reporting and generalisability.

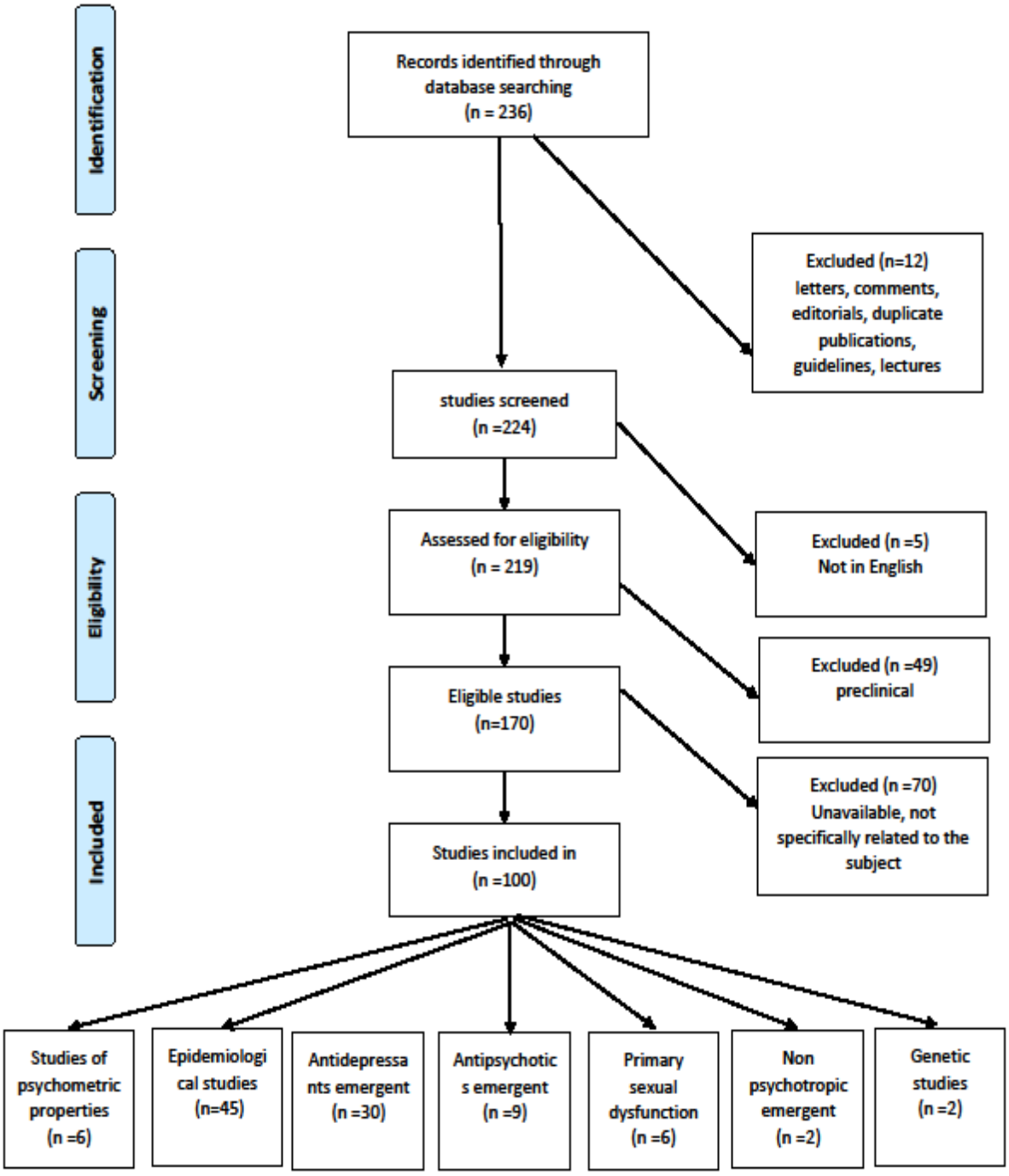
2.3 Results

I identified 236 records: after excluding letters and duplicates, 224 were screened. Five were excluded as they were not in English, the remaining 219 were assessed for eligibility. From this group, 49 pre-clinical studies were excluded, and another 70 were excluded as they were not obtainable or specifically related to the subject. The final dataset therefore includes 100 papers (Figure 2.1).

The overall findings are that the ASEX appears to have good reliability, validity, internal consistency, test-retest reliability, sensitivity, specificity, and positive and negative predictive values, across a variety of populations. It appears useful in a range of clinical situations including patients with primary sexual dysfunction (n=7), specific psychiatric disorders (n=9), specific physical illnesses

(n=44) and treatment-emergent sexual dysfunction (n=42). Higher ASEX scores in populations with treatment-emergent dysfunction appear to be associated with the 5-HT2A receptor -1438 AA genotype, and with the CYP2D6 poor metabolic status phenotype (n=2) in female patients. The specific features in each category are considered in more detail below.

Figure 2.1 **ASEX literature review**


Identification
Screening
Eligibility
Included
Records identified through database searching (n = 236)
Excluded (n=12) letters, comments, editorials, duplicate publications, guidelines, lectures
studies screened (n =224)
Excluded (n =5) Not in English
Assessed for eligibility (n = 219)
Excluded (n =49) preclinical
Eligible studies (n=170)
Excluded (n =70) Unavailable, not specifically related to the subject
Studies included in (n =100)
Studies of psychometric properties (n =6)
Epidemiological studies (n=45)
Antidepressants emergent (n =30)
Antipsychotics emergent (n =9)
Primary sexual dysfunction (n =6)
Non psychotropic emergent (n =2)
Genetic studies (n =2)

2.3.1 Studies of psychometric properties

The search identified six studies which examined psychometric properties of the ASEX (McGahuey et al., 2000; Soykan et al., 2004; Byerly et al., 2006; de Boer et al., 2013; Nakhli et al., 2014; Jitkritsadakul et al., 2014) (see Table 2.1). In order to establish its psychometric characteristics, the ASEX authors administered it to 107 control subjects (hospital employees, staff, residents, and faculty members of the University of Arizona) and 58 psychiatric patients. Female and male patients demonstrated higher scores on the ASEX (mean=20.3±4.8 and 17.2 ±5.4, respectively) than did the controls (mean=13.5±3.9 and 10.9±2.6, respectively): in both cases, women scored higher than men. Cronbach's alpha analysis indicated that the ASEX had excellent internal consistency and scale reliability (α=0.9055) and strong test–retest reliability (for patients, $r=0.801$, $p<0.01$; for controls, $r=0.892$, $p<0.01$). Analyses of variance (ANOVAs) revealed significant differences in total ASEX scores between patients and controls (for males F 18.1, $p<0.000$; for females $F=31.71$, $p<0.000$) and between females and males (for patients $F=5.22$, $p=0.026$; for controls $F=5.05$, $p=0.031$). Further ANOVAs revealed significant gender differences for patients on the ASEX items for drive and arousal ($F=4.69$, $p=0.035$ and $F=5.88$, $p=0.019$, respectively), with a trend on the item for ability to reach orgasm ($F=3.72$, $p=0.059$). For controls, there were trends for gender differences on the items for drive, arousal, and ability to reach orgasm ($F=3.57$, $p=0.067$; $F=3.51$, $p=0.069$; and $F=3.83$, $p=0.058$, respectively) (McGahuey et al., 2000).

In further exploration by the authors, items on the ASEX correlated with factors and related items on the Brief Index of Sexual Functioning (BISF) (Taylor et al., 1994, Reynolds et al., 1988), but not with depression score, on either the Beck Depression Inventory (BDI) (Beck et al., 1996), or the Hamilton Depression Rating Scale (HDRS) (Hamilton 1960), The accuracy of patient self-ratings of sexual dysfunction was verified with a four-item Gold Standard Clinician Rating scale (GSR), which was developed by the ASEX authors and administered during a semi structured brief interview at each time interval. Gold Standard Clinician Rating scale (GSR) scores correlated 100% with the patient's belief of the presence of sexual dysfunction.

The sensitivity and specificity of the ASEX at identification of sexual dysfunction were 82% and 90%, respectively, the positive predictive value was 88% and negative predictive value was 85%. Receiver Operating Characteristic (ROC) analysis revealed an area under the curve (AUC) value of 0.929±0.029. ROC analysis of the BISF revealed an AUC value of 0.786±0.050. The independent area test revealed a significant difference between the two ROC curves (F=2.4752, p=0.0133) (McGahuey et al., 2000).

In an investigation involving administration of the Turkish-language version of the ASEX to patients with end-stage renal failure (n=43), it showed good internal consistency (Cronbach's alpha's 0.89 and 0.90) and test-retest reliability (r=0.88, P<0.001). The convergent validity of the ASEX was measured by means of the correlation with the psychiatrists' assessment for the presence of sexual dysfunction (r=0.53, P<0.001). The results of ROC analysis for criterion validity revealed that ASEX scores could discriminate well [(0.85+/-0.06) (95% confidence interval, 0.73-0.90)], P<0.001) between patients with 'no sexual dysfunction' (n=26) and with 'sexual dysfunction' (n=17). The total ASEX score of $\leq$11 was found to be the best cut-off point (sensitivity=100%, specificity=52%) for screening in this group of patients (Soykan et al., 2004).

A study involving administration of the ASEX to patients with either schizophrenia or schizoaffective disorder (n=247), found a high degree of agreement between a one-item specific screening question for sexual dysfunction and the ASEX. Overall, the sensitivity (85%), specificity (63.7%), and positive (83%) and negative (67.1%) predictive values for the specific one-item screening question were deemed satisfactory by the authors. By contrast a single-item general side effect question performed rather poorly (sensitivity 11.3%; specificity 92.5%; positive predictive value 76%; negative predictive value 33%) (Byerly et al., 2006).

Another study which administered the ASEX in patients with schizophrenia (n=30) found that the correlation coefficients for calculating convergent validity were modest to good when comparing the Abbreviated Female Sexual Dysfunction Questionnaire (ASFQ) (Williams et al., 2010), with the

corresponding items on the Subject's Response to Antipsychotics (SRA) questionnaire (Wolters et al., 2006) and with the ASEX (de Boer et al., 2013).

A study which included administration of an Arabic-language version to patients with schizophrenia (n=100), found that the internal consistency between the five ASEX Items was good (α=0.82), and the test-retest reliability was satisfactory (r=0.92, p<10(-3)) (Nakhli et al., 2014). Finally, in an investigation involving administration of the Thai-language version in patients with Parkinson's disease (n=40), a cut-off point of ≥16 points was found to represent a good threshold for sexual dysfunction (sensitivity 96.2%, specificity 92.9%). Reliability was documented with the Cronbach's alpha of all items at baseline and at two-month follow-up, with values of 0.948 and 0.962 respectively. The Pearson's correlation showed highly significant test-retest reliability for individual items [Item 1 (r =0.959, p <0.001), Item 2 (r= 0.914, p <0.001), Item 3 (r =0.944, p <0.001), Item 4 (r =0.992, p <0.001), Item 5 (r=0.930, p<0.001), and for ASEX total score (r=0.883, p<0.001)] (Jitkritsadakul et al., 2014).

Table 2.1 **Studies of ASEX psychometric properties**

Study	**Principal features**
McGahuey et al., 2000	Group: 58 patients with psychiatric diagnoses versus 107 controls. Internal consistency and scale reliability: excellent (α = 0.9055). Test–retest reliability: strong (for patients, r = 0.801, p < 0.01, for controls, r = 0.892, p < 0.01). Significant differences on total ASEX scores between patients and controls and between females and males. Sensitivity 82%, specificity 90%, positive predictive value 88%, negative predictive value 85%. Significant gender differences for patients on: drive and arousal (F = 4.69, p = .035 and F = 5.88, p = 0.019, respectively) and a trend on ability to reach orgasm.
Byerly et al., 2006	Group: 247 patients with schizophrenia or schizoaffective disorder. Sensitivity 85%, specificity 63.7%, PPV 83% and 67.1% for the specific single-item screening question were satisfactory. Single general side effect question performed poorly, sensitivity=11.3%, specificity=92.5%, positive predictive value=76%, negative predictive value=33%.
de Boer et al., 2013	Study group: 30 patients with schizophrenia. Convergent validity: correlation coefficients for calculating were modest to good.
Soykan et al., 2004	Group: 43 patients with end-stage renal failure. ASEX-Turkish version. Internal consistency: good (Cronbach's alpha's 0.89 (baseline) and 0.90 (follow up)). Test-retest reliability (r=0.88, P<0.001). ROC analysis for criterion validity: scores could discriminate well (0.85+/-0.06 (95% confidence interval, 0.73-0.90), P<0.001).
Nakhli et al., 2014	Group: 100 patients with schizophrenia. ASEX-Arabic version. Good Internal consistency (Cronbach's alpha's =0.82). Test-retest reliability: satisfactory (r=0.92, p<10(-3)).
Jitkritsadakul et al., 2014	Group: 40 patients with Parkinson's disease (18 with comorbid depression) ASEX-Thai version. Sensitivity 96.2%, specificity 92.9%. Reliability: Cronbach's alpha (baseline and at a 2-month follow-up), 0.948 and 0.962. Test-retest reliability: highly significant correlation [Item 1 (r = 0.959, p < 0.001), Item 2 (r = 0.914, p < 0.001), Item 3 (r = 0.944, p < 0.001), Item 4 (r = 0.992, p < 0.001), Item 5 (r = 0.930, p < 0.001), and total ASEX-Thai score (r = 0.883, p < 0.001)].

2.3.2 Epidemiological studies

Many studies have employed the ASEX to ascertain the prevalence of comorbid sexual dysfunction in samples of patients with a range of psychiatric diagnoses (Table 2.2) or physical health problems (Table 2.3).

Substance use disorders. The ASEX has been utilised in patients with a range of alcohol and/or substance use disorders (Dişsiz et al., 2010; Venkatesh et al., 2014; Diehl et al., 2016; Gerra et al., 2016; Pendharkar et al., 2016). In the first such study, 89.9% of women with alcohol and substance dependence (n=126), were found to have ASEX-determined sexual dysfunction (Dişsiz et al., 2010). In a second investigation among treatment-seeking men with opioid dependence (n=100), the prevalence of ASEX-determined dysfunction was found to be 48%, and there was strong correspondence with reported dysfunction in at least one of the domains of the International Index of Erectile Dysfunction (IIEF) (Rosen et al., 1997) (92%), and at least one of the domains of the Sexual Functioning Questionnaire Short-Form (CSFQ-14) (90%) (Venkatesh et al., 2014).

A cross-sectional study in women with substance-dependence (n=213) utilised both the ASEX and non-standardised questions about sexual functioning, along with the Drug Abuse Screening Test (Skinner 1982), the Short Alcohol Dependence Data questionnaire (Davidson et al., 1986), and the Fagerström Test for Nicotine Dependence (Heatherton et al., 1991): there was a similar prevalence of sexual dysfunction using the two methods (Diehl et al., 2016).

Patients undergoing long-term methadone treatment (n=40), scored significantly higher than controls (n=40) on the ASEX, the Care and Abuse-Questionnaire (CECA-Q) (Bifulco et al., 2005) and the Symptoms Check List 90 (SCL-90) (Derogatis et al., 1977). ASEX scores were directly and significantly correlated with CECA-Q neglect score and SCL 90 psychiatric symptoms total score. Methadone dosages were not significantly correlated with sexual dysfunction scores, except for 'erectile dysfunction', for which an inverse association was seen. Plasma testosterone levels were significantly lower but prolactin levels significantly higher in cases than in controls: levels were significantly inversely correlated with ASEX scores, CECA-Q neglect scores and psychiatric symptom

at SCL 90 among methadone patients. Prolactin levels were directly and significantly correlated with sexual dysfunction scores, psychiatric symptoms at SCL 90 and CECA-Q neglect scores. Neither testosterone nor prolactin levels were correlated with methadone dosage (Gerra et al., 2016).

In a case-control study in patients with alcohol dependence (n=101), 58.4% of patients had ASEX-determined sexual dysfunction: the highest frequency of dysfunction according to individual items was for arousal (57.4%), followed by problems in desire (54.4%), erection (36.6%), satisfaction with orgasm (34.6%) and ability to reach orgasm (12.87%). Patients and controls (n=50), differed significantly in overall dyadic adjustment, in the domains of dyadic satisfaction and affective expression (Pendharkar et al., 2016).

Depressive and anxiety disorders. Few studies have utilised the ASEX scale to determine the prevalence of sexual dysfunction in depressed patients (Montejo et al., 2011; Dunlop et al 2015; Tekin et al., 2016; Williams et al., 2016). In an early investigation, the prevalence of ASEX-determined dysfunction in patients with major depressive disorder (n=514) was 73.4% (Montejo et al., 2011): ASEX scores were significantly associated with score on the Inventory of Depressive Symptomology, self-report version (IDS-SR) (Rush et al., 1996), but not correlated with the Quality of Marriage Index (QMI) (Norton 1983). An investigation in patients with social anxiety disorder (n=113, 30.1% with comorbid depression) found the proportion of ASEX-determined sexual dysfunction was 36.3% (36.3% of the sample reported childhood physical abuse, and 14.2% childhood sexual abuse) (Tekin et al., 2016). In a further investigation of ASEX scores in patients with depression at baseline and 2 months follow up (n=433), there were marked correlations between the Depression and Family Functioning Scale (DFFS) (Williams et al., 2016); the CGI-S (Zaider et al., 2003) ; the Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery et al., 1979); HAM-A (Hamilton 1959); Sheehan Disability Scale (SDS) (Leon et al., 1997); ASEX; Patient Health Questionnaire-9 (PHQ-9) (Kroenke et al., 2001) and Work Productivity and Activity Impairment Questionnaire (WPAI) (Reilly et al., 1993) Williams et al., 2016). A further investigation which used two models to further elucidate associations between symptoms and childhood sexual

abuse (CSA) found that depression severity and anxious arousal mediated the relationship between CSA and adult sexual function, and anxious arousal and sexual functioning mediated the association between CSA and depressive symptoms: when the models were combined, anxious arousal was the most important mediator of CSA on depression, which in turn mediated associations with adult sexual satisfaction and relationship quality (Dunlop et al., 2015).

Table 2.2 **ASEX assessed sexual dysfunction and psychiatric diagnoses**

Study	**Principal features**
Dişsiz et al., 2010	126 female patients with alcohol or substance use disorders Turkish language version Medication free Elevated ASEX-reported dysfunction rates in women with alcohol and substance misuse, compared to controls.
Montejo et al., 2011	514 patients with major depressive disorder Mixed sample (drug-naive, previous treatment, current treatment) ASEX-reported dysfunction in 73.4% of patients with major depression.
Venkatesh et al., 2014	100 opioid-dependent male patients, 50 healthy controls English language version Medication free ASEX-reported dysfunction in 48% of patients with opioid dependence.
Dunlop et al., 2015	808 patients with major depressive disorder English language version Mixed sample (drug-naive, previous treatment, current treatment) ASEX-reported dysfunction correlated with IDS-SR.
Gerra et al., 2016	40 opioid-dependent male patients, 40 healthy controls English language version Long-term methadone treatment Childhood adversity and comorbid psychiatric symptoms contribute to sexual dysfunction and hormonal changes in methadone using patients.
Diehl et al., 2016	213 opioid-dependent female patients Portuguese language version Undergoing inpatient treatment in addiction unit Similar prevalence of sexual dysfunction in women with substance misuse, using non-standardised questioning and ASEX.
Williams et al., 2016	478 patients with major depressive disorder English language version Mixed sample (drug-naive, previous treatment, current treatment) Positive correlations between DFFS and the CGI-S, MADRS, HAM-A, SDS, ASEX, PHQ-9, and WPAI scores.
Pendharkar et al., 2016	101 alcohol-dependent male patients English language version Medication free Sexual dysfunction prevalence of 58.4%
Tekin et al., 2016	113 patients with social anxiety disorder Turkish language version Mixed sample (drug-naive, previous treatment, current treatment) ASEX-reported dysfunction in 36.3%

Gastro-intestinal diagnoses and relevant interventions. Four investigations have included the ASEX in samples of patients with gastro-intestinal and related conditions (Soykan et al., 2005; Eugenio et al., 2012; Yakoot et al., 2012; Zhu et al., 2017) (Table 3). A study of patients with chronic hepatitis C (n=46), found a 35% overall prevalence ASEX-reported sexual dysfunction, the prevalence being higher in women (50%): the most frequent problems in men were in drive (25%), arousal (17%) and erection (17%); in women the most frequent problems were in drive (55%), arousal (50%), and reaching orgasm (59%). ASEX scores correlated significantly with age and education. After controlling for other variables, gamma glutamyl transpeptidase (GGT) levels predicted ASEX-scores (Soykan et al., 2005). Another study in patients with chronic hepatitis C (n=66), who received dietary supplements, found that ASEX scores were more significantly improved with administration of *Spirulina platensis* than with Silymarin (Yakoot et al., 2012). An investigation in women with irritable bowel syndrome (n=616), randomised to comprehensive self-management, found that those meeting ASEX criteria for sexual dysfunction were older, had higher lifetime depression and antidepressant use, more primary care visits, fewer mental healthcare visits, and greater sleep disturbance than those individuals without sexual dysfunction, but no significant group differences in gastrointestinal or somatic symptoms: when compared with 'usual care' treatment, comprehensive self-management improved sexual quality of life scores, with a weaker effect on ASEX scores (Eugenio et al., 2012). Finally, a prospective study found the mean total ASEX score to be 20.56 in patients undergoing ostomy surgery (n=75): significant differences in ASEX score were observed in sub-groups of age, gender, educational level, family relations, operation modes, stoma type, operation time, complications, supporters, self-care ability, and sexual life guidance. Multiple stepwise regression analysis indicated that family relations, operation modes, ostomy type, complications, and sexual life guidance all affected sexual experience (Zhu et al., 2017).

Renal diseases. The ASEX has been included in a series of investigations of patients with renal disease (Soykan et al., 2005; Ozdemir et al., 2007; Koca et al., 2012; Kurdoglu et al., 2012; Dikici et al., 2014; Hekmat et al., 2016). A point prevalence study in patients with end-stage renal disease (n=98) determined that 69.4% had ASEX-defined sexual dysfunction (Ozdemir et al., 2007). In a

longitudinal investigation among end stage renal disease patients who had undergone dialysis treatment for at least 12 months (n=43), ASEX-defined sexual dysfunction was found to be present in 47% at baseline and 42% at 6-month follow-up, and total and item-by-item ASEX scores did not change significantly during this period: in female patients, Hamilton Depression Rating Scale (Hamilton 1960) scores were significantly higher in patients with ASEX-reported sexual dysfunction, both at baseline assessment and at follow-up (Soykan et al., 2005). A study of female patients undergoing long-term haemodialysis (n=140) found significant correlations between total ASEX score, age and duration of haemodialysis, though no correlation between serum haemoglobin, parathyroid hormone, creatinine, iron, calcium, phosphorus, and urea reduction ratio and the ASEX score: there was also a significant difference in total ASEX score between cases and controls (Hekmat et al., 2016). Another investigation in haemodialysis patients (n=246) found higher ASEX in patients with comorbid restless legs syndrome (RLS) than those without RLS, and significant relationships between ASEX scores and demographic variables including educational achievements, occupation and marital status (Dikici et al., 2014). An investigation in female patients who underwent renal replacement therapy found that ASEX-determined sexual dysfunction rates were significantly higher in a haemodialysis group (n=39) compared to the peritoneal dialysis group (n=43) and the kidney transplant group (n=33), and sexual dysfunction rates were higher in kidney transplant and dialysis patients when compared with controls: multivariate analysis indicated that marital duration and haemodialysis were independent risk factors for sexual dysfunction in the renal replacement population (Koca et al., 2012). A further investigation found that total ASEX scores, ability to reach orgasm, and BDI scores were significantly higher among peritoneal-dialysis (n=22) and haemodialysis (n=25) patients than controls (n=30): peritoneal-dialysis patients with depressive symptoms were 24 times more likely to experience sexual dysfunction than those without depression, and serum FSH and LH levels were positively correlated with arousal and erection/lubrication scores in the depressed peritoneal-dialysis patients (Kurdoglu et al., 2012).

Dermatological conditions. The ASEX has been used to ascertain the point prevalence of sexual dysfunction in a range of dermatological conditions (Sukan et al., 2007; Mercan et al., 2008;

Kucukunal et al., 2013; Janse et al., 2017). An early investigation in female patients with vitiligo (n=50) or chronic urticaria (n=50) found that ASEX total scores were significantly higher than in controls (n=50): sexual drive and satisfaction item scores were significantly lower in both patient groups, female patients had more difficulties in reaching orgasm, and male patients reported less orgasm satisfaction (Sukan et al., 2007). A healthy-control study among patients with neurodermatitis (n=31) or psoriasis (n=24) found that neurodermatitis patients reported more sexual (ASEX-defined) and depressive symptoms (assessed with the BDI), than patients with psoriasis or controls (n=33) (Mercan et al., 2008). An investigation in patients with hidradenitis suppurativa (n=300) found that female sex and later age of onset were both associated with poor sexual function: poor quality of life was associated with anogenital involvement, early age of onset, and disease severity, whereas sexual health was positively associated with quality of life in female but not male patients (Janse et al., 2017). Finally, ASEX scores were significantly higher in male patients with genital warts (n=116) than controls (n=71), there being positive correlations between BDI and BAI scores with ASEX total and item scores (Kucukunal et al., 2013).

Malignancies. A series of investigations of sexual function have employed the ASEX to assess sexual function among groups of patients with various forms of malignancy (Mathias et al., 2006; Cleary et al., 2011; Yilmaz et al., 2015; Batıoğlu-Karaaltın et al., 2017; Surbeck et al., 2017). A descriptive, correlational study on women with reproductive system malignancies (cervical, ovarian, endometrial, and vulvar) (n=106), found higher ASEX scores 6 weeks post-diagnosis (Cleary et al., 2011). An investigation in patients with laryngeal carcinoma (n=74) found that ASEX scores in total or partial laryngectomy patients were not significantly different (13.98 ± 6.32 and 13.08 ± 4.96, respectively), though mean BDI scores were significantly higher in total laryngectomy patients (13.20 ± 10.41 versus 7.76 ± 8.14): BDI scores correlated with Rosenberg Self-Esteem Scale (RSES) (Rosenberg et al., 1965) scores, and ASEX scores correlated with age (Yilmaz et al., 2015). In a second investigation in patients with laryngeal carcinoma patients, 90.3% of total laryngectomy patients and 63.9% of partial laryngectomy patients had experienced negative effects on sexual function, and ASEX scores were correlated with average scores on the sexuality sub-unit (QL-35 59-

60) of the Cancer and Head and Neck module (Sherman et al., 2000), (Batıoğlu-Karaaltın et al., 2017). An investigation in patients who underwent surgical resection for diffuse low-grade glioma (n=32) found that ASEX-determined sexual dysfunction was present in 44% of patients (60% of women, 29% of men): 53% reported post-operative changes in sexual function (with deterioration in 88%, but improvement in 12%). Right-sided resections were associated with more difficulties in reaching orgasm than left-sided resections, temporal lobe resection was linked to lower sexual drive and sexual arousal in men than in women, and continued antiepileptic drug treatment in patients who underwent right-sided resection was associated with higher ASEX scores in men than women (Surbeck et al., 2017). An investigation of the effects of eight weeks of bupropion (150 mg per day) treatment on sexual function in breast cancer patients who had undergone chemotherapy but were currently receiving radiotherapy (n=20) found mean ASEX scores declined from 23.45 at baseline to 18.95 at endpoint (Mathias et al., 2006).

Non-malignant gynaecological or post-menopausal conditions. A number of studies have employed the ASEX to assess sexual function in patients with a range of conditions (Kovalevsky et al., 2008; Bachmann et al., 2010; Veras et al., 2011; Portman et al., 2014; Senturk et al., 2015; Pinkerton et al., 2016). An investigation in women with polycystic ovarian syndrome (n=88) found a mean ASEX score of 14.4 and an overall prevalence of sexual dysfunction of 13.3%: with negative correlations between the ASEX scores and the levels of total testosterone, luteinizing hormone and dehydroepiandrosterone sulfate (Veras et al., 2011). An investigation among postmenopausal women (n=229) found a mean ASEX score of 19.97, with a positive correlation to the mean total score on the Menopause Rating Scale (Hauser et al., 1994), (Senturk et al., 2015). In a randomised, double-blind, placebo-controlled study involving post-menopausal patients with symptoms of moderate or severe vulvar and/or vaginal atrophy (n=652), treatment with bazedoxifene /conjugated oestrogens was associated with a significantly greater improvement from baseline to endpoint in ASEX lubrication item score from baseline, when compared with placebo (but with no significant difference in change in total ASEX score). There were also significant advantages over placebo in vasomotor function, sexual function and total scores on the Menopause-Specific Quality

of Life questionnaire (QLS) (Hilditch et al., 1996) and in satisfaction with treatment, satisfaction with control of hot flushes, quality of sleep, and mood or emotions on the Menopause Symptoms Treatment Satisfaction Questionnaire (Hill et al., 2007) (Bachmann et al., 2010). A randomised, double-blind, placebo-controlled investigation in non-hysterectomized post-menopausal women (n = 664) which also involved conjugated oestrogens/bazedoxifene found that at baseline, 52% reported pain with intercourse, 35% vaginal dryness and 13% vaginal itching/irritation as bothersome symptoms: at the end of treatment, there was a significant reduction in ASEX-lubrication sub-score in those with pain with intercourse, and significant improvements in vaginal cell counts in women with dryness or pain at intercourse as their most bothersome symptom (Pinkerton et al., 2016). A large randomised double-blind, placebo-controlled study (n=1174), found no clinically or statistically significant changes in ASEX-scores from baseline in the paroxetine 7.5 mg treatment group (Portman et al., 2014). A prospective randomized double-blind study in women using a levonorgestrel subcutaneous implant (LNG-SI), who were treated with doxycycline (20mg) or placebo, found no differences in ASEX-scores changes between the placebo and doxycycline groups (Kovalevsky et al., 2010).

Neurological conditions. The ASEX has been used to determine the prevalence of sexual dysfunction among patients with Parkinson's disease (Celikel et al., 2008; Jitkritsadakul et al., 2015; Özcan et al., 2015) and multiple sclerosis (Celik et al., 2013). A case-control study among patients with Parkinson's disease (n=45) found that female patients had reduced sexual drive and were less satisfied with orgasm than controls, whereas male patients reported easier orgasms than controls: regression analysis identified increased age and female sex as predictive of reduced sexual drive and sexual arousal (Celikel et al., 2008). In an investigation of sexual function which found the point prevalence of ASEX-determined dysfunction to be 81.6% in Parkinson's patients (n=60) compared to 48.3% of controls, ASEX score was correlated with disease severity and depressive symptoms: logistic regression analysis found factors related to sexual dysfunction included absence of recent sexual intercourse, postural instability, and HAMD item 14 (sexual symptoms) (Jitkritsadakul et al., 2015). In a separate investigation in patients with Parkinson's disease (n=89) which found a mean

ASEX total score of 18.54 (SD ±7.27), ASEX total scores were correlated with age, disease stage and HAMA scores: there was no correlation between disease duration and ASEX item scores, but motor symptom scores were correlated with difficulties in erection or lubrication, HAMD score with orgasm dissatisfaction, and HAMA score with difficulties in stimulation and orgasm (Özcan et al., 2015). An investigation of sexual function among patients with multiple sclerosis (n=89) found that women reported ASEX-arousal difficulties significantly more than frequently than men (7.9% versus 1.1%): women also had significantly higher scores on the Multiple Sclerosis Intimacy and Sexuality Questionnaire-19 (MSISQ-19) (Sanders et al., 2000) than men (42.6 ± 12.9 versus 36.6 ± 13.3) (Celik et al., 2013).

Cardiovascular function. In a study among male patients with major depressive disorder (n=46), regression analysis indicated that ASEX scores were predicted by greater Framingham risk score and lower flow-mediated dilation of the brachial artery (FMD), but not by BDI scores: erectile dysfunction, measured by ASEX item 3, was associated with greater risk of cardiovascular disease and impaired vascular endothelial function, suggesting cardiovascular risk factors may adversely affect erectile function through impairment of vascular endothelial function (Hoffman et al., 2010). Two investigations have employed the ASEX to determine the point prevalence of sexual dysfunction in patients with cardiovascular disease (Eyada et al., 2007; Kaya et al., 2014). A limited study in female patients with non-ST-elevation myocardial infarction (n=34) found high levels of reported sexual non- satisfaction and reduced sexual drive (Eyada et al., 2007). In a sample of women with diabetes mellitus (n=38), in which 47·4% expressed problems with sexual relationships, ASEX total score was correlated with the type of hypoglycaemic treatment, duration and complications of illness, spousal relationship, HbA1c level and blood pressure (Kaya et al., 2014).

Other medical conditions. The ASEX has been used to explore sexual function in other medical conditions. In male patients with a pelvic fracture (n=40) but without consequent vascular, neural or urogenital problems, sexual dysfunction was infrequent (10%) (Copuroglu et al., 2017). A case-

controlled investigation of a mixed group of patients with migraine or tension-type headache (n=74) found that ASEX items 1-4 were all significantly higher than in migraine patients than controls, and ASEX total and item scores were higher in patients with tension-type headaches than controls: there were no significant relationships between headache features and ASEX score in either group of patients (Bestepe et al., 2011). Finally, a case-controlled investigation in patients with Behçet's disease (n=50) found that ASEX, HDRS, HARS and Golombok Rust Sexual Satisfaction Scale (GRISS) (Rust et al., 1986) scores were all significantly higher in patient group than controls (n=50) (Gül et al., 2013).

Table 2.3 **ASEX in patients with physical illness**

Study	**Condition**	**Principal findings**
Zhu et al., 2017	Ostomy	47 male and 28 female patients. Chinese language version Mean ASEX score was 20.56 in patients with ostomy.
Soykan et al., 2005	Hepatitis C	24 males and 22 female patients. Turkish language version ASEX-reported sexual dysfunction in 35%, more pronounced in females (50%). GGT levels predicted ASEX-scores in chronic hepatitis C patients.
Yakoot et al., 2012	Hepatitis C	66 patients. Arabic language version Spirulina platensis, (a cynobacterium used frequently as a dietary supplement) Vs Silymarin treated group. ASEX scores were more improved in patients treated with Spirulina platensis than with Silymarin.
Eugenio et al., 2012	Irritable bowel syndrome	616 female patients. English language version. 5% on TCA; 45% on SSRI. Women with ASEX-reported dysfunction were older and had longer history of depression compared to those with without sexual dysfunction.
Ozdemir et al., 2007	Renal disease	98 patients. Turkish language version. ASEX–determined dysfunction in 69.4% patients.
Hekmat et al., 2016	Renal disease	140 female patients. English language version. Significant correlations between total ASEX score and age and duration on haemodialysis.
Koca et al., 2012,	Renal disease	115 female patients and 103 healthy controls. Turkish language version. Higher ASEX-reported dysfunction with haemodialysis and peritoneal-dialysis compared to controls.
Kurdoglu et al., 2012	Renal disease	47 female patient and 20 healthy controls. Turkish language version. Peritoneal-dialysis patients with depressive symptoms were 24 times more likely to develop ASEX-reported dysfunction.
Soykan et al., 2005	Renal disease	25 male and 18 female patients. Turkish language version. ASEX–determined dysfunction in 47% patients which did not improve with dialysis treatment.
Dikici et al., 2014	Renal disease	246 patients. Turkish language version. ASEX scores were 24.6 ± 5.7 with comorbid restless legs syndrome and 22.5 ± 6.8 without.
Janse et al., 2017	Hidradenitis suppurativa	66 male and 234 female patients. English language version.

		ASEX-reported sexual dysfunction associated with poor quality of life and disease severity in female patients.
Kucukunal et al., 2013	Genital warts	116 male patients and 71 healthy controls. Turkish language version. ASEX scores were statistically significantly higher in male patients.
Mercan et al., 2008	Dermatological conditions	31 with neroudermatitis; 24 with psoriasis and 33 controls Turkish language version. Higher ASEX-reported dysfunction with neurodermatitis than with psoriasis and controls.
Sukan et. Al 2007	Dermatological conditions	100 female patients, 50 vitiligo; 50 chronic urticarial and 50 healthy controls. Turkish language version. Higher ASEX-reported dysfunction with vitiligo and urticaria than controls: difficulties more pronounced in females.
Yilmaz et al., 2015	Laryngeal cancer	74 male patients Turkish language version. Significant increase in ASEX total scores correlated with age in patients who underwent laryngectomy.
Batıoğlu-Karaaltın et al., 2017	Laryngeal cancer	108 male patients (36 partial and 72 total laryngectomy). Turkish language version. Significant increase in ASEX total scores correlated with average scores on sexuality in patients who underwent laryngectomy.
Surbeck et al., 2017	Glioma	17 male and 15 female patients. French language version. 53% reported sexual change after resection, with 44% ASEX-determined dysfunction.
Cleary et al., 2011	Gynaecological malignancy	106 female patients. English language version. Higher ASEX scores 6 weeks after diagnosis.
Mathias et al., 2006	Breast cancer	20 female patients. Portuguese language version. Bupropion treatment associated with reduction in ASEX scores.
Senturk et al., 2015	Post-menopausal symptoms	229 female patients. Turkish language version. ASEX mean score 19.97, positively correlated with MRS scores.
Portman et al., 2014	Post-menopausal symptoms	1175 female patients. English language version. undergoing paroxetine treatment. No change in ASEX-scores with paroxetine treatment.
Veras et al., 2011	Polycystic ovarian syndrome	88 female patients. Portuguese language version. Mixed group on various oral contraceptives; Psychotropic medications and Metformin. Negative correlation between ASEX score and testosterone, luteinizing hormone and adehydroepiandrosterone sulfate level.

Pinkerton et al., 2016.	Post-menopausal symptoms	664 female patients. English language version. Improved ASEX-lubrication item scores with conjugated oestrogens/bazedoxifene administration
Bachmann et al., 2010	Post-menopausal symptoms (vulvar/vaginal atrophy)	652 female patients. English language version. Improved ASEX-vaginal lubrication item score: improvement correlated with improved MENQOL and MS-TSQ scores.
Kovalevsky et al., 2010	Healthy women using (LNG-SI	36 healthy females. English language version. Undergoing doxycycline treatment. No change in ASEX scores following treatment with duloxetine.
Jitkritsadakul et al., 2015	Parkinson's disease	35 males; 25 female patients and 60 healthy controls. Thai language version. ASEX-determined sexual dysfunction prevalence of 81.6%.
Özcan et al., 2015	Parkinson's disease	89 patients (male: female= 1.87). Turkish language version. UPDRS motor score correlated with erection/lubrication, HAMD score with orgasm satisfaction, HAMA score with stimulation and orgasm.
Celikel et al., 2008	Parkinson's disease	45 patient and 45 healthy controls. Turkish language version. Female patients had reduced sexual drive and less orgasm satisfaction, male patients reported easier orgasms than controls.
Celik et al., 2013	Multiple sclerosis	45 male and 44 female patients. Turkish language version. Female patients reported ASEX-arousal difficulties significantly more frequently than male patients.
Gül et al., 2013	Behçet's disease.	50 patients and 50 healthy controls. 13 patients undergoing corticosteroids treatment. ASEX scores, HDRS, HARS and GRISS were significantly higher in patients with Behçet's disease.
Eyada et al., 2007	Myocardial infarction	34 female patients. Arabic language version. Non-ST-elevation myocardial infarction associated with elevated ASEX-reported sexual non-satisfaction and reduced drive.
Hoffmann et al., 2010	Cardiovascular risk	46 male patients. Excluded patients using antidepressants. ASEX scores were predicted by the greater Framingham risk score and lower FMD, but not by BDI scores.
Kaya et al., 2014	Diabetes mellitus	38 female patients. 20 undergoing insulin treatment and 18 with Oral hypoglycaemics. ASEX-determined prevalence of dysfunction in 47·4% female patients.

Copuroglu et al., 2017	Pelvic fracture	40 male patients. Turkish language version. ASEX-determined 10% prevalence of dysfunction following surgery after excluding vascular, neural and urogenital system pathologies.
Bestepe et al., 2011	Persistent headache	74 patients and 30 healthy controls. Excluded patients on antidepressants ASEX subscales: 1, 2, 3 and 4 were significantly higher in patients with migraines than in controls.

2.3.3 Treatment-emergent sexual dysfunction during antidepressant treatment

Many studies have utilised the ASEX to determine the prevalence of treatment-emergent sexual dysfunction with antidepressant drugs in patients with depressive and/or anxiety disorders (Detke et al., 2004; Westenberg et al., 2004; Baldwin et al., 2006; Perahia et al., 2006; Khan 2009; Rickels et al., 2009; Williams et al., 2010; Dueñas et al., 2011; Márquez et al., 2011; Schutters et al., 2011; Calandra et al., 2012; Clayton et al., 2013; Tufan et al., 2013; Mahableshwarkar et al., 2014; Clayton et al., 2015; Mahableshwarkar et al., 2015; Genek et al., 2016; Mahableshwarkar et al., 2013) (Table 2.4).

In a double-blind, randomised, placebo-controlled treatment study in depressed patients (n=342), the incidence of ASEX-determined treatment emergent sexual dysfunction was in 46.5% of patients who received duloxetine, compared to 62.8% with paroxetine and 40.5% with placebo. The same study found that ASEX-determined sexual dysfunction rates, after 8 weeks (n=256), were 21.4% for duloxetine, 21.6% for paroxetine and 37.9% for placebo (Detke et al., 2004). Further studies with duloxetine found non-inferiority versus paroxetine for ASEX-determined sexual difficulties (n=392) (Perahia et al., 2006), and the probability of emergent sexual dysfunction of 49.6% (in non-responders) and 33.2% (in responders) during initial treatment (60-120 mg/day for up to 34 weeks, n=514): treatment responders (n=288) were randomly assigned to duloxetine or placebo during a further 52-week double-blind maintenance phase, there being no difference in ASEX score between the placebo and duloxetine groups (Montejo et al., 2011). In a comparative study in patients with major depressive disorder but without baseline sexual dysfunction (n=1647), the prevalence of

ASEX-determined dysfunction after six months of treatment were similar with duloxetine (23.4%) and SSRI monotherapy (28.7%) (Dueñas et al., 2011).

A double-blind, randomized study in patients with major depressive disorder (n=323), who received either escitalopram (10-20 mg/day) or paroxetine (20-40 mg/day), found a high prevalence of ASEX-determined dysfunction at baseline, with a slight increase in ASEX scores above baseline values during acute treatment in both groups, but subsequent slight decline below baseline values towards the end of maintenance treatment (Baldwin et al., 2006). A randomised, placebo-controlled study in patients with major depressive disorder (n=410), found no significant differences in ASEX scores between patients allocated to vilazodone or placebo, in men or women (Rickels et al., 2009); these findings being repeated in a further study, that found no significant difference between placebo and vilazodone in ASEX-defined sexual dysfunction (Khan 2009).

A cross-sectional survey investigated the impact of sexual dysfunction in patients receiving antidepressant treatment (n=704) in three European countries. ASEX scores generally exceeded the threshold defining sexual dysfunction: 67.2% in the German, 79.4% in the Spanish, and 73.3% in the Dutch samples. The prevalence of antidepressant-associated sexual dysfunction was conservatively estimated to be between 37.1% (German sample) and 61.5% (Spanish sample). Overall, 46.4% of male and 52.1% of female participants were classified as having antidepressant-associated sexual dysfunction (Williams et al., 2010).

A twelve-week double-blind, randomised placebo-controlled study of desvenlafaxine (50 mg/day) in patients with major depressive disorder (n=422) found no significant adverse effect on sexual function (with the exception of orgasmic dysfunction in men without pre-existing sexual dysfunction). Greater orgasmic dysfunction at Week 12 was observed in the sub-group of men without baseline sexual dysfunction treated with desvenlafaxine, relative to placebo. Conversely, women without baseline sexual dysfunction experienced poorer overall sexual functioning and orgasm satisfaction at Week 12 with placebo, compared to desvenlafaxine. Sub-group analyses of treatment responders and non-responders found no difference in the proportion of men or women

who developed or had resolution of sexual dysfunction in the desvenlafaxine and placebo groups (Clayton et al., 2013). In a further analysis of the incidence of sexual dysfunction during desvenlafaxine treatment, rates of ASEX-determined dysfunction were comparable with different doses of desvenlafaxine, comparisons for desvenlafaxine versus placebo of change from baseline in ASEX total score and individual item scores were not significantly different, neither was there a significant treatment-by-gender interaction (Clayton et al., 2015).

A small study in patients with major depressive disorder (n=33) receiving SSRI or placebo found a prevalence of ASEX-determined dysfunction of 73.7% with SSRIs and 85.7% with controls, with no significant differences between groups: dysfunction was associated with female gender, regardless of treatment (Tufan et al., 2013). A survey in patients with various depressive and anxiety disorders (n=82), found 69.50 % had been diagnosed with sexual dysfunction prior to antidepressant treatment: after 3 months of treatment, 24 patients in this group (42.1%) showed no impairment on ASEX-scores, whereas scores in 33 patients (57.9%) still indicated dysfunction. By contrast, eight patients of the 25 (32%) who were not diagnosed with sexual dysfunction prior to treatment were later diagnosed with sexual dysfunction. The presence of dysfunction correlated with patients' level of functioning, independent of anxiety and depressive symptoms (Genek et al., 2016).

An 8-week randomised placebo-controlled study of vortioxetine in patients with major depressive disorder (n=469) found that ASEX total scores during treatment were similar, with no significant differences in depressive symptoms (Mahableshwarkar et al., 2015). In a comparison of vortioxetine (2.5 or 5.0 mg), duloxetine (60 mg) and placebo rates of ASEX-determined sexual dysfunction were 51.0%, 37.5%, 46.9%, and 33.3% in the vortioxetine 2.5 mg, vortioxetine 5 mg, duloxetine, and placebo groups, respectively (Mahableshwarkar et al., 2013).

Antidepressant drugs are often used in patients with diagnoses other than depressive illness. A double-blind placebo-controlled study of fluvoxamine controlled-release in patients with generalised social anxiety disorder (n=300), found that fluvoxamine did not cause ASEX-determined sexual dysfunction (Westenberg et al., 2004). In patients with generalised anxiety disorder, sexual

dysfunction was present in 50% of patients treated with paroxetine combined with placebo, compared to 38% of patients treated with paroxetine combined with mirtazapine (Schutters et al., 2011). A double-blind randomised, controlled study of sublingual alprazolam tablets in acute treatment of patients (n=190) with panic disorder found that there was no improvement in ASEX scores, despite improvements in scores on the Clinical Global Impressions (CGI-S/CGI-I) (Guy 1976; Busner et al., 2007), Hamilton Rating Scale for Anxiety (HAM-A) (Hamilton 1959), Patient Global Impression (PGI) (Guy 1976), Psychological General Well-Being Index (PGWBI) (Dupuy 1984),and Panic Disorder Severity Scale (PDSS) (Shear et al., 1997) (Márquez et al., 2011). In a retrospective cohort study in patients with comorbid binge eating disorder and major depressive disorder, bupropion was superior to sertraline in reducing weight and improving ASEX scores (Calandra et al., 2012). In a double-blind, randomised placebo-controlled study in patients (n=781) with primary generalised anxiety disorder, rates of treatment-emergent sexual dysfunction in vortioxetine-treated groups were similar to those with placebo (Mahableshwarkar et al., 2014).

Some studies have employed the ASEX to investigate the management of sexual dysfunction in patients receiving antidepressants. Switching to tianeptine (n=23) resulted in a significant difference between baseline and week 4 or week 8 in ASEX scores, associated with significant improvement in HAM-D scores (Atmaca et al., 2003). A 6-week randomised control trial (n=101) found that aripiprazole augmentation and antidepressant switching had comparable effect on sexual dysfunction, as assessed by ASEX scores (Han et al., 2015). Switching to agomelatine in patients with acute depressive episodes (n=25) led to improved ASEX scores after 3 weeks of treatment (mainly in women rather than men): visual analogue scales for desire, arousal, time, and intensity of orgasm and vaginal lubrication showed improvement in all stages of sexual response in women, with minimal changes in men, and treatment was associated with reduction in depressive symptoms (Sapetti et al., 2012). The 5-HT 1A agonist and 5-HT 2A antagonist flibanserin was found to be associated with low rates of ASEX-reported treatment-emergent sexual dysfunction in women with major depressive disorder (n=523). 70% of flibanserin-treated women with baseline sexual dysfunction reported an improvement in sexual function, compared with 30% of placebo-treated

women (Kennedy et al., 2010). Switching to mirtazapine (open-label) for up to 6 weeks (n=19), led to return of normal sexual functioning on ASEX in 58% of patients, and 11% reported a significant improvement in sexual functioning (Gelenberg et al., 2000). Treatment augmentation with *Maca* 3.0 g/day (a Peruvian plant), (n=20) had a significant improvement in ASEX and Massachusetts General Hospital Sexual Function Questionnaire (MGH-SFQ) (Dording et al., 2008). Augmentation with VML-670 (a 5-HT1A receptor agonist), (n=88) had no significant advantage (Baldwin et al., 2008). Augmentation with bupropion (n=41) (DeBattista et al., 2005), (n=30) (Masand et al., 2001) or methylphenidate (Pae et al., 2009), also had no significant advantage on ASEX-scores. A placebo controlled trial investigated the use of kavalactones in patients with generalised anxiety disorder (n=75). Kavalactone administration significantly increased ASEX-sexual drive in female participants when compared to placebo, with no negative effects seen in male participants: and there was a highly significant correlation between ASEX reduction (improved sexual function and performance) and anxiety reduction in the whole sample (Sarris et al., 2013).

An investigation involving drug-naïve patients with major depressive disorders (n=56), found that the 5-HT-2A receptor -1438 AA genotype was significantly over-represented among the sub-group of patients who experienced sexual dysfunction during SSRI or venlafaxine monotherapy: mean baseline HAMD-17 score, mean baseline ASEX score, and mean end-point ASEX score were all significantly higher than in patients without sexual dysfunction group, though the mean end-point HAMD-17 score did not differ significantly between the two groups (Liang et al., 2012). Another study in patients with paroxetine-induced sexual dysfunctions (n=55), found a significantly higher rate of ASEX-determined dysfunction among females with a ‘poor’ metabolic status-CYP2D6-phenotype (Zourková et al., 2007).

Table 2.4 **ASEX-determined sexual dysfunction during antidepressant treatment**

Study	**Principal findings**
Genek et al., 2016	82 male and female patients. Mixed sample with various depressive and anxiety disorders. Turkish language version. Mixed sample. undergoing various psychotropic treatments. Baseline prevalence of ASEX-reported dysfunction in patients with depression and anxiety was 69.5%. 42.11% of which showed no sexual impairment after taking antidepressants. The incidence of – de novo-treatment emergent with antidepressants was 32%.
Williams et al., 2010	207 male and 497 female patients. Mixed sample with various depressive and anxiety disorders. English language version. The prevalence of ASEX-reported antidepressant-emergent sexual dysfunction was, 46.4% in males and 52.1% in females.
Montejo et al., 2011	514 male and female patients. MDD. English language version. Undergoing duloxetine treatment. Treatment with duloxetine 60-120 mg/day for up to 34 weeks, found a probability of treatment emergent sexual dysfunction of 49.6% in non-responders and 33.2% in responders for patients with MDD.
Perahia et al., 2006	119 male and 237 female patients. MDD. English language version. Undergoing paroxetine, duloxetine or placebo. Non-inferiority of duloxetine versus paroxetine in ASEX-determined sexual difficulties in patients with MDD.
Detke et al., 2004	256 patients. MDD. English language version. Undergoing paroxetine or duloxetine treatment. The incidence of ASEX-reported treatment emergent sexual dysfunction was 46.5% with duloxetine and 62.8% with paroxetine.
Baldwin et al., 2006	232 patients. MDD. English language version. Undergoing citalopram or paroxetine treatment. Slight increase in ASEX-scores during acute treatment with paroxetine or escitalopram, ASEX scores decreasing during longer-term treatment.
Clayton et al., 2015	909 patients. MDD. English language version. Undergoing desvenlafaxine treatment. No difference between desvenlafaxine and placebo in ASEX-determined sexual dysfunction in patients with MDD.
Mahableshwarkar et al., 2015	469 patients. MDD.

	English language version. Undergoing vortioxetine treatment. No significant difference in ASEX scores between vortioxetine and placebo in patients with MDD.
Mahableshwarkar et al., 2013	611 patients. MDD. English language version. Undergoing vortioxetine or duloxetine treatment. Incidences of ASEX-determined dysfunction of 51.0%, 37.5%, 46.9%, and 33.3% with vortioxetine 2.5 mg, vortioxetine 5 mg, duloxetine and placebo, respectively, in patients with MDD.
Clayton et al., 2013	422 patients. MDD. English language version. Undergoing desvenlafaxine treatment. No significant negative effect on ASEX-assessed sexual function over 12 weeks of treatment with desvenlafaxine, with the exception of orgasmic dysfunction in men without pre-existing sexual dysfunction.
Tufan et al., 2013	33 patients. MDD. Turkish language version. Undergoing SSRI treatment. The prevalence of ASEX-reported sexual dysfunction with SSRIs was 73.7% and in 85.7% of controls, with MDD.
Dueñas et al., 2011	1647 patients. MDD. English language version. Undergoing duloxetine treatment. ASEX-reported dysfunction at 6 months treatment with duloxetine of 23.4%, comparable to that with 28.7% with SSRIs, in patients with MDD.
Rickels et al., 2009, Khan 2009	410 patients. MDD. English language version. Undergoing vilazodone treatment. Treatment with vilazodone was associated with no clinically-significant differences in ASEX scores for either gender at the end of treatment.
Calandra et al., 2012	30 patients. MDD and binge eating disorder. English language version. Undergoing bupropion and sertraline treatment. Bupropion effective in reducing weight and improving ASEX scores in patients with comorbid major depressive disorder and binge eating disorder.
Mahableshwarkar et al., 2014	781 patients. GAD. English language version. Undergoing vortioxetine treatment. No difference between vortioxetine and placebo in ASEX scores in patients GAD.
Schutters et al., 2011	21 patients. Social anxiety disorder.

	English language version. Undergoing paroxetine and mirtazapine treatment. The prevalence of ASEX-determined dysfunction in GAD was 50% for patients treated with paroxetine plus placebo, and 38% of patients treated with paroxetine plus mirtazapine.
Márquez et al., 2011	190 patients. Panic disorder. English language version. Undergoing alprazolam treatment. ASEX scores showed no improvement with alprazolam for acute panic disorder.
Westenberg et al., 2004	300 patients. Social anxiety disorder. English language version. Undergoing fluvoxamine treatment. No ASEX-reported difference between fluvoxamine and placebo in patients with generalised social anxiety disorder.
Atmaca et al., 2003	23 patients. MDD. Turkish language version. Undergoing tianeptine treatment. Switching to tianeptine resulted in a significant difference in ASEX scores between Baseline and Week 4 or Week 8.
Han et al., 2016	101 patients. MDD. English language version. Undergoing aripiprazole augmentation treatment. Aripiprazole augmentation and antidepressant switching had comparable effect on sexual dysfunction, as assessed by ASEX scores.
Sapetti 2012	25 patients. MDD. Spanish language version. Undergoing agomelatine treatment. Improvement in ASEX scores in women after switching to agomelatine treatment.
Kennedy et al., 2010	523 patients. MDD. English language version. Undergoing flibanserin treatment. 70% of flibanserin-treated female patients with major depressive disorder with sexual dysfunction at baseline reported an improvement in sexual function.
Gelenberg et al., 2000	19 patients. MDD. English language version. Undergoing mirtazapine treatment. On switching to mirtazapine, 58% of patients reported the return of normal sexual functioning, and 11% reported a significant improvement in sexual functioning.

Dording et al., 2008	3 males and 17 female patients. MDD, in remission. Mixed group, psychotropic; amphetamine, thyroid hormone. Augmentation with maca (a Peruvian plant). Improvement in ASEX-scores with *Maca* root preparation.
Baldwin et al., 2008	84 male and 2018 female patients. Patients with a history of SSRI-induced sexual side effects. English language version. Undergoing VML-670 augmentation treatment. Augmentation with VML-670 has no significant advantage over placebo in reducing ASEX-scores in patients with SSRI-associated sexual dysfunction.
DeBattista et al., 2005, Masand et el., 2001	41 patients. Patients with SSRI-induced sexual side effects. English language version. Undergoing bupropion treatment. Augmentation with bupropion had no significant advantage over continuation on SSRIs, without augmentation, in reducing ASEX-scores.
Pae et al., 2009	Patients with antidepressant-related sexual dysfunction. English language version. Undergoing methylphenidate augmentation treatment. Augmentation with methylphenidate had no significant advantage over continuation on SSRIs, without augmentation, in reducing ASEX-scores.
Sarris et al., 2013	37 male and 38 female patients. GAD. Medication free subjects, undergoing Kavalactones augmentation treatment. Kavalactone significantly improved drive in, medication free, women with GAD.
Liang et al., 2012	56 patients. MDD. English language version. Mixed group, drug-naïve; prescribed SSRI or venlafaxine. 5-HT-2A receptor -1438 AA genotype was significantly over-represented patients experiencing sexual dysfunction with SSRI or venlafaxine treatment
Zourková et al., 2007	55 patients. MDD. English language version. Undergoing paroxetine treatment. Higher ASEX-determined dysfunction with paroxetine in female patients with poor CYP2D6 phenotype.

2.3.4 Treatment-emergent sexual dysfunction during antipsychotic treatment

A number of studies have employed the ASEX scale to determine the incidence of treatment emergent sexual dysfunction during antipsychotic drug treatment (Table 2.5) (Byerly et al., 2004; Atmaca et al., 2005; Uçok et al., 2007; Nakonezny et al., 2007; Byerly et al., 2008; Hanssens et al., 2008; Konarzewska et al., 2009; Kalkavoura et al., 2013; Nunes et al., 2013).

An early small case series (n=8) involving a switch to quetiapine in patients with sexual dysfunction associated with previous antipsychotic treatment found a clinically and statistically significant improvement in ASEX total scores, significantly decreased total score on the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), and decreased plasma prolactin levels after transition to quetiapine (Byerly et al., 2004). A subsequent study with quetiapine in patients with schizophrenia (n=36), found a statistically significant increase in mean ASEX score after four weeks of treatment with quetiapine, compared with scores at baseline: the most frequent dysfunction was diminished libido, both in men (31.8%) and women (28.6%), but there was no significant correlation between ASEX scores and plasma prolactin levels (Atmaca et al., 2005). A cross-sectional survey in symptom-remitted male and female patients with schizophrenia receiving antipsychotic medication (n=827) found that 52.6% had ASEX-determined dysfunction (54.2% reported low sexual desire and 41.7% reported problems in orgasm). In men, erectile dysfunction and ejaculatory problems were seen in 48.1% and 64.2% respectively, and amenorrhea was seen in 24.9% of women. ASEX scores were affected significantly and independently by disease severity in men; ASEX scores were higher in cigarette smokers; low sexual desire was more prevalent among women prescribed first-generation drugs; men undergoing second generation antipsychotic monotherapy had lower ASEX scores than men undergoing combination treatment; and men undergoing combination therapy had more ejaculation problems (Uçok et al., 2007).

A small (n=22) randomised comparator-controlled investigation of the relationship between prolactin and sexual function in outpatients undergoing treatment with risperidone or quetiapine found that higher serum prolactin levels were related to greater ASEX-determined sexual

dysfunction in men treated with risperidone, but not with quetiapine (Nakonezny et al., 2007). A small (n=42) randomized double-blind study of continued risperidone or switch to quetiapine in patients with risperidone-associated sexual dysfunction found no significant treatment effect for either ASEX total score or ASEX items, and no significant treatment x time interaction for either ASEX total scores or ASEX items (Byerly et al., 2008). A large (n=555) comparative investigation in patients with schizophrenia found a significantly greater improvement from baseline in ASEX score with aripiprazole than with comparator drugs: in addition, although serum prolactin levels were similar in the two treatment groups at baseline, mean decreases in serum prolactin were 34.2 mg/dL with aripiprazole, compared with 13.3 mg/dL with comparators (Hanssens et al., 2008).

A study in male patients with schizophrenia undergoing antipsychotic drug treatment (n=89) found that ASEX scores were significantly higher in patients on risperidone, compared to patients on olanzapine: sexual dysfunction and treatment non-adherence were not related to either prolactin or gonadal hormone levels (Konarzewska et al., 2009). An investigation of augmentation with cabergoline in patients (n=80) receiving a range of antipsychotics found a reduction in prolactin levels with cabergoline treatment in all patients, with mean levels of 73.3 ng/ml (±46.8) to 42.0 ng/ml (±27.8) at month 3 and 27.1 ng/ml (± =20.4) at month 6: mean total ASEX scores also declined, from 19.1 (±5.1) to 17.6 (±5.5) at month 3 and 15.0 (±6.5) at month 6 (Kalkavoura et al., 2013). Finally, a randomized, double-blind, crossover, placebo-controlled investigation of lodenafil in male patients (n=50) with schizophrenia and erectile dysfunction found that both lodenafil and placebo were associated with an improvement in ASEX, IIEF scale, PANSS, and QLS scores, with no statistical differences between treatment groups in all sexual domains or in hormone levels (Nunes et al., 2013).

Table 2.5 **ASEX-determined sexual dysfunction during antipsychotic treatment**

Study	**Principal findings**
Uçok et al., 2007	827 patients. Schizophrenia (in remission). Turkish language version. Mixed group, first and second generation antipsychotics. 52.6% of patients with schizophrenia in remission who received antipsychotics has ASEX-determined dysfunction.
Atmaca et al., 2005	22 male and 14 female patients. Schizophrenia. Turkish language version. Undergoing quetiapine treatment. A statistically significant increase in mean ASEX score after four weeks of treatment with quetiapine, compared with scores at baseline, in patients with schizophrenia.
Konarzewska et al., 2009	89 male patients. Schizophrenia. Polish language version. Undergoing risperidone and olanzapine treatment. ASEX scores were significantly higher in patients on risperidone, compared to patients on olanzapine, in patients with schizophrenia.
Nakonezny et al., 2007	22 male patients. schizophrenia and schizoaffective disorders. English language version. Undergoing risperidone and quetiapine treatment. Higher serum prolactin level was related to greater ASEX-determined sexual dysfunction in male outpatients treated with risperidone (but not with quetiapine).
Byerly et al., 2004	8 patients. Schizophrenia. English language version. Undergoing quetiapine treatment. Decreased plasma prolactin levels and improved ASEX-scores after transition to quetiapine in patients with schizophrenia.
Byerly et al., 2008	22 male and 20 female patients. Schizophrenia. English language version. Undergoing risperidone and quetiapine treatments. No significant difference in ASEX-scores when switching to quetiapine was compared to risperidone continuation.
Kalkavoura et al., 2013	80 patients. Schizophrenia. Greek language version. Undergoing risperidone; haloperidol; amisulpride and risperidone, treatments. Improved ASEX-scores on augmentation with cabergoline in patients with schizophrenia receiving antipsychotics.

Nunes et al., 2013	50 male patients. Schizophrenia. Portuguese language version. Undergoing lodenafil augmentation treatment. No difference between augmentation with lodenafil and placebo in antipsychotic-treated patients with schizophrenia with erectile dysfunction.
Hanssens et al., 2008	332 male and 223 female patients. Schizophrenia. English language version. Undergoing aripiprazole treatment. Significantly greater improvement from baseline in ASEX score with aripiprazole than with comparator drugs, in patients with schizophrenia.

2.3.5 Primary sexual dysfunction

Primary sexual dysfunction and the potential benefit of pharmacological agents to modulate sexual drive and function, was investigated using ASEX in some studies (Table 2.6). A study on military personnel (n=367) found 8.45% ASEX-reported dysfunction. This was correlated with erectile dysfunction in 33.24% measured by the International Index of Erectile Function (IIEF) (Rosen et al., 1997). The study identified risk factors for sexual dysfunction were: aged 21-40 years, poor physical and psychosocial health (Wilcox et al., 2014).

Male patients with congenital hypogonadotropic hypogonadism (n=39) had significantly higher scores for BDI, BAI, and ASEX than the control subjects (n=40) at baseline. ASEX and BDI scores significantly improved after testosterone replacement treatment, while the improvement in the BAI score was not statistically significant. Treatment naïve hypogonadal patients had more severe symptoms of sexual dysfunction, anxiety, depression, and worse quality of life. Six months of testosterone replacement treatment was associated with improvement all parameters, suggesting that low endogenous levels of testosterone might be related to the increased incidence of psychological symptoms at baseline (Aydogan et al., 2012).

A randomised controlled trial, studying placebo and nocebo responses in heterosexual men (n=48), found increased levels of sexual function after administration of cabergoline with significant effects for several parameters measured by ASEX, and the Acute Sexual Experience Scale (ASES) (Krüger et

al., 2003). Placebo effects were induced only to a small degree. No negative effects on sexual parameters in the nocebo condition were noted. This paradigm could induce only small placebo and nocebo effects (Kruger et al., 2016). Intranasal oxytocin administration to healthy participants (n=58), did not alter "classical" parameters of sexual function, such as sexual drive, arousal or penile erection and lubrication. However, analysis of variance and a hierarchical linear model, found that oxytocin increased the intensity of orgasm, contentment after sexual intercourse and the effect of study participation. According to ANOVA, these effects were more pronounced in men. Men additionally indicated higher levels of sexual satiety after sexual intercourse with oxytocin administration. Women felt more relaxed and subgroups indicated better abilities to share sexual desires or to empathize with their partners (Behnia et al., 2014).

A randomized double-blind crossover in women hypoactive sexual desire disorder (n=10), found significantly improved ASEX-item 2 (arousal) on testosterone gel versus placebo. Similar trends found with Sexual Function Questionnaire (SFQ-V1) (Quirk et al., 2002), (Chudakov et al., 2007).

A cluster-analytic study on use of pornography (n=875), found that recreational users reported higher ASEX-satisfaction and lower sexual compulsivity, avoidance, and dysfunction, whereas users with a compulsive profile presented lower ASEX- satisfaction and dysfunction and higher sexual compulsivity and avoidance. Highly distressed less active users were sexually less satisfied and reported less sexual compulsivity and more sexual dysfunction and avoidance. A larger proportion of women and of dyadic users was found among recreational users, whereas solitary users were more likely to be in the highly distressed less active profile and men were more likely to be in the compulsive profile (Vaillancourt-Morel et al., 2017).

Table 2.6 **ASEX rated treatment response in primary sexual dysfunction**

study	findings
Wilcox et al., 2014	367 males, active duty military personnel, aged 40 or younger. English language version. ASEX-reported dysfunction 8.45% in military personnel.
Aydogan et al., 2012	39 male patients and 40 healthy controls. congenital hypogonadotropic hypogonadism. Turkish language version. Undergoing testosterone replacement treatment. Improvement of ASEX, BDI and BAI with testosterone replacement therapy in male patient with primary hypogonadism.
Kruger et al., 2016	48 healthy heterosexual males. English language version. Undergoing cabergoline treatment. Significant improvement of ASEX and ASES with cabergoline.
Behnia et a. 2014	29 healthy heterosexual couples. English language version. Undergoing oxytocin treatment. Intranasal oxytocin administration exerted differential effects on parameters of sexual function and partner interactions.
Chudakov et al., 2007	10 female patients. hypoactive sexual desire disorder. English language version. Undergoing testosterone gel or placebo treatments. Significant improvement of ASSEX-arousal subdomain in women with hypoactive sexual desire disorder.
Vaillancourt-Morel et al., 2017	875 Cyberpronography users. French language version. Less ASEX-satisfaction associated with higher dysfunction in compulsive pornography users.

2.3.6 Other studies which employed the ASEX

Fewer studies used the ASEX to determine potential dysfunction associated with non-psychotropic medication (Table 2.7).

A study on patients receiving finasteride (n=79), found 40.5% of participants had difficulties achieving and maintaining erection, and 3.8% never achieved erection. Achieving orgasm was difficult in 16.5%, and never achieved by 2.5%. By the ad hoc questionnaire, the most frequent sexual symptoms referred were loss of penis sensitivity (87.3%), decreased ejaculatory force (82.3%), and low penile temperature (78.5%). The most frequent non-sexual symptoms were

reduced feeling of life pleasure or emotions (anhedonia) (75.9%); lack of mental concentration (72.2%), and loss of muscle tone/mass (51.9%) (Chiriacò et al., 2016).

Healthy young men without any baseline sexual dysfunction (n=54), who were taking finasteride for male pattern hair loss, had ASEX-reported sexual side effects associated with finasteride (89%), after 9-16 months (mean 14 months). Neither the length of finasteride use nor the duration of the sexual side effects correlated to changes in scores of sexual dysfunction. Persistent sexual side effects (≥3 months) despite the discontinuation of finasteride, were reported by some patients where the sexual dysfunction continued for many months or years (Irwig et al., 2012).

One study investigated ASEX-scores in women with overactive bladder (n=30). This study found that tolterodine immediate release improved mean of the total ASEX score relative to baseline. The mean of scores for sexual desire, arousal, vaginal lubrication, orgasm, and orgasm satisfaction improved significantly with each follow-up (Hajebrahimi et al., 2008).

Table 2.7 **ASEX rated non-psychotropic treatment emergent sexual dysfunction**

study	findings
Chiriacò et al., 2016	79 male patients. Alopecia. Italian language version. Undergoing finasteride treatment. 48.3% of participants had erectile dysfunction. 19% had problems with orgasm.
Irwig et al., 2012)	45 health males with male pattern hair loss. English language version. Undergoing finasteride treatment. 89% of healthy patients who received finasteride for male pattern hair loss.
Hajebrahimi et al., 2008	30 female patients. Overactive bladder syndrome. English language version. Undergoing tolterodine treatment. Tolterodine improved total ASEX score in women with overactive bladder syndrome.

2.4 Discussion

The ASEX scale has been found to have excellent internal consistency and scale reliability and strong test–retest reliability; furthermore, ASEX scores appear to correlate well with factors and related items on other validated questionnaires for assessing sexual dysfunction. ASEX has very high sensitivity and specificity, and very high positive and negative predictive values. ASEX is available in 43 languages. Studies which examined the psychometric properties of the Turkish, Thai and Arabic versions of ASEX found the translated versions to have psychometric properties comparable to those of the original English version. Validation studies have utilised cohorts with various psychiatric disorders, schizophrenia, schizoaffective disorder, and end-stage renal failure.

The ASEX was found to have satisfactory validity and reliability in studies of sexual dysfunction in specific patient groups: primary sexual dysfunction (n=7); specific psychiatric disorders (n=9) and specific physical illnesses (n=44). More studies employed the ASEX to investigate treatment emergent sexual dysfunction (n=42), principally with antidepressants (n=30) and antipsychotics (n=9). A notable observation is that many studies found that ASEX-reported dysfunction correlated positively with the presence and severity of affective symptoms. Another important observation is that some studies found no significant correlation between ASEX scores and plasma prolactin levels with quetiapine or aripiprazole in patients with schizophrenia. Only two studies have investigated potential links between ASEX-reported dysfunction and biological/genetic markers. The psychometric properties of ASEX in cohorts with anxiety disorders are not established. Little is known about the utility of ASEX in anxiety disorders or the relation between anxiety related biological markers and ASEX scores.

2.5 Conclusion

The ASEX appears to be a reliable clinical instrument for identifying and quantifying sexual dysfunction across a range of populations in various clinical settings. The ASEX was utilised by some studies to investigate sexual dysfunction in mood disorders. Little is known about either the utility of ASEX in patients with anxiety disorders or possible relationships between ASEX scores and potential biological markers.

Chapter 3 Methods

3.1 Recruitment pathways

I invited referrals of patients with a diagnosis of an anxiety disorder (in accordance with DSM-5 criteria) as potential study participants. Patients were recruited from existing and recently-referred outpatients currently attending outpatient mental health services. In addition, letters with an information sheet were sent to local general practitioners and consultant psychiatrists working within Southern Health NHS Foundation Trust and Northamptonshire Healthcare NHS Foundation Trust, inviting the referral of potentially suitable patients. Potentially eligible patients were sent a letter with the participant information sheet; contact information return slip and stamped addressed envelope. They were provided with contact details for the research team and had an opportunity to ask any questions about the study aims and procedures. Then, when a potential participant got in touch with the research team or when a contact information slip was returned, the researcher contacted them to make an appointment for possible provision of consent and the study baseline assessments. Study participants were invited to attend a screening assessment, which included the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998).

3.2 Cross-sectional investigation

Patients who met threshold criteria for an anxiety disorder could be included in an initial cross-sectional investigation of the relationships between the presence of an anxiety disorder and sexual difficulties. Patients were considered eligible for the study if they were aged between 18-70 years; had the primary diagnosis of an anxiety disorder or anxiety-related disorder, defined according to DSM-5 criteria, and were competent to provide written consent. Patients were excluded from the study if they met any of the following criteria:

- outside the age range 18-70 years;
- the primary diagnosis is not an anxiety disorder;
- unable to provide written, informed consent;

- clinically significant alcohol or substance use in the previous three months;
- physical illness that was unlikely to be stable over the course of the study;
- pregnancy and breast feeding.

The following assessment measures were used:

- Arizona Sexual Experiences Scale (ASEX) (McGahuey et al., 2000);
- Warwick-Edinburgh Mental Well-Being Scale (WEMWEBS) (Tennant et al., 2007);
- Hospital Anxiety and Depression Scale (HADS) (Zigmond et al., 1983);
- Oxford Questionnaire of Emotional Side Effects of Antidepressants (OQuESA) (Price et al., 2012);
- Clinical Global Impression of Illness Severity (CGI-S) (Guy et al., 1976);
- Emotional Quality of the Relationship Scale (EQR) (Kreuter et al., 1996).

3.3 Prospective phase of treatment as usual

Patients who were not undergoing pharmacological treatment for an anxiety disorder at the time of referral were offered six weeks of treatment with usual evidence-based interventions, taking account of their preference. Enquiries about treatment history and current treatment status were made. Assessment of sexual dysfunction was obtained by sensitive interviewing and through using the psychometric measures employed in the cross-sectional investigation.

To determine the incidence of treatment-emergent sexual difficulties, the above assessments were repeated after 6 weeks for patients in whom new treatment was clinically indicated. Treatment adherence was determined by patient report and tablet counts. Endocrine factors were assessed through sampling hair for cortisol levels and blood for prolactin levels. Inflammatory markers were assessed using venous blood sampling. To examine the potential influence of endocrine factors, sample of scalp hair from the vertex area (3cm. in length) were collected from study participants at baseline and after 6 weeks. Descriptive sub-group analysis included consideration of cortisol levels across differing anxiety disorders, and possible influences of medication.

To examine the potential influence of inflammation, venous blood samples were collected from participants at baseline and after 6 weeks, with assays of interleukins and tumour necrotic factor alpha. Sub-group analysis included consideration of inflammatory markers across differing anxiety disorders, and the possible influences of medication.

3.4 Non-steroidal anti-inflammatory drug (celecoxib) treatment phase (augmentation phase)

Patients who showed poor response to 6 weeks of treatment as usual and continued to meet the clinical threshold of an anxiety disorder (measured by HADS) were offered six weeks of treatment augmentation with celecoxib. Enquiries about treatment history and current treatment status were made. Assessment of sexual dysfunction was obtained by sensitive interviewing and through using the psychometric measures shown above. The degree of adherence to the prescribed medication was assessed by sensitive questioning. Endocrine factors were assessed through sampling hair for cortisol levels and blood for prolactin levels. Inflammatory markers were assessed using venous blood sampling. Exclusion criteria for the augmentation phase comprised:

- medical contra-indication for celecoxib; history of hypersensitivity to NSAID, patient with cardiac impairment, thromboembolic disease, renal impairment, hepatic impairment or history of recurrent gastro-intestinal ulceration.
- concomitant use of NSAIDS, ciclosporins, cumarins, dabigatran, ketorolac, lithium, methotrexate, phenindione, quinolones and sulfonylureas.

3.4.1 Sample size

To determine the required number of subjects for adequate study power, I have taken into account the study design of two independent groups (augmentation versus treatment as usual) and a dichotomous primary end point (the presence of anxiety disorder determined by HADS). I used the anticipated reduction in symptoms of 45% (as per previous published evidence Abbasi et al., 2012), type I error rate (alpha) 0.05 and 80% power (beta). The calculation suggested a total sample size of 6 participants (3 in each group).

3.4.2 Dosage Schedule

The dose used was 200 mg twice daily, as previous studies suggested efficacy of celecoxib in SSRI augmentation in depressed patients at a dose of 400 mg once daily or 200mg twice daily (Akhondzadeh et al., 2009; Abbasi et al., 2012; Nery et al., 2008).

3.4.3 Treatment withdrawal criteria

Participants were reminded of their right to withdraw their consent and from the study at any point. Treatment would be stopped immediately for patient who experienced any of the following serious adverse events (occurred in <0.1% of patients) in either the prospective or augmentation phase, and where appropriate patients were advised to seek medical help from their general practitioner.

Cardiovascular:	Syncope, congestive heart failure, ventricular fibrillation, pulmonary embolism, cerebrovascular accident, peripheral gangrene, thrombophlebitis, vasculitis, deep venous thrombosis
Gastrointestinal:	Intestinal obstruction, intestinal perforation, gastrointestinal bleeding, colitis with bleeding, oesophageal perforation, pancreatitis, ileus
Liver and biliary:	Cholelithiasis, hepatitis, jaundice, liver failure
Hemic and lymphatic:	Thrombocytopenia, agranulocytosis, aplastic anaemia, pancytopenia, leucopoenia
Metabolic:	Hypoglycaemia, hyponatremia
Nervous:	Ataxia, aggravated suicidal thoughts, aseptic meningitis, ageusia, anosmia,

	fatal intracranial haemorrhage.
Renal:	Acute renal failure, interstitial nephritis
Skin:	Erythema multiform, exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis drug rash with eosinophilia and systemic symptoms (DRESS, or hypersensitivity syndrome)
General:	Sepsis, sudden death, anaphylactic reaction, angioedema. Patients on Warfarin, Aspirin, ACE-inhibitors and Angiotensin II antagonists, Fluconazole, Furosemide, concomitant use of other NSAIDs.

Patients were advised to get emergency help right away if they have any of the following symptoms:

- shortness of breath or trouble breathing
- chest pain
- weakness in one part or side of your body
- slurred speech
- swelling of the face or throat

Patients were advised to stop Celecoxib and call their general practitioner immediately if they have any of the following symptoms:

• nausea	• vomit blood
• more tired or weaker than usual	• there is blood in your bowel movement or it is black
• itching	and sticky like tar
• your skin or eyes look yellow	• skin rash or blisters with fever
• stomach pain	• unusual weight gain
• flu-like symptoms	• swelling of the arms and legs, hands and feet

3.5 Study assessments

3.5.1 Warwick-Edinburgh Mental Well-Being Scale (WEMWBS)

This was developed to enable monitoring of mental wellbeing in the general population and the evaluation of projects, programmes and policies which aim to improve mental wellbeing. WEMWBS is a 14 item scale with 5 response categories, summed to provide a single score ranging from 14-70. National survey reports have been published by Warwick medical school, and they show population norms for England 2011 (https://warwick.ac.uk/fac/sci/med/research/platform/wemwbs/researchers/interpretations/wemwbs_population_norms_in_health_survey_for_england_data_2011.pdf). The items are all worded positively and cover both feeling and functioning aspects of mental wellbeing (Tennant et al., 2007). The scale has good content validity and a Cronbach's α score of 0.91. WEMWBS has a high correlation with mental health and well-being but lower correlations with overall health. Its distribution is near normal and the scale did not show ceiling effects. It discriminated between population groups in a way that is largely consistent with the results of other population surveys. Test-retest reliability at one week was high (0.83). Social desirability bias was lower or similar to that of other comparable scales (Tennant et al., 2007).

3.5.2 Hospital Anxiety and Depression Scale (HADS)

This questionnaire comprises seven questions for anxiety and seven questions for depression. Anxiety and depression questions are interspersed within the questionnaire; these are scored separately. Each item has a possible score of 0-3. A total score of 8-10 indicates a borderline case and a score of 11-21 indicates a probable case (Zigmond et al., 1983).

The mean correlations between HADS-A and HADS-D is 0.56. The mean Cronbach's α for HADS-A is 0.83 and 0.82 for HADS-D. An optimal balance between sensitivity and specificity was achieved when caseness was defined by a score of 8 or above on both HADS-A and HADS-D. The sensitivity and specificity for both HADS-A and HADS-D of approximately 0.80 are very similar to the sensitivity and specificity achieved by the General Health Questionnaire (GHQ-28). Correlations between HADS and: BDI; GHQ-28; Clinical Anxiety Scale (SCI); Spielberger's State-Trait Anxiety Inventory (STAI); Symptom Checklist (SCL-90) and subscales of Anxiety and Depression Montgomery Asberg Depression Rating Scale, were in the range 0.49 to 0.83 (Bjelland et al., 2002).

3.5.3 Oxford Questionnaire of Emotional Side Effects of Antidepressants (OQuESA)

This was developed to measure emotional symptoms present in patients treated with antidepressants (Price et al., 2012). It has 26 items; each has a possible scored of 1-5. OQuESA items are sub-classified into four dimensions: not caring (NC), emotional detachment (ED), reduction in positive emotions (RP), and general reduction in emotions (GR). A further attributional dimension can be scored: antidepressant as cause (AC). RP and NC may be closely related to the phenomenon of depression as well as to the phenomenon of antidepressant-associated emotional blunting, whereas the two remaining dimensions (GR & ED) are less closely related to depression (Price et al., 2012).

For participants whose gold standard response increased by one or more, the mean increase in OQuESA total score was 2.81, but this did not reach statistical significance (mean increase 2.81, 95% Cis 5.72 to −0.99, t=1.96, df=36, p= 0.058. For participants whose gold standard response did not

change, the total score increased by 0.980, which was not statistically significant (mean increase 0.980, 95% Cis −1.06 to 3.01, t=0.956, df=98, p=0.342) (Price et al., 2012).

3.5.4 Clinical Global Impression (CGI)

This is an assessment of the clinician's view of the patient's global functioning prior to and after initiating a treatment. It provides an overall clinician-determined summary measure that takes into account all available information, including a knowledge of the patient's history, psychosocial circumstances, symptoms, behaviour, and the impact of the symptoms on the patient's ability to function. The CGI comprises two parts; one item measures the severity of psychopathology (CGI-S) and the second measures change from the initiation of treatment (CGI-I). Each domain has a possible score of 1-7 (Guy et al., 1976). CGI ratings are positively correlated with self-reported and clinician-administered measures in patients with social anxiety (Zaider et al., 2003). The CGI-I was found to be highly correlated (r=0.71), with measures of change from Health of the Nation Outcomes Scales (HONOS), the Michigan Hand Outcomes Questionnaire (MHQ) and Depression Anxiety Stress Scales (DASS-2) (Berk et al., 2008). The limitations of this simple and short scale are poor distribution properties and a presumably restricted significance of change ratings has been recognised (Beneke et al., 1992).

3.5.5 Emotional Quality of the Relationship Scale (EQR)

This measures affection, emotional intimacy, communication and satisfaction with these areas of the relationship as a whole. It has 7 sub-domains and items are scored on a four-point ordinal scale ranging from 4 (very great) to 1 (very poor). Scores are summed resulting in a composite score that ranges from a minimum score of 7 to a maximum of 28. Higher scores indicate that the emotional quality of the relationship is stronger (Kreuter et al., 1996). Internal consistency of the EQR is High (α=0.85). The EQR is significantly ($p<0.01$) and moderately correlated with the: Sexual Behaviour Scale (r=0.45); Hospital Anxiety and Depression Scale (HADS) (r=-0.38) and the Quality of Life Visual Analog Scale (r=0.37). No cut-points or normative data have been established (Kreuter et al., 1996).

3.5.6 Sexual Activity and Satisfaction Scales (SAS)

This is a sub-scale of the EQRS which was developed by Kreuter at al., 1996 to investigate sexual activity and satisfaction for patients with spinal injury and their partners. The first item investigates the frequency of sexual activity, with or without intercourse, which is scored on the scale of 1-8; the second and third items investigate sexual satisfaction and satisfaction of the relationship as a whole, each is scored on the scale of 1-4. Higher scores indicate greater sexual activity and satisfaction. Internal consistency is high for the SAS scale (Cronbach's α=0.87). In patients with spinal injury, SAS was found to be correlated with, EQRS r=0.57. No cut-points or normative data have been established (Kreuter et al., 1996).

3.5.7 Multiplex Arrays Enzyme-linked immunosorbent assay for inflammatory markers

3.5.7.1 Sampling

To determine the potential influence of interleukins and tumour necrosis factor alpha, venous blood samples were collected from participants at baseline and after 6 weeks. Blood sampling was performed as per NHS procedure, observing sterile conditions, with infection control by either a nurse trained in phlebotomy or by a qualified medical practitioner. An 8-10ml sample of venous blood was collected by venepuncture into a vacutainer containing no preservative (red top).

3.5.7.2 Sample preparation

Blood samples were centrifuged at 1600 g (4000 RPM, setting 4) on a Capricorn 2000 bench centrifuge for 10 min. The plasma fraction created from the serum sample was then transferred using a Pasteur pipette to suitably labelled vial tubes. Serum samples are then placed in a ziplock bag and an airtight sealed container inside a lockable box for storage at -20^{o}C to be transferred to the -80^{o}C freezer for longer-term storage.

3.5.7.3 Quantification

The Luminex multi-analyte profiling (xMAP) technology from Luminex employs proprietary bead sets which are distinguishable under flow cytometry. Each bead set is coated with a specific capture antibody, and fluorescence or streptavidin-labelled detection antibodies bind to the specific cytokine-capture antibody complex on the bead set. Multiple cytokines in a biological liquid sample can thus be recognized and measured by the differences in both bead sets, with chromogenic or fluorogenic emissions detected using flow cytometric analysis.

We used the commercially available Proinflammatory Panel 1 (human) Kit, from V-PLEX, MESO SCALE DISCOVERY, Rockville, MD, USA, to measure, IL-1β; IL-2; IL-4; IL-6; IL-8; IL-10; IL-12p70; IL-13; TNF-α, and IFN-γ in the same sample.

The kit was reportedly validated following fit-for-purpose principles (Lee et al., 2006) and MSD design control procedures. V-PLEX assay components go through an extensive critical reagents program to ensure that the reagents are controlled and well characterised. Prior to the release of each V-PLEX panel, at least three independent kit lots are produced. Using results from multiple runs (typically greater than 50) and multiple operators, these lots were used to establish production specifications for sensitivity, specificity, accuracy, and precision. During validation, each individual assay is analytically validated as a single plex and is also independently evaluated as a multiplex component by running the full multiplex plate using only the single detection antibody for that assay. These results were compared with the results from the multiplex panel when using all detection antibodies. This demonstrates that each assay is specific and independent, allowing them to be multiplexed in any combination. The lot-specific certificate of analysis (COA), provided with the kit outlined the kit release specifications for sensitivity, specificity, accuracy, and precision. In general, assays in the single spot format yielded a lower overall signal compared to the 10-plex format. The spots on single-spot plates have a larger binding surface than those on multiplex plates, but the same amount of calibrator was used for each test; therefore, the bound calibrator was spread over a larger surface area reducing the average signal.

3.5.8 Enzyme-linked immunosorbent assay for hair cortisol

3.5.8.1 Sampling

To determine the potential influence of endocrine factors, scalp hair samples (3 cm in length) were collected from study participants at baseline and after 6 weeks. Hair strands were carefully cut with fine scissors as close as possible to the scalp from a posterior vertex position. The number of strands obtained differed in accordance with the subject's permission to cut more or less hair.

3.5.8.2 Sample preparation

Each hair strand was repeatedly washed using isopropanol, dried for 6 hours, and thereafter analysed based on non-pulverized hair. Cortisol was extracted by incubating each specimen for 18 hours in 1800 µL methanol at room temperature for cortisol extraction. 1600 µL of the resulting suspensions were purged with nitrogen at 50 °C and a pressure of 0.1 bar for at least 40 min. Samples were spun in a centrifuge at 10,000 rpm for 2 min and 1 mL of the clear supernatant was transferred into a new 2 mL tube. The alcohol was evaporated at 65 ◦C under a constant stream of nitrogen until the samples were completely dried (duration: approximately 20 min). Thereafter, the supernatants were re-suspended in 225 µL of distilled water and 50 microliters were submitted to liquid-chromatography coupled to tandem-mass spectrometry (LC-MS/MS). The lower limits of quantification of this assay method were below 0.1 pg cortisol per mg hair. The median coefficient of variation (CV) of all replicates was 4.9% (interquartile range: 1.3–13.9%) (Gao et al., 2013).

3.5.8.3 Quantification

Following milling of hair segments, two 50 mg aliquots of powdered hair from a single hair segment were processed in parallel. Twenty microliters were removed from the vial and used for cortisol determination with a commercially available immunoassay with chemiluminescence detection (CLIA, IBL-Hamburg, Germany). An unknown amount of antigen present in the sample and a fixed amount of enzyme-labelled antigen compete for the binding sites of the antibodies coated onto the wells. After incubation the wells are washed to stop the competition reaction. After the substrate

reaction the intensity of the developed colour is inversely proportional to the amount of the antigen in the sample. Results of samples can be determined directly using the standard curve.

3.5.9 Enzyme-linked immunosorbent assay for prolactin

3.5.9.1 Sampling

To determine the potential influence of prolactin, venous blood samples were collected from participants at baseline and after 6 weeks. Blood sampling was performed as per NHS procedure, observing sterile conditions with infection control by a nurse trained in first aid or phlebotomy or by a qualified medical practitioner. An 8-10ml sample of venous blood was collected by venepuncture into a serum separator tube (SST) vacutainer (gold top, with gel as a separator).

3.5.9.2 Sample preparation

Blood samples were sent to the University Hospital of Southampton pathology laboratory for analysis. The sample was obtained from blood cells and serum supernatant after centrifugation (1750 g for 10 minutes).

3.5.9.3 Quantification

A human prolactin standard is provided to generate a standard curve for the ELISA assay. We used the commercially available kit from R&D system (Minneapolis, MN, USA). The kit has a reported high sensitivity and excellent specificity for detection of human Prolactin. No significant cross-reactivity or interference between human Prolactin and analogues was observed. The kit manufacturer reported a standard curve range of 15.6-1000 pg/ml, sensitivity of 12.5 pg/ml, inter-assay coefficients of variability (CV%) of <10% and Intra Assay CV of <8%.

Standards or diluted samples (10% bovine serum albumin (BSA)); were pipetted into a clear microtiter plate coated with a monoclonal antibody to capture the prolactin present. After a 2 hours' incubation, the plate is washed (with 25X concentrated solution of buffered surfactant with preservative), and a peroxidase-conjugated prolactin polyclonal antibody is added. The plate is again incubated for 2 hours and washed (4 times). 200 µL of Anti-G substrate (stabilized

tetramethylbenzidine) is then added to the plate, which reacts with the bound prolactin antibody conjugate. After a third, 30 min, incubation, the reaction is stopped by adding 50 µL of the stop solution (2N sulphuric acid), and the intensity of the generated colour is detected in a microtiter plate reader capable of measuring at 450 nm.

3.6 Data analysis

Patients undergone investigations as per protocol, psychometric tests; blood sampling for prolactin levels, inflammatory markers and hair sampling for cortisol concentration (Table 3.1). Some participants preferred not to provide blood sampling, but collaborated on other tests.

Data was analysed using IBM SPSS® Statistics 25.0. To determine normality of distribution, I used the descriptive normality plot tool which tests skewness and kurtosis to calculate z-values. Z-values between -1.96 and +1.96 indicated some skewness and kurtosis but overall normality of distribution. I used canonical correlation analysis to identify and measure the associations among two sets of variables. I used multiple stepwise logistic partial regression analysis to adjust for possible confounding factors (e.g. age, gender).

Table 3.1 **Data collection matrix**

	First contact	Baseline interview (Week 0)	Follow up 1 (Week 6)	Follow up 2 (Week 12)
Provide information and forms	**√**			
Obtain consent		**√**		
Mini International Neuropsychiatric Interview (MINI) and treatment history		**√**		
Hair sample (cortisol)		**√**	**√**	**√**
Blood sample (prolactin level)		**√**	**√**	**√**
Blood sample (inflammatory markers)		**√**	**√**	**√**
Arizona Sexual Experiences Scale (ASEX)		**√**	**√**	**√**
Warwick- Edinburgh Mental Well-Being Scale (WEMWBS)		**√**	**√**	**√**
Hospital Anxiety and Depression Scale (HADS-A, HADS-D)		**√**	**√**	**√**
Oxford Questionnaire of Emotional Side Effects of Antidepressants (OQUESA)		**√**	**√**	**√**
Clinical Global Impression of Illness Severity (CGI)		**√**	**√**	**√**
Emotional Quality of the Relationship Scale (EQRS)		**√**	**√**	**√**
Compliance with treatment check (direct questioning)		**√**	**√**	**√**

Chapter 4 Results: Baseline

4.1 Recruitment and testing

A total of 170 referrals were received from primary care or secondary care mental health services, of patients who expressed an interest in being contacted about the study. Of these, 135 patients dropped out following the initial explanation of the study (53 males [39%], 82 females [61%]: mean age,34 years). Reasons for dropping out were as follows: feeling too unwell to take part in the study (22% [too anxious 21%, too depressed 1%]); concerns about time commitments (15%); the lack of financial compensation/reward (14%); not feeling comfortable talking about sexual life (10%); and no reason given (39%). A sub-group of 35 participants consented to take part and completed the Baseline assessment. Two patients dropped out before the Week 6 review, and six patients dropped out before the Week 12 review. Eighteen patients underwent open-label augmentation with celecoxib, and nine patients completed twelve weeks of 'treatment as usual'.

4.2 Participants' demographic and clinical characteristics

Of the 35 participants who consented to take part in the study, 12 (35%) were males and 23 (65%) were females. The age distribution is shown in Table 4.1. All participants had English as their first language: 29 were white British, four Asian British, and one black British. Twenty participants (57%) were professionally active at the time of enrolment; and 25 participants (71%) reported being in a stable relationship at the time of enrolment.

Nineteen participants (54.3%) were within the range of healthy body mass index (BMI) (18.5-24.9) but 13 (37.1%) were overweight and 3 (8.6%) were underweight.

Table 4.1 **Age (years) distribution at Week 0 (Baseline)**

		Frequency	Percent
Age group	18-24	18	51.4
	25-39	7	20.0
	40-49	6	17.1
	≥50	4	11.4
	Total	35	100.0

Interview with the MINI generated at least one DSM-5 diagnosis in each participant. Thirteen participants (37.1%) met diagnostic criteria for generalised anxiety disorder (GAD), 8 (22.9%) for panic disorder with agoraphobia, 7 (20%) for social phobia, 4 (11.4%) for obsessive compulsive disorder (OCD), and 3 (8.6%) for panic disorder.

4.3 Psychometric properties at Baseline

The mean scores and standard error of the means (SEM) on rating scales at Baseline were as follows: WEMWBS 27 (SEM 1.81); HADS-A 15.42 (SEM 0.88); HADS-D 13 (SEM 0.82); EQRS 18.4 (SEM 1.04); SAS 7.88 (SEM 0.58); ASEX 17.4 (SEM 1.21); CGI-S 4.56 (SEM 0.22); OQUESA-GR 15.5 (SEM 1.17); OQUESA-RP 22.18 (SEM 0.75); OQUESA-ED 15.09 (SEM 3.17) and OQUESA-NC 18 (SEM 1.27) (Table 4.2).

Table 4.2 **Rating scale and questionnaire scores at Week 0 (Baseline)**

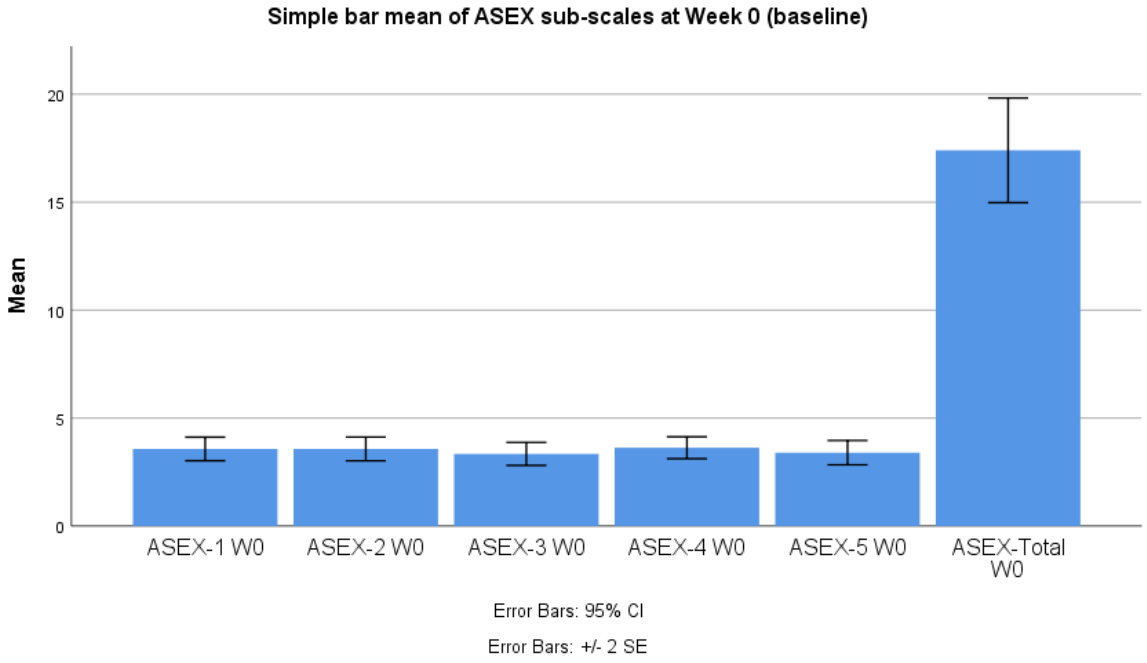
	Mean	N	Std. Deviation	Std. Error of Mean
WEMWBS-total W0	27.00	12	6.27	1.81
HADS-D W0	13.00	12	2.83	0.82
HADS-A W0	15.42	12	3.06	0.88
EQRS-Total W0	18.14	29	5.63	1.04
SAS-Total W0	7.88	33	3.33	0.58
ASEX-Total W0	17.40	35	7.17	1.21
CGI-S W0	4.56	34	1.31	0.22
OQUESA-GR W0	15.55	11	3.88	1.17
OQUESA-RP W0	22.18	11	2.48	0.750
OQUESA-ED W0	15.09	11	10.51	3.17
OQUESA-NC W0	18.00	11	4.22	1.27

4.4 Sexual function at Baseline

The ASEX total mean score at Baseline was 17.40 (SEM 1.21). ASEX item mean scores were as follows: item 1 (sex drive), 3.57 (SEM 0.27); item 2 (arousal), 3.57 (SEM 0.28); item 3 (erection/vaginal lubrication), 3.34 (SEM 0.27); item 4 (ability to reach orgasm), 3.63 (SEM 0.25) and item 5 (orgasm satisfaction), 3.40 (SEM 0.28) (Figure 4.1).

Categorisation of sexual dysfunction in the study sample using ASEX criteria identified 20 participants (57.1%) with sexual dysfunction: 5 (25%) males and 15 (75%) females. The 15 participants who were not classified as having sexual dysfunction were more balanced in gender (7 males (46.7%), 8 females (53.3%). Participants who were classified as having sexual dysfunction at Baseline had the following primary diagnoses: GAD (7 participants, 35%), panic disorder with agoraphobia (5 participants, 25%), social phobia (3 participants, 15%), OCD (3 participants, 15%), and panic disorder (2 participants, 10%).

Figure 4.1 **Mean ASEX scores at Week 0 (Baseline)**



4.5 Plasma prolactin levels

Seven participants provided blood samples at Baseline for analysis of plasma prolactin levels by ELISA. All values were found to be within the normal concentration ranges of 57.5-276 mu/L for males and 57.5-561 mu/L for females. The plasma prolactin concentrations for the one male tested at Week 0 was 85 mu/L and the mean prolactin concentration was 383 mu/L (SEM 62.992) for the six female participants (Table 4.3).

Table 4.3 **Week 0 (Baseline) prolactin levels (mu/L)**

Gender	Mean	N	Std. Deviation	Std. Error of Mean
Male	85.00	1	.	.
Female	383.00	6	154.30	62.99
Total	340.43	7	180.35	68.17

4.6 Inflammatory markers

A broad range of inflammatory cytokines (IFN-γ, IL-1β, IL-10, IL-12p70, IL-13, IL-2, IL-4, IL-6, IL-8, TNF-α) was analysed from the plasma of six participants by multiplex ELISA kit (V-PLEX proinflammatory panel 1). At Baseline, mean plasma cytokines concentrations were found to be within the normal concentration ranges (Table 4.4), apart from a low mean concentration of IL-12p70 (0.11 pg/mL, SEM 0.04 (normal range 0.26-0.38 pg/mL) and an elevated mean concentration of TNF-α (2.37 pg/mL, SEM 0.43) (normal range 0.10-1.75 pg/mL).

Table 4.4 **Cytokines normal concentration range (pg/mL)**

	Range	Median
TNF-α	0.10-1.75	1.02
IFN-γ	0.64-14.4	3.77
IL-1β	0.11-24.3	0.16
IL-10	0.06-3.08	0.20
IL-12p70	0.26-0.38	0.29
IL-13	0.60-2.78	1.65
IL-2	0.22-2.68	0.52
IL-4	NA	NA
IL-6	0.16-27.2	0.47
IL-8	1.48-1720	9.61

In patients with panic disorder, there were low mean concentrations when compared to normal concentration ranges, for IFN-γ (0.46 pg/mL), IL-1β (0.00 pg/mL) and IL-6 (0.11 pg/mL). Patients with panic disorder with agoraphobia had a low mean IL-13 concentration (0.223 pg/mL); a low mean IL-2 concentration (0.15 pg/mL) and an elevated mean TNF-α concentration (2.30 pg/mL), compared to normal concentration ranges. In patients with GAD, there were low mean concentrations, compared to normal concentration ranges, for IL-1β (0.11 pg/mL); IL-12p70 (0.00 pg/mL), IL-13 (0.00 pg/mL) and IL-2 (0.15 pg/mL), but a higher level of TNF-α (3.96 pg/mL) when compared to normal concentration ranges. Patients with social phobia had low mean IL-2 concentration (0.11 pg/mL) but an elevated mean TNF-α concentration (2.11 pg/mL), compared to normal concentration ranges (Table 4.5).

Table 4.5 **Cytokine mean concentration per diagnosis at Week 0 (Baseline) (pg/mL)**

Diagnosis		IFN-γ	IL-1β	IL-10	IL-12p70	IL-13	IL-2	IL-4	IL-6	IL-8	TNF-α
Panic disorder	Mean	.46	.00	.06	.07	.26	.076	.000	.11	1.91	1.46
	N	1	1	1	1	1	1	1	1	1	1
	SD	.	.	.	.	.	.	.	.	.	.
	SEM	.	.	.	.	.	.	.	.	.	.
GAD	Mean	3.74	.01	.51	.00	.00	.15	.00	.53	5.86	3.96
	N	1	1	1	1	1	1	1	1	1	1
	SD	.	.	.	.	.	.	.	.	.	.
	SEM	.	.	.	.	.	.	.	.	.	.
Panic disorder with agoraphobia	Mean	4.06	.60	1.27	.09	.23	.15	.036	.36	5.85	2.30
	N	2	2	2	2	2	2	2	2	2	2
	SD	4.81	.85	1.61	.00	.11	.104	.02	.15	6.00	1.42
	SEM	3.40	.60	1.14	.00	.08	.07	.02	.10	4.24	1.00
Social phobia	Mean	1.34	.02	.22	.20	.26	.11	.00	.32	1.66	2.11
	N	2	2	2	2	2	2	2	2	2	2
	SD	.42	.03	.01	.09	.36	.01	.00	.09	1.87	.015
	SEM	.29	.02	.005	.07	.26	.01	.00	.07	1.32	.01
Total	Mean	2.50	.21	.59	.11	.20	.12	.01	.33	3.80	2.37
	N	6	6	6	6	6	6	6	6	6	6
	SD	2.70	.49	.90	.0	.20	.06	.02	.16	3.60	1.05
	SEM	1.10	.20	.37	.04	.08	.02	.01	.06	1.47	.43

* Highlight, grey: lower than manufacturer's specified range of normal concentration. Red higher than manufacturer's specified range of normal concentration.

Participants who were found to have sexual dysfunction and provided blood samples at Baseline (n=5) had low mean concentrations of, IL-1β (0.11 pg/mL), IL-12p70 (0.11 pg/mL), IL-13 (0.18 pg/mL) and IL-2 (0.10 pg/mL) but an elevated mean concentration of TNF-α (2.19 pg/mL), when compared to normal concentration ranges. The Participant who were found not to have sexual dysfunction and provided blood samples at Baseline (n=1) had low mean concentrations of IL-12p70 (0.10 pg/mL) and IL-13 (0.31 pg/mL) but an elevated concentration of TNF-α (3.30 pg/mL), when compared to normal concentration ranges (Table 4.6).

Table 4.6 **Cytokines mean concentration at Baseline by ASEX caseness (pg/mL)**

		IFN-γ	IL-1β	IL-10	IL-12p70	IL-13	IL-2	IL-4	IL-6	IL-8	TNF-α
With sexual dysfunction	Mean	1.51	.011*	.230	.11*	.18*	.10*	.012	.35	2.54	2.19*
	N	5	5	5	5	5	5	5	5	5	5
	SD	1.33	.021	.169	.101	.214	.033	.023	.171	2.08	1.06
	SEM	.59	.01	.08	.045	.10	.015	.010	.08	.93	.47
Without sexual	Mean	7.46	1.21	2.41	.10*	.31*	.22	.019	.25	10.1	3.30*
	N	1	1	1	1	1	1	1	1	1	1
	SD	.	.	.	.	.	.	.	.	.	.
	SEM	.	.	.	.	.	.	.	.	.	.
Total	Mean	2.50	.21	.59	.11	.20	.12	.013	.33	3.80	2.374
	N	6	6	6	6	6	6	6	6	6	6
	SD	2.70	.49	.90	.09	.20	.06	.02	.16	3.60	1.05
	SEM	1.10	.20	.37	.037	.08	.02	.01	.06	1.47	.43

* Highlight, grey: lower than manufacturer's specified range of normal concentration. Red higher than manufacturer's specified range of normal concentration.

4.7 Hair cortisol concentration

Hair cortisol analyses were performed by chemiluminescence immunoassay on samples purified by LC-MS/MS from 11 participants who provided hair samples at Baseline. Hair cortisol concentration (HCC) at Baseline had a mean concentration of 26.66 pg/mg and a median of 6.14 pg/mg (Table 4.7). Mean HCC for male participants and female participants were 30.74 pg/mg [SEM 14.79] and 24.19 pg/mg [SEM 19.963], respectively. The mean HCC was found to be higher than the normal

range (1-30 pg/mg), in patients with panic disorder with agoraphobia (n=2) (72.37 pg/mg, SEM 71.48). Mean HCC in participants with other diagnoses were within the normal range: GAD (n=3), (25.32 pg/mg, SEM 17.30); social phobia (n=5) (14.07 pg/mg, SEM 9.51); panic disorder, (n=1) (1.24 pg/mg). Participants with sexual dysfunction at Baseline were found to have an elevated mean HCC of 52.22 pg/mg (SEM 32.36), whereas participants without sexual dysfunction at Baseline had a mean value within the normal range, a mean HCC of 11.91 pg/mg (SEM 8.08).

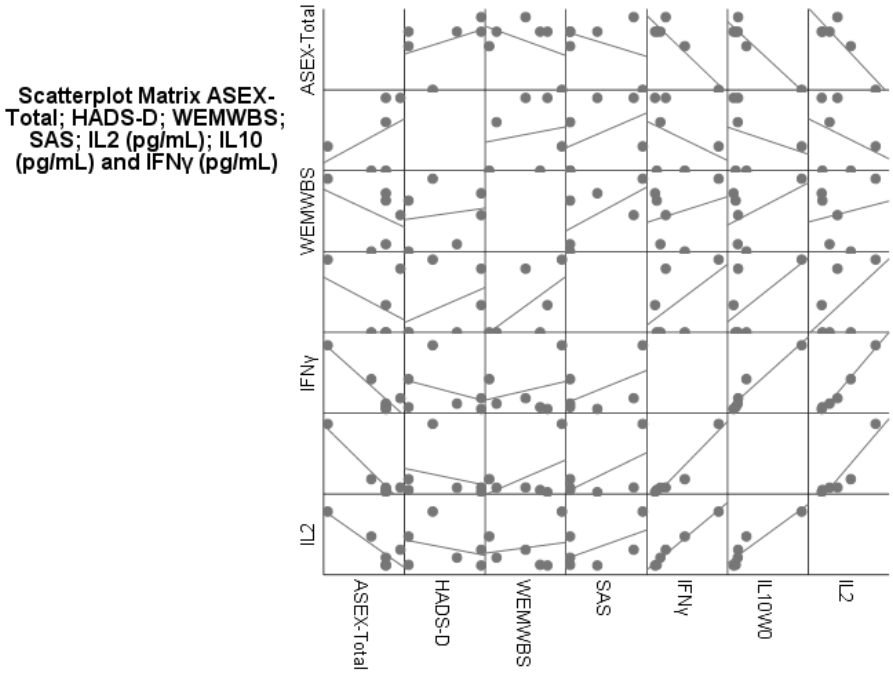
Table 4.7 **HCC at Baseline (Week 0) pg/mg**

N	11
Range	142.96
Minimum	0.89
Maximum	143.85
Median	6.14
Mean	26.66
SEM	13.3
Std. Deviation	44.099

4.8 Correlations at Baseline

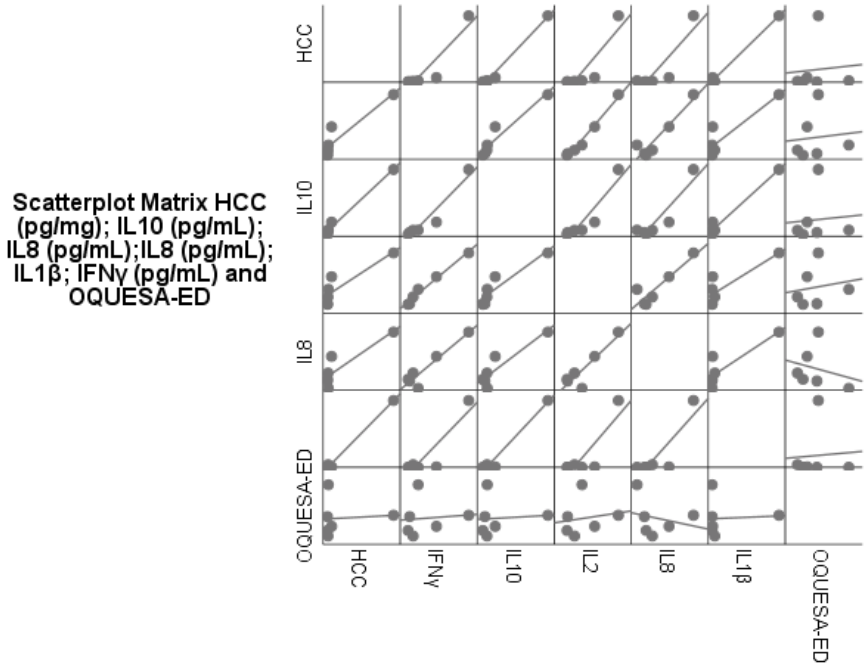
A list of Baseline mean values and correlations are listed in Appendix B.2. Canonical multivariate correlation analysis of multiple-X multiple-Y correlation found a significant correlation between ASEX total mean score and CGI-S mean score (p=0.048), HADS-D mean score (p=0.01) and a significant inverse correlation with WEMWBS mean score (p=0.00), SAS mean score (p=0.01), IFN-γ mean concentration (pg/mL) (p=0.00), IL-10 mean concentration (pg/mL) (p=0.00) and IL-2 mean concentration (pg/mL) (p=0.02) (Figure 4.2). These correlations remained significant after adjusting for age, diagnosis and gender, using logistic regression partial correlation. After further adjustment for EQRS and SAS, ASEX total mean score had significant correlations with HADS-D mean score (p=0.00) and with OQUESA-ED (p=0.00). After further adjustment for HADS-D, no statically significant correlations between ASEX and any of the tested parameters were found.

Figure 4.2 **Correlations at Week 0 (Baseline).** Canonical multivariate correlation analysis at Baseline.



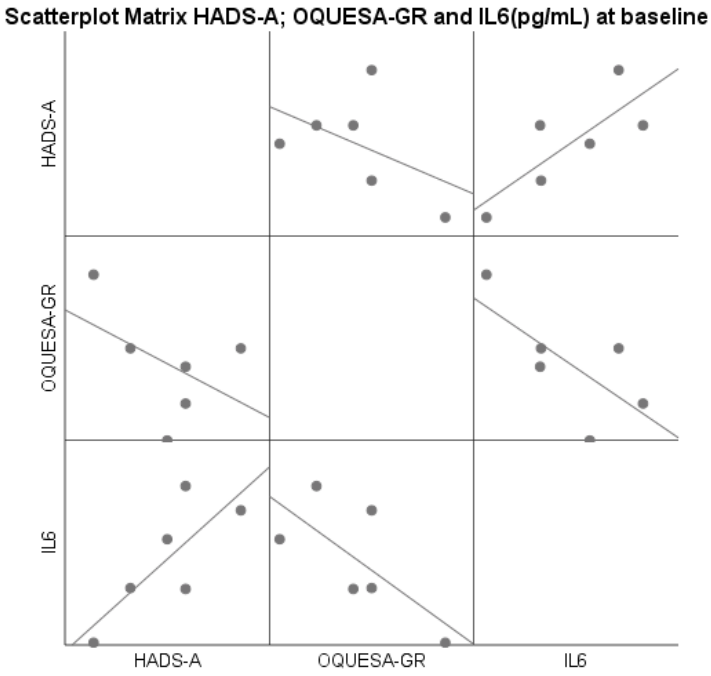
HCC levels (pg/mL) in the six participants were significantly correlated with plasma concentrations of IFN-γ (p=0.01), IL-10 (p=0.00); IL-2 (p=0.02) and IL-8 (p=0.02). After adjusting for age, diagnosis and gender, using logistic regression partial correlation, the correlation remained significant between HCC (pg/mg) and IL-10 mean concentration (pg/mL) (p=0.00), and there was a significant correlation between mean HCC (pg/mg) and IL-1β mean concentration (pg/mL) (p=0.00). After further adjusting for EQRS and SAS, the mean HCC (pg/mg) was correlated with OQUESA-ED (p=0.01) (Figure 4.3). However, after further adjustment for HADS-D, no significant correlations between mean HCC (pg/mg) and other parameters were found.

Figure 4.3 **Mean HCC correlations at Week 0 (Baseline)**



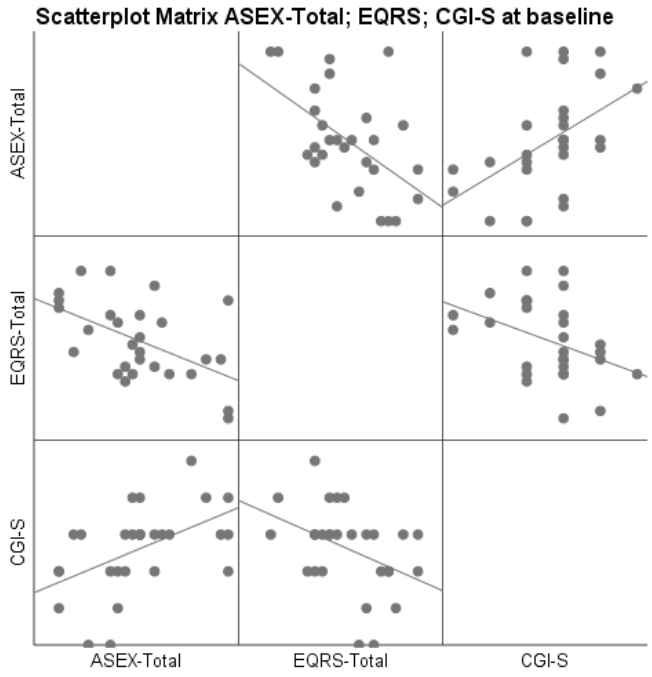
A significant correlation between HADS-A mean score and OQUESA-GR at Baseline was found (p= 0.02), which persisted after adjusting for age; diagnosis and gender (p=0.03), using logistic regression partial correlation, with an emerging significant correlation with IL-6 mean concentration (pg/mL) (p=0.00) (Figure 4.4). After further adjustment for EQRS and SAS, no significant correlations between HADS-A and any of the tested parameters were found.

Figure 4.4 **Mean HADS-A score correlations at Week 0 (Baseline)**



A significant correlation between CGI-S mean score and ASEX-total mean score (p=0.048) was found. A significant inverse correlation between CGI-S mean score and EQRS mean score (p=0.03) was also found (Figure 4.5). The correlation with ASEX mean score persisted (p=0.03) after adjusting for age and diagnosis, using logistic regression partial correlation, with an emerging significant correlation between CGI-S and prolactin mean concentration (mu/L) (p=0.00) and EQRS mean score (p=0.03). After further adjustment for EQRS and SAS, no significant correlations between CGI-S and any of the tested parameters were found.

Figure 4.5 **Mean CGI-S correlations at Week 0 (Baseline)**



4.9 Interpretation

These findings suggest that in patients with a diagnosis of anxiety disorders at Baseline, there was a significant correlation between sexual dysfunction (ASEX scores) and depressive symptoms (HADS-D) and with emotional detachment (OQUESA-ED). This continued to be significant after adjusting for age, sex, and quality of relationship. The findings suggest no significant correlation between anxiety symptoms (HADS-A) and ASEX scores.

Patients with a diagnosis of panic disorder with agoraphobia at Baseline were found to have higher than normal HCC, whereas patients with GAD; social phobia and panic disorder were found to have normal HCC. Patients with sexual dysfunction at Baseline, were found to have elevated HCC at Baseline.

Patient with a diagnosis of any anxiety disorder at Baseline had low IL-12p70 and elevated TNF-α concentrations. Analysis by diagnosis found, low IL-12p70 in GAD, high TNF-α in panic disorder; GAD and social phobia, low IFN-γ in panic disorder, low IL-1β in GAD, low IL-6 in panic disorder, low IL-13 in GAD, and low IL-2 in GAD and social phobia. Patients who were found to have sexual dysfunction at Baseline had low IL-1β, IL-2p70, IL-13 and IL-2 but an elevated TNF-α. Participants who were found not to have sexual dysfunction at Baseline had low IL-2p70 and IL-13 but an elevated concentration of TNF-α. A significant correlation between HADS-A and IL-6 was found after adjusting for age, diagnosis and gender.

Chapter 5 Results- effects of treatment

5.1 Antidepressant treatment

Participants received six weeks of 'treatment as usual', from their usual clinician. At Week 6, nineteen patients (57.7%) had undergone treatment with an SSRI; six patients (18.3%) with an SNRI; three patients with a NASSA (9%); two patients (6%) with CBT; and a single patient with a β-Blocker (3%): two patients (6%) had not undergone any treatment by the Week 6 review.

5.2 Rating scale scores at Week 6

The mean psychometric scores at Week 6 were as follows: WEMWBS 33.30 (SEM 1.75); HADS-A 13.70 (SEM 0.73); HADS-D 10.82 (SEM 0.68); EQRS 20.08 (SEM 0.93); SAS 7.77 (SEM 0.59); ASEX 20.18 (SEM 0.96); CGI-S 4.27 (SEM 0.23); CGI-I 2.69 (SEM 0.16); OQUESA-GR 16.30 (SEM 0.75); OQUESA-RP 18.97 (SEM 0.95); OQUESA-ED 11.06 (SEM 0.87); OQUESA-NC 16.10 (SEM 0.86); and OQUESA-AC 14.48 (SEM 1.25).

The psychometric scores by antidepressant treatment sub-group are shown in Figure 5.1 and Table 5.1. Mean scores for the SSRI sub-group were as follows: WEMWBS 35.3 (SEM 2.54); HADS-A 12.95 (SEM 1.01); HADS-D 10.10 (SEM 0.93); EQRS 19.94 (SEM 1.29); SAS 7.74 (SEM 0.66); ASEX 20.15 (SEM 1.33); CGI-S 4.40 (SEM 0.34); CGI-I 2.42, (SEM 0.22); OQUESA-GR 16.67 (SEM 0.91); OQUESA-RP 18.26 (SEM1.37); OQUESA-ED 10.16 (SEM 1.07); OQUESA-NC 15.32 (SEM 1.09); and OQUESA-AC 14.47 (SEM 1.76).

Figure 5.1 **Mean psychometric scores at Week 6**

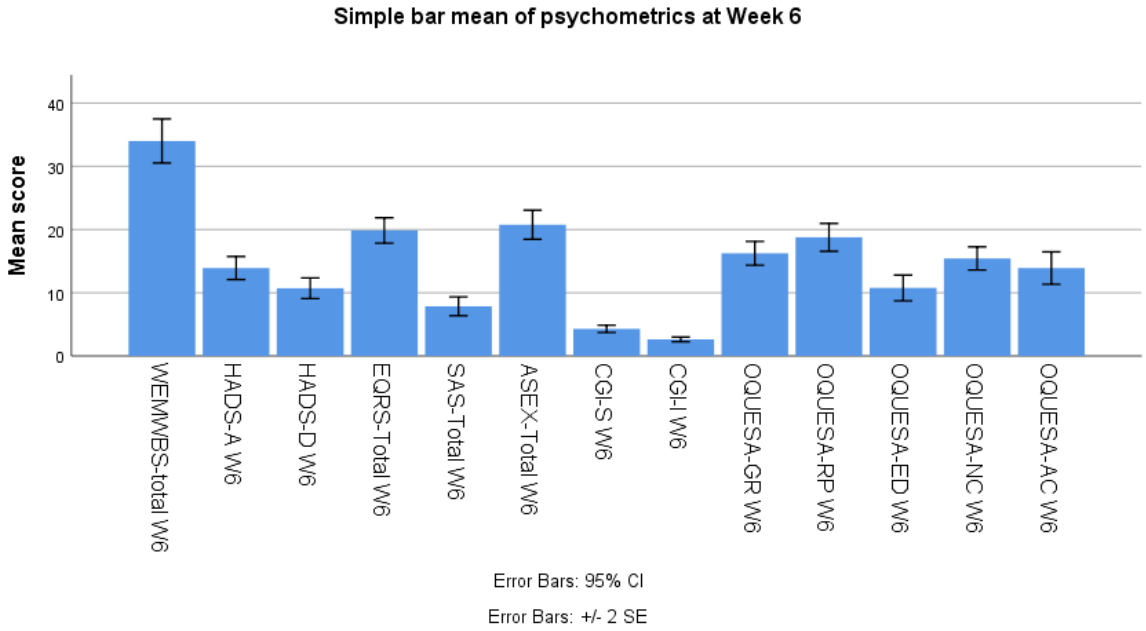
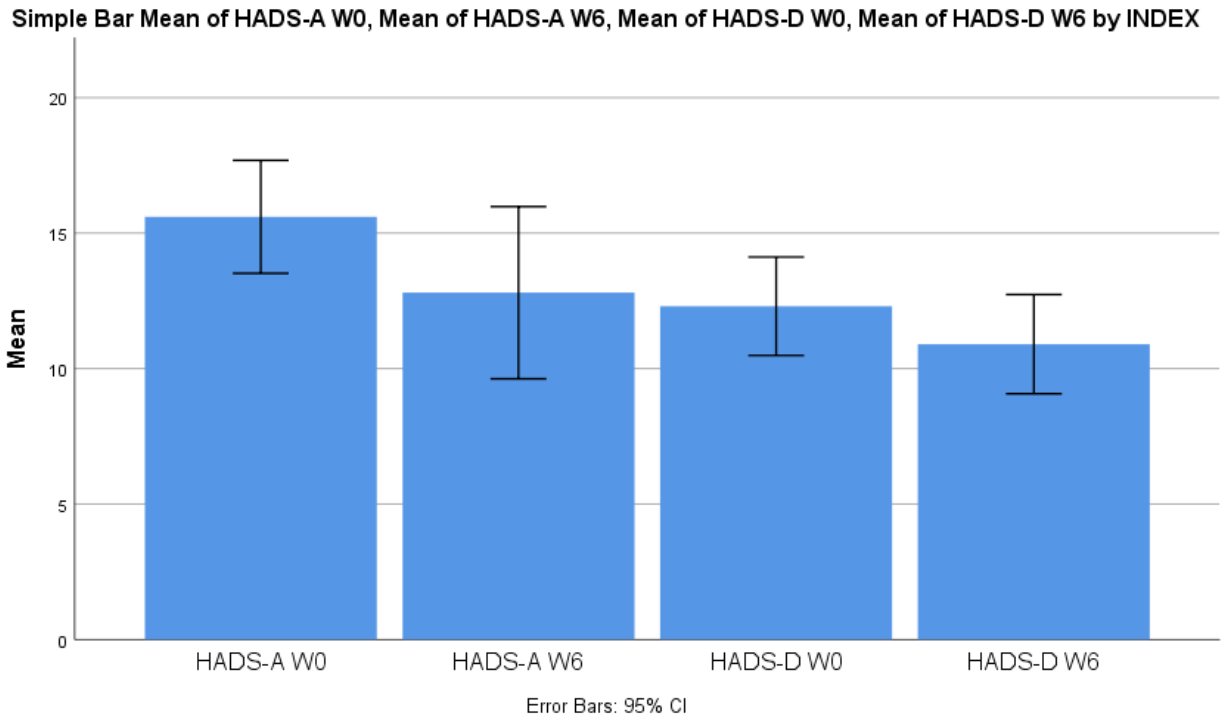


Table 5.1 **Psychometric findings at Week 6**

Week 6 treatment		WEMWBS-total W6	HADS-A W6	HADS-D W6	EQRS-Total W6	SAS-Total W6	ASEX-Total W6	CGI-S W6	CGI-I W6	OQUESA-GR W6	OQUESA-RP W6	OQUESA-ED W6	OQUESA-NC W6	OQUESA-AC W6
No treatment	Mean	30.00	13.00	12.00	15.00	9.00	13.00	4.00	3.00					
	N	1	1	1	1	1	1	1	1					
	SD	.	.	.	.	.	.	.	.					
	SEM	.	.	.	.	.	.	.	.					
SSRI	Mean	35.30	12.95	10.10	19.94	7.74	20.15	4.40	2.42	16.67	18.26	10.16	15.32	14.74
	N	20	20	20	17	19	20	20	19	18	19	19	19	19
	SD	11.38	4.51	4.17	5.31	2.86	5.94	1.50	.96	3.85	5.97	4.67	4.76	7.69
	SEM	2.54	1.01	.93	1.29	.66	1.33	.34	.22	.91	1.37	1.07	1.09	1.76
SNRI	Mean	28.33	15.67	12.67	21.33	8.50	20.67	4.33	3.17	15.17	20.17	11.83	18.00	11.83
	N	6	6	6	3	4	6	6	6	6	6	6	6	6
	SD	7.97	4.08	4.13	3.51	3.87	2.07	1.03	.98	6.55	3.54	5.91	4.82	4.02
	SEM	3.25	1.67	1.69	2.03	1.94	.84	.42	.40	2.68	1.45	2.41	1.97	1.64
NASSA	Mean	29.00	16.67	11.67	20.50	8.00	21.00	4.33	2.67	17.00	22.00	12.67	20.67	19.00
	N	3	3	3	2	3	3	3	3	3	3	3	3	3
	SD	2.65	2.52	2.52	3.54	6.24	6.08	1.15	.58	1.73	2.00	5.69	4.04	1.73
	SEM	1.53	1.45	1.45	2.50	3.61	3.51	.67	.33	1.00	1.15	3.28	2.33	1.00
β-Blocker	Mean	41.00	11.00	8.00	18.00	3.00	30.00	4.00	3.00	17.00	12.00	14.00	12.00	12.00
	N	1	1	1	1	1	1	1	1	1	1	1	1	1
	SD	.	.	.	.	.	.	.	.	.	.	.	.	.
	SEM	.	.	.	.	.	.	.	.	.	.	.	.	.
CBT	Mean	32.50	12.50	12.00	22.50	8.00	16.50	3.00	3.50	15.00	21.00	13.50	13.00	
	N	2	2	2	2	2	2	2	2	2	2	2	2	
	SD	10.61	3.54	4.24	4.95	2.83	4.95	.00	.71	.00	4.24	4.95	.000	
	SEM	7.500	2.50	3.00	3.50	2.00	3.50	.00	.50	.000	3.00	3.50	.000	
Total	Mean	33.30	13.70	10.82	20.08	7.77	20.18	4.27	2.69	16.30	18.97	11.06	16.10	14.48
	N	33	33	33	26	30	33	33	32	30	31	31	31	29
	SD	10.09	4.21	3.92	4.73	3.24	5.50	1.31	.93	4.10	5.27	4.84	4.79	6.71
	SEM	1.76	.73	.68	.93	.59	.96	.23	.16	.75	.95	.87	.86	1.25

The mean scores of HADS-A AND HADS-D decreased from Baseline (week 0) to Week 6 (Figure 5.2). Paired sample t test found non-statistically significant changes in mean psychometric scores for anxiety symptoms (HADS-A) (p=0.069) depression (HADS-D) (p=0.338).

Figure 5.2 **Changes in HADS mean scores from Baseline (Week 0) to Week**



5.3 Sexual function

At Week 6, 75.1% of the participants were found to have sexual dysfunction (as defined by ASEX criteria), compared to 57.1% at Week 0 (Baseline). Reassessment at Week 6 indicated the presence of ASEX-defined sexual dysfunction in 85% who had undergone treatment with an SSRI; 100% with an SNRI; 67% with a NASSA; 100% with β-Blockers; and 50% with CBT. ASEX findings at Week 6 are shown in Table 5.2.

The mean ASEX total score at Week 6 was 20.18 (SEM 0.96). ASEX sub-item scores were as follows: Item 1 (sex drive) 4.52 (SEM 0.22); Item 2 (arousal) 3.94 (SEM 0.22); Item 3, (erection/vaginal lubrication) 3.45 (SEM 0.27); Item 4 (ability to reach orgasm) 4.42 (SEM 0.22) and Item 5 (orgasm satisfaction) 3.97 (SEM 0.28).

Table 5.2 **ASEX scores at Week 6**

Week6 treatment		ASEX-1 W6	ASEX-2 W6	ASEX-3 W6	ASEX-4 W6	ASEX-5 W6	ASEX-Total W6
No treatment	Mean	3.00	3.00	1.00	3.00	3.00	13.00
	N	1	1	1	1	1	1
	SD	.	.	.	.	.	.
	SEM	.	.	.	.	.	.
SSRI	Mean	4.65	3.95	3.35	4.30	3.90	20.15
	N	20	20	20	20	20	20
	SD	1.27	1.28	1.56	1.32	1.71	5.94
	SEM	.28	.28	.35	.30	.38	1.33
SNRI	Mean	4.50	3.83	3.50	5.17	4.33	20.67
	N	6	6	6	6	6	6
	SD	1.05	1.17	1.38	.75	1.63	2.07
	SEM	.43	.48	.56	.31	.67	.84
NASSA	Mean	5.00	4.33	4.00	4.33	3.33	21.00
	N	3	3	3	3	3	3
	SD	1.00	1.15	1.73	1.15	1.15	6.08
	SEM	.58	.67	1.00	.67	.67	3.51
β-Blocker	Mean	6.00	6.00	6.00	6.00	6.00	30.00
	N	1	1	1	1	1	1
	SD	.	.	.	.	.	.
	SEM	.	.	.	.	.	.
CBT	Mean	2.50	3.00	3.50	3.50	4.00	16.50
	N	2	2	2	2	2	2
	SD	.71	1.41	.71	.71	1.41	4.95
	SEM	.50	1.00	.50	.50	1.00	3.50
Total	Mean	4.52	3.94	3.45	4.42	3.97	20.18
	N	33	33	33	33	33	33
	SD	1.28	1.25	1.54	1.25	1.59	5.50
	SEM	.22	.22	.27	.22	.28	.96

5.4 Change in ASEX from Week 0 (Baseline) to Week 6

ASEX mean scores increased from Week 0 (Baseline) to Week 6 (Table 5.3), with a change in ASEX 3.15 (SEM 1.22, p=0.01).

Table 5.3 **ASEX paired samples statistics for Week 0 (Baseline) and Week 6**

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	ASEX-Total W0	17.03	33	7.01	1.23
	ASEX-Total W6	20.18	33	5.53	.96
Pair 2	ASEX-1 W0	3.45	33	1.58	.28
	ASEX-1 W6	4.52	33	1.28	.22
Pair 3	ASEX-2 W0	3.48	33	1.62	.28
	ASEX-2 W6	3.94	33	1.25	.22
Pair 4	ASEX-3 W0	3.27	33	1.59	.28
	ASEX-3 W6	3.45	33	1.54	.27
Pair 5	ASEX-4 W0	3.61	33	1.46	.25
	ASEX-4 W6	4.42	33	1.25	.22
Pair 6	ASEX-5 W0	3.33	33	1.65	.29
	ASEX-5 W6	3.97	33	1.51	.28

Some ASEX item scores changed significantly from Week 0 (Baseline) to Week 6: Item 1 (sexual drive) 1.061 (SEM 0.298, p=0.001) and Item 4 (ability to reach orgasm) 0.82 (SEM 0.28, p=0.01). The changes in other items were non-significant: Item 2 (arousal) 0.45 (SEM 0.26, p=0.10); Item 3 (erection/vaginal lubrication) 0.18 (SEM 0.25, p=0.47); Item 5 (orgasm satisfaction) 0.64 (SEM 0.34, p=0.07) (Table 5.4).

Further analysis by antidepressant treatment found an increase in ASEX-total score by 2.80 (p=0.098) in the SSRI sub-group and significant increases in mean scores for Item 1 (sex drive) of 1.05 (SEM 0.41, p=0.00) and Item 5 (orgasm satisfaction) of 0.65 (SEM 0.42, p=0.14) (Table 5.5). In patients who underwent treatment with an SNRI there was a significant increase in the mean score of Item 1 (sex drive) of 2.33 (SEM 0.42, p=0.00) and mean score for Item 2 (arousal) of 1.67 (SEM 0.49, p=0.02). In patients who underwent treatment with a NASSA, there were no statistically significant changes. This was also the case for patients who underwent treatment with CBT (Figure 5.3).

Figure 5.3 **Mean ASEX sub-scores from Week 0 to Week 6 by treatment**

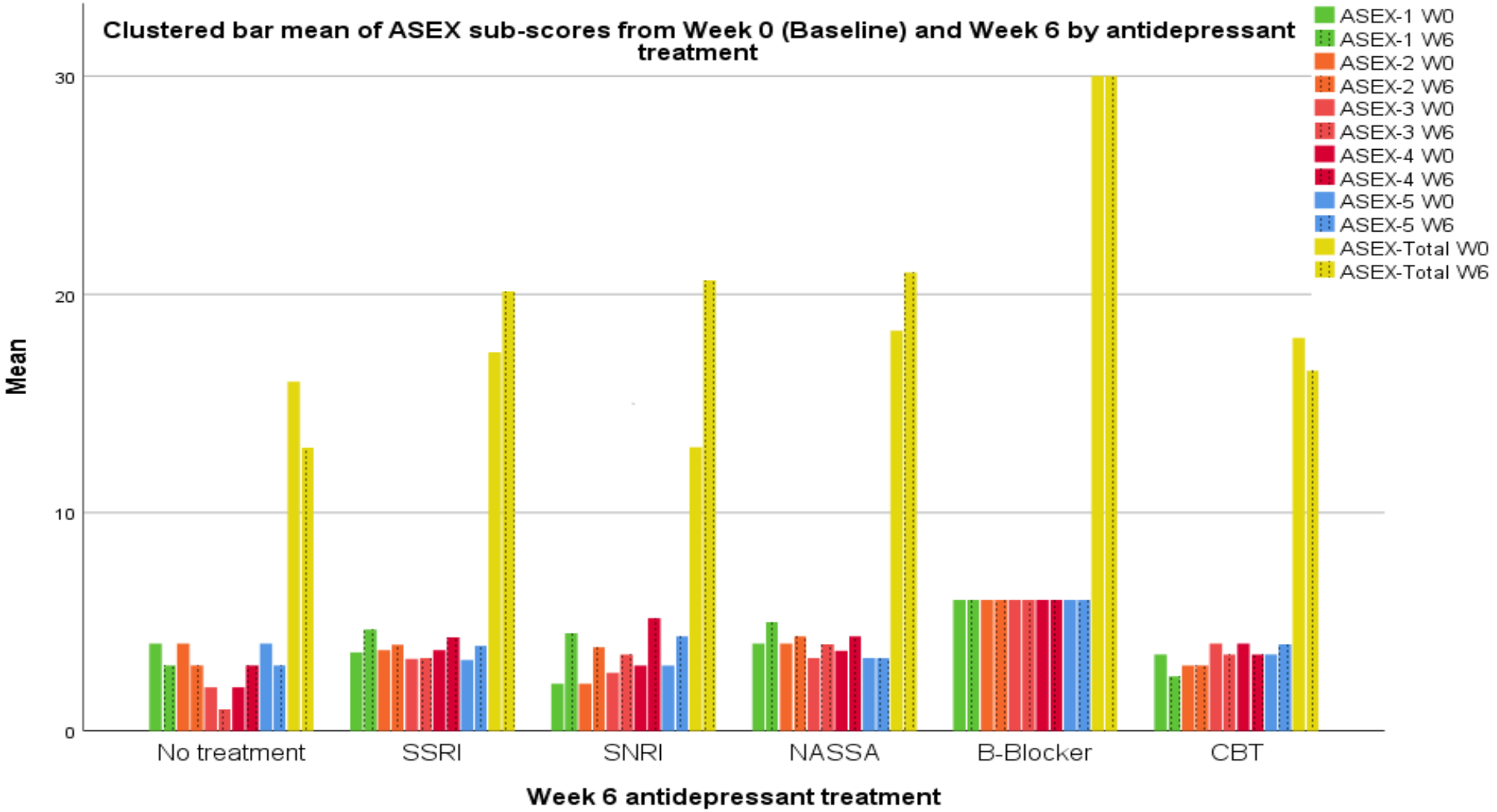


Table 5.4 **Paired samples test ASEX sub-scores from Week 0 (Baseline) to week 6**

		Paired Differences					t	df	Sig. (2-taIL-ed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	ASEX-Total W0 - ASEX-Total W6	-3.15	6.99	1.22	-5.63	-.67	-2.59	32	.01
Pair 2	ASEX-1 W0 - ASEX-1 W6	-1.06	1.71	.30	-1.67	-.45	-3.56	32	.00
Pair 3	ASEX-2 W0 - ASEX-2 W6	-.45	1.52	.26	-.99	.08	-1.71	32	.10
Pair 4	ASEX-3 W0 - ASEX-3 W6	-.18	1.45	.25	-.69	.31	-.72	32	.47
Pair 5	ASEX-4 W0 - ASEX-4 W6	-.82	1.61	.28	-1.39	-.25	-2.92	32	.01
Pair 6	ASEX-5 W0 - ASEX-5 W6	-.64	1.97	.34	-1.33	.06	-1.86	32	.07

Table 5.5 **Paired samples test, ASEX sub-scores from Week 0 (Baseline) to week 6 for the SSRI sub-group**

		Paired Differences					t	df	Sig. (2-taIL-ed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	ASEX-Total W0 - ASEX-Total W6	-2.80	7.20	1.61	-6.17	.57	-1.74	19	.1
Pair 2	ASEX-1 W0 - ASEX-1 W6	-1.05	1.82	.41	-1.90	-.20	-2.58	19	.02
Pair 3	ASEX-2 W0 - ASEX-2 W6	-.25	1.58	.35	-.99	.49	-.70	19	.50
Pair 4	ASEX-3 W0 - ASEX-3 W6	-.05	1.43	.32	-.72	.62	-.16	19	.88
Pair 5	ASEX-4 W0 - ASEX-4 W6	-.60	1.43	.32	-1.27	.07	-1.88	19	.08
Pair 6	ASEX-5 W0 - ASEX-5 W6	-.65	1.87	.42	-1.53	.23	-1.55	19	.14

* Red highlight: statistical significance p≤0.05.

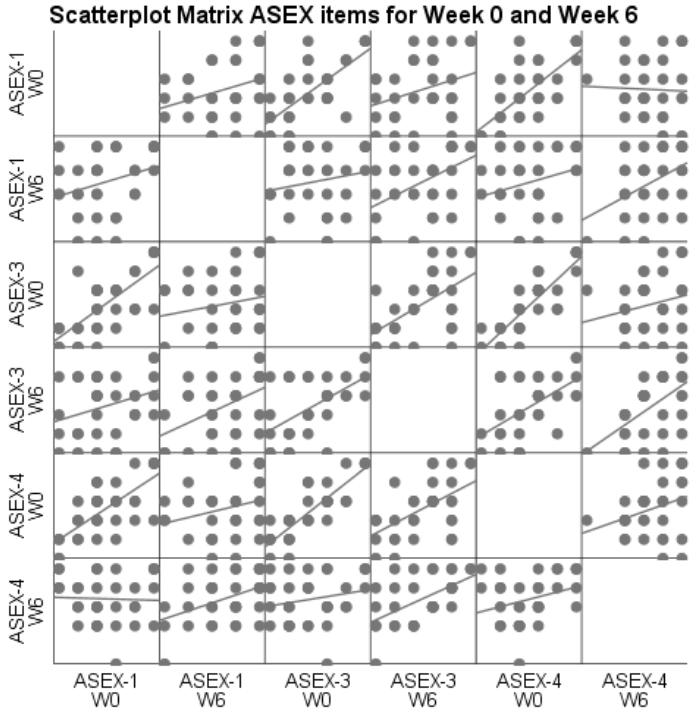
Correlation analysis between ASEX scores at Week 0 (Baseline) and Week 6 found significant correlations for the mean scores of ASEX-total (p=0.02), Item 2 (arousal) (p=0.01) and Item 4 (ability to reach orgasm) (p=0.00) (Table 5.6 and Figure 5.4).

Table 5.6 **Paired samples correlations ASEX sub-items, Week 0 (Baseline) to Week 6**

		N	Correlation	Sig.
Pair 1	ASEX-Total W0 & ASEX-Total W6	33	.41	.02
Pair 2	ASEX-1 W0 & ASEX-1 W6	33	.30	.09
Pair 3	ASEX-2 W0 & ASEX-2 W6	33	.42	.01
Pair 4	ASEX-3 W0 & ASEX-3 W6	33	.57	.00
Pair 5	ASEX-4 W0 & ASEX-4 W6	33	.30	.09
Pair 6	ASEX-5 W0 & ASEX-5 W6	33	.26	.13

* Red highlight: statistical significance p≤0.05.

Figure 5.4 **ASEX items correlations for Week 0 and Week 6.** Correlations between ASEX subscale scores at Baseline (week 0) and Week 6.



Pearson's correlation analysis (Table 5.7) found that ASEX total score at Week 6 was positively and significantly correlated with ASEX-total score at Week 0 (Baseline) (r=0.407, p=0.019). Regression analysis (Table 5.8) found a positive predictability of ASEX total score at Week 6 from ASEX total score at Week 0 (Baseline). The predictability follows the prediction equation shown below.

Equation 1 **ASEX total Week 6 predictability**

ASEX-total post treatment Week 6 = 0.316 × (ASEX-total at Week 0) + 14.807

Table 5.7 **ASEX-total Baseline to week 6 coefficients.** Measuring the strength of the association between ASEX total scores at Baseline (Week 0) and at Week 6.

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	14.807	2.344		6.318	.000
	ASEX-Total W0	.316	.127	.407	2.479	.019

a. Dependent Variable: ASEX-Total W6

Table 5.8 **Table 5.8 ANOVA**[a]

Model		Sum of Squares	d.f.	Mean Square	F	Sig.
1	Regression	160.276	1	160.276	6.144	.019[b]
	Residual	808.633	31	26.085		
	Total	968.909	32			

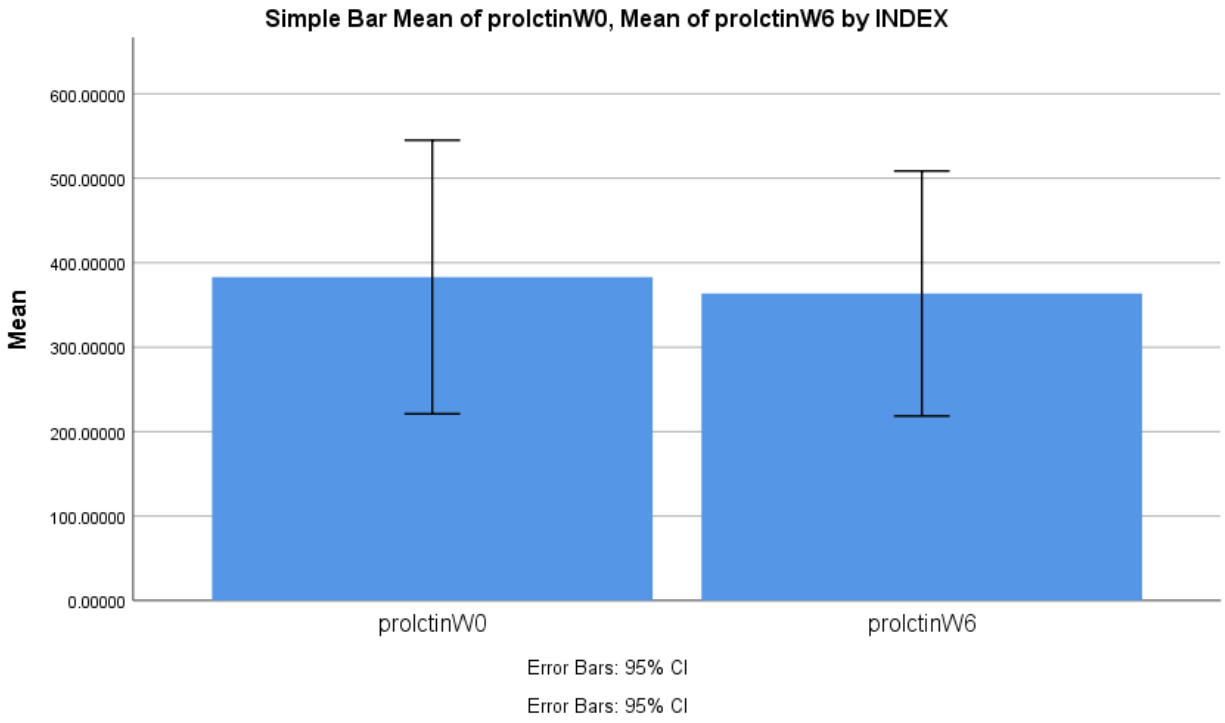
a. Dependent Variable: ASEX-Total W6

b. Predictors: (Constant), ASEX-Total W0

5.5 Plasma prolactin levels

Patients who provided blood samples (n=25) at Week 6 for analysis of plasma prolactin levels by ELISA were found to have prolactin levels between 57.5-276 mu/L for males and 57.5-561 mu/L for females, with a total sample mean of 244.42 mu/L (SEM 22.190). There was a non-significant reduction in prolactin plasma concentration compared to Baseline (85 mu/L for 1 male and 383 mu/L [SEM 62.99] for females, total sample mean 340.43 [SEM 180.35]) (Figure 5.5).

Figure 5.5 **Changes in prolactin levels from Baseline (week 0) to Week 6mu/L**



5.6 Inflammatory markers

Analysis of cytokine (IFN-γ, IL-1β, IL-10, IL-12p70, IL-13, IL-2, IL-4, IL-6, IL-8, TNF-α) levels in participants who provided blood samples at Week 6 (n=25) found a low mean concentration of IL-2 [0.22 pg/mL (median 0.17 pg/mL), normal range 0.22-2.68 pg/mL] and a high mean concentration of TNF-α [2.16 pg/mL (median 1.60 pg/mL), normal range 0.10-1.75 pg/mL]. Paired sample t-test for cytokines concentrations found that changes from Week 0 (Baseline) to Week 6 were not significant (Table 5.9).

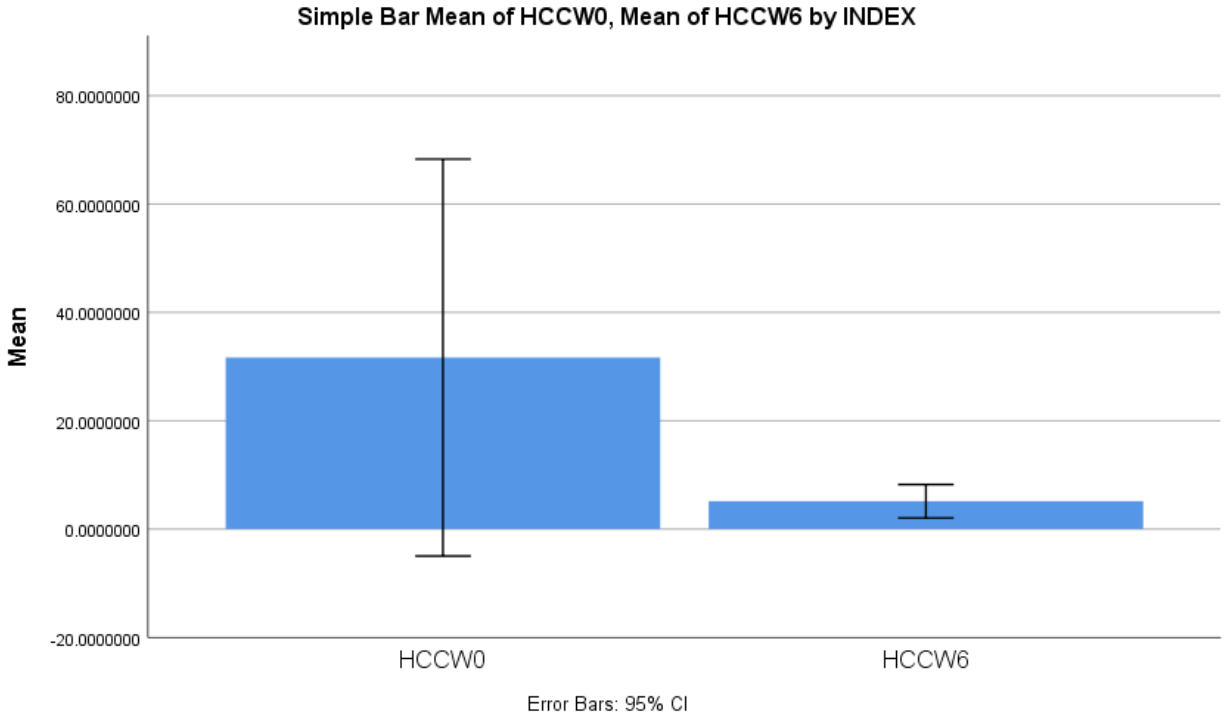
Table 5.9 **Paired samples test cytokines from Week 0 (Baseline) to Week 6 (pg/mL)**

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	IFN-γW0 – IFN-γW6	-2.11	7.11	3.180	-10.94	6.72	-.66	4	.54
Pair 2	IL-1βW0 – IL-1βW6	.23	.54	.24	-.44	.89	.95	4	.40
Pair 3	IL-10W0 – IL-10W6	.48	1.00	.45	-.77	1.73	1.07	4	.34
Pair 4	IL-12p70W0 – IL-12p70W6	.02	.05	.02	-.03	.08	1.22	4	.29
Pair 5	IL-13W0 – IL-13W6	-.03	.36	.16	-.48	.41	-.21	4	.85
Pair 6	IL-2W0 – IL-2W6	-.07	.13	.06	-.23	.09	-1.20	4	.30
Pair 7	IL-4W0 – IL-4W6	.00	.02	.01	-.03	.03	.07	4	.95
Pair 8	IL-6W0 – IL-6W6	-.19	.25	.11	-.50	.12	-1.72	4	.16
Pair 9	IL-8W0 – IL-8W6	.34	4.35	1.94	-5.06	5.74	.18	4	.88
Pair 10	TNF-αW0 – TNF-αW6	.66	1.09	.49	-.69	2.01	1.35	4	.25

5.7 Hair cortisol concentration

Chemiluminescence immunoassay of hair samples (n=29) at Week 6 found a mean HCC of 5.94 pg/mg (SEM 1.21), which lies within the normal range (1-30 pg/mg). This was lower than the mean HCC value at Week 0 (Baseline) of 26.66 pg/mg (SEM 13.30). HCC values at Week 0 (Baseline) and at Week 6 were significantly correlated (p=0.00). Paired sample t-test for HCC concentration found a non-significant change from Week 0 (Baseline) to Week 6 of 26.51 pg/mg (p=0.11) (Figure 5.6).

Figure 5.6 **Changes in HCC from Baseline (Week 0) to Week 6 pg/mg**



5.8 Augmentation phase

By Week 12, eighteen participants had undergone augmentation with the COX2 inhibitor celecoxib, and nine participants had continued 'treatment as usual'. The two sub-groups were comparable in age, treatment and Week 6 psychometric scores. Patients who opted for celecoxib augmentation had diagnoses of panic disorder with agoraphobia (n=6), social phobia (n=5), GAD (n=4), OCD (n=2) and panic disorder (n=1). Patient participants who continued with treatment as usual to Week 12 had diagnoses of GAD (n=5), social phobia (n=2), panic disorder with agoraphobia (n=1) and panic disorder (n=1) (Table 5.10).

Table 5.10 **Comparative analysis of celecoxib augmentation subgroup and treatment as usual subgroup**

Celecoxib augmentation

Diagnoses

	Frequency	Percent
Panic disorder	1	5.6
GAD	4	22.2
Panic disorder with agoraphobia	6	33.3
Social phobia	5	27.8
OCD	2	11.1
Total	18	100.0

Antidepressant treatment

	Frequency	Percent
SSRI	10	55.6
SNRI	4	22.2
NASSA	3	16.7
B-Blocker	1	5.6
Total	18	100.0

Age

	Frequency	Percent
18-24	9	50.0
25-39	3	16.7
40-49	3	16.7
≥50	3	16.7
Total	18	100.0

Gender

	Frequency	Percent
Male	5	27.8
Female	13	72.2
Total	18	100.0

Week 6 psychometric mean scores

	Mean	N	SD	SEM
WEMWBS	33.22	18	6.151	1.45
HADS-A W6	14.11	18	3.513	.8328
HADS-D W6	10.17	18	3.682	.8768
SAS-Total W6	8.25	16	3.661	.915
ASEX-Total W6	20.67	18	4.935	1.163
CGI-S W6	4.28	18	1.1327	.2766
OQUESA-GR W6	15.18	17	4.142	1.005
OQUESA-RP W6	18.89	18	5.2768	1.242
OQUESA-ED W6	10.39	18	4.0217	.9547
OQUESA-NC W6	15.78	18	4.360	1.0328
OQUESA-AC W6	15.83	18	6.653	1.5768

Treatment as usual

Diagnoses

	Frequency	Percent
Panic disorder	1	11.1
GAD	5	55.6
Panic disorder with agoraphobia	1	11.1
Social phobia	2	22.2
Total	9	100.0

Antidepressant treatment

	Frequency	Percent
SSRI	5	55.6
SNRI	2	22.2
CBT	2	22.2
Total	9	100.0

Age

	Frequency	Percent
18-24	4	44.5
25-39	2	22.2
40-49	2	22.2
≥50	1	11.1
Total	9	100.0

Gender

	Frequency	Percent
Male	4	44.4
Female	5	55.6
Total	9	100.0

Week 6 psychometric mean scores

	Mean	N	SD	SEM
WEMWBS	36.89	9	16.42	5.473
HADS-A W6	12.11	9	5.819	1.94
HADS-D W6	10.22	9	4.711	1.57
SAS-Total W6	7.78	9	2.863	0.954
ASEX-Total W6	17.78	9	5.019	1.673
CGI-S W6	3.78	9	1.481	0494
OQUESA-GR W6	17.75	8	3.732	1.319
OQUESA-RP W6	18	8	6.188	2.188
OQUESA-ED W6	10.38	8	5.975	2.112
OQUESA-NC W6	14.5	8	5.952	2.104
OQUESA-AC W6	10.17	6	3.817	1.558

5.8.1 Change in Psychometric scales scores

In the celecoxib augmentation group, there were significant correlations between Week 6 scores and Week 12 scores for ASEX-total (p≤0.0001), HADS-A (p≤0.0001), HADS-D (p=0.02), EQRS (p=0.00), SAS (p=0.00), CGI-S (p=0.00), OQUESA-GR (p=0.01) and OQUESA-RP (p=0.02). Analysis using paired t-tests in the augmentation sub-group found significant changes in mean scores from Week 6 to Week 12: ASEX-total score 4.06 reduction (SEM 0.98, p=0.00); WEMWBS 7.50 increase (SEM 2.63, p=0.01); HADS-A 3.17 reduction (SEM 0.52, p=0.00); HADS-D 2.11 reduction (SEM 0.80, p=0.02); CGI-S 1.11 reduction (SEM 0.18, p=0.00); CGI-I 0.78 reduction (SEM 0.32, p=0.03); OQUESA-RP 3.56 reduction (SEM 1.19, p=0.01) and OQUESA-AC 4.22 reduction (SEM 1.25, p=0.00).

In the non-augmentation group, there were significant correlations between Week 6 and Week 12 psychometric scores of ASEX (p=0.02), WEMWBS (p=0.00), HADS-A (p=0.00), HADS-D (p=0.01), SAS (p=0.01), OQUESA-RP (p=0.00), OQUESA-ED (p=0.01), and OQUESA-NC (p=0.01). Analysis using paired sample t-test in this group found changes in mean scores from Week 6 to Week 12 as follows: ASEX-total 0.78 increase (SEM 1.47, p=0.61); WEMWBS 1.22 increase (SEM 2.10, p=0.58); HADS-A 0.11 increase (SEM 0.82, p=0.90); HADS-D 0.78 decrease (SEM 1.11, p=0.50); EQRS 1.29 decrease (SEM 1.57, p=0.44); SAS 0.56 increase (SEM 0.60, p=0.38); CGI-S 0.33 decrease (SEM 0.28, p=0.28); CGI-I 0.44 increase (SEM 0.41, p=0.31); OQUESA-GR 1.12 decrease (SEM 1.80, p=0.55); OQUESA-RP 2.00 decrease (SEM 0.82, p=0.05); OQUESA-ED no change (SEM 1.18, p=1.00); OQUESA-NC 1.87 decrease (SEM 1.09, p=0.13) and OQUESA-AC 0.40 increase (SEM 1.03, p=0.72).

5.8.2 Sexual function

ASEX item scores in the celecoxib augmentation group at Week 12 were as follows: Item 1 (sexual drive) 3.72 (SEM 0.34); Item 2 (arousal) 3.17 (SEM 0.38); Item 3 (erection/vaginal lubrication) 3.17 (SEM 0.35); Item 4 (ability to reach orgasm) 3.53 (SEM 0.32); Item 5 (orgasm satisfaction) 3.00 (SEM 0.33) and ASEX total 16.61 (SEM 1.52). Week 12 item scores were significantly correlated with Week 6 scores in the celecoxib augmentation sub-group: Item 1 (sexual drive) (p=0.01); Item 2 (arousal) (p=0.00); Item 3

(erection/vaginal lubrication) (p=0.00); Item 4 (ability to reach orgasm) (p=0.01); Item 5 (orgasm satisfaction) (p=0.04) and ASEX total score (p=0.00). Paired sample t-test for ASEX items found significant changes from Week 6 to Week 12 in Item 1 (sexual drive) 1.06 reduction (SEM 0.27, p=0.00); Item 2 (arousal) 0.83 reduction (SEM 0.25, p=0.00); Item 4 (ability to reach orgasm) 1.12 reduction (SEM 0.26, p=0.00); Item 5 (orgasm satisfaction) 0.83 reduction (SEM 0.35, p=0.03) and ASEX total score 4.06 reduction (SEM 0.98, p=0.00). Paired sample t-test found a non-significant change in Item 3 (erection/vaginal lubrication) 0.33 reduction (SEM 0.24, p=0.19).

ASEX item scores in the 'treatment as usual' group at Week 12 were as follows: Item 1 (sexual drive) 3.78 (SEM 0.60); Item 2 (arousal) 3.67 (SEM 0.47); Item 3 (erection/vaginal lubrication) 3.67 (SEM 0.50); Item 4 (ability to reach orgasm) 4.0 (SEM 0.53); Item 5 (orgasm satisfaction) 3.90 (SEM 0.56) and ASEX total score 18.56 (SEM 2.18). ASEX item scores were significantly correlated with Week 6 item scores, in the treatment at usual sub-group for: Item 1 (sexual drive) (p=0.00); Item 2 (arousal) p=0.00); Item 4 (ability to reach orgasm) (p=0.04) and ASEX total score (p=0.02). Paired sample t-test for ASEX items found changes from Week 6 to Week 12 in: Item 1, (sexual drive) 0.11 increase (SEM 0.26, p=0.68); Item 2 (arousal) 0.11 increase (SEM 0.26, p=0.68); Item 3 (erection/vaginal lubrication) 0.56 increase (SEM 0.53, p=0.32); Item 4 (ability to reach orgasm) 0.00 no change (SEM 0.41, p=1.00); Item 5 (orgasm satisfaction) 0.00 no change (SEM 0.55, p=1.00) and ASEX total score 0.78 increase (SEM 1.47, p=0.61).

Most patients with sexual dysfunction met more than one ASEX criterion at every time point. The study found that at each time point, each participant with sexual dysfunction moved between different ASEX-defined sexual dysfunction criteria. This followed the patterns of change shown in Table 5.11.

Table 5.11 **Patterns of change of ASEX-defined sexual dysfunction criteria**

ASEX criteria pattern of change	**N**
No sexual dysfunction at Week 0 (Baseline)- Criteria1, 2 and 3 at Week 6- Citeria1, 2 and 3 at Week 12	4
No sexual dysfunction at Week 0 (Baseline)- Criteria 2 at Week 6- No sexual dysfunction at Week 12	1
No sexual dysfunction at Week 0 (Baseline)- Criteria 2 and 3 at Week 6- No sexual dysfunction at Week 12	1
No sexual dysfunction at Week 0 (Baseline)- Criteria1, 2 and 3 at Week 6- No sexual dysfunction at Week 12	2
Criteria1, 2 and 3 at Week 0 (Baseline)- Criteria1, 2 and 3 at Week 6- Criteria1, 2 and 3 at Week 12	5*
Criteria1, 2 and 3 at Week 0 (Baseline)- Criteria1, 2 and 3 at Week 6- Criteria 1and 3 at Week 12	1
Criteria1, 2 and 3 at Week 0 (Baseline)- Criteria1 and 3 at Week 6- Criteria1 at Week 12	1
Criteria1, 2 and 3 at Week 0 (Baseline)- Criteria1, 2 and 3 at Week 6- No sexual dysfunction at Week 12	2
Criteria1and 2 at Week 0 (Baseline)- Criteria1, 2 and 3 at Week 6- Criteria1, 2 and 3 at Week 12	1
Criteria 2 Week 0 (Baseline)- Criteria 2 Week 6- No sexual dysfunction at Week 12	1
Criteria 2 at Week 0 (Baseline)- Criteria1, 2 and 3 at Week 6- Criteria1, 2 and 3 at Week 12	1
Criteria 2 at Week 0 (Baseline)- Criteria 3 at Week 6- Criteria 2 at Week 12	1
Criteria 2 at Week 0 (Baseline)- Criteria 2 at Week 6- Criteria1, 2 and 3 at Week 12	1

Criteria 3 at Week 0 (Baseline)- No sexual dysfunction at Week 6- No sexual dysfunction at Week 12	1
Criteria 3 at Week 0 (Baseline)- Criteria 2 and 3 at Week 6- Criteria 3 at Week 12	1
Criteria 3 at Week 0 (Baseline)- Criteria1, 2 and 3 at Week 6- Criteria 2 Week 12	2*

* Number includes one participant with missing Week 12 ASEX scores.

5.8.3 Inflammatory markers

Analysis of cytokine levels (IFN-γ, IL-1β, IL-10, IL-12p70, IL-13, IL-2, IL-4, IL-6, IL-8, TNF-α) at Week 12 in the celecoxib augmentation group (n=18) found a low mean concentration of IL-1β (0.04 pg/mL, SEM 0.024: normal range 0.11-24.3 pg/mL); low mean concentration of IL-12p70 (0.12 pg/mL, SEM 0.015: normal range 0.26-0.38 pg/mL); low mean concentration of IL-13 (0.11 pg/mL, SEM 0.05: normal range 0.60-2.78 pg/mL) and a high mean concentration of TNF-α (2.33 pg/mL, SEM 0.21: normal range 0.10-1.75 pg/mL). Concentrations at Week 12 in the celecoxib augmentation sub-group were correlated with Week 6 concentrations for IL-10 (p=0.00); IL-13 (p=0.00); IL-2 (p=0.00); IL-6 (p=0.00); IL-8 (p=0.00) and TNF-α (p=0.00). Paired sample t-test found a significant change from Week 6 to Week 12, in the mean concentration of IL-2 0.06 pg/mL (SEM 0.02, p=0.00).

Analysis of cytokines concentration in the treatment as usual group at Week 12 (n=4) found low mean concentrations of IL-1β (0.43 pg/mL, SEM 0.018: normal range 0.11-24.3 pg/mL); IL-12p70 (0.102 pg/mL, SEM 0.04: normal range 0.26-0.38 pg/mL); IL-13 (0. 27 pg/mL, SEM 0.11: normal range 0.60-2.78 pg/mL); and IL-2 (0.21 pg/mL, SEM 0.03: normal range 0.22-2.68 pg/mL): and a high mean concentration of TNF-α (2.33 pg/mL: normal range 0.10-1.75 pg/mL). There was no significant correlation between concentrations at Week 12 and at Week 6 in this group and paired sample t-test, from Week 6 to Week 12, found no significant change.

5.8.4 Plasma prolactin levels

Patients who provided blood samples in the celecoxib augmentation group (n=16) at Week 12 for analysis of plasma prolactin levels by ELISA were found to have prolactin levels between 105-432 mu/L for males and 94-490 mu/L for females, with a total sample mean of 239 mu/L (34.02 SEM). There was a non-significant increase in prolactin plasma concentration compared to Week 6 (6.56 mu/L, p=0.78). Patients who provided blood samples in the treatment as usual group (n=6) at Week 12 for analysis of plasma prolactin levels by ELISA were found to have prolactin levels between 149-168 mu/L for males and 300-498 mu/L for females, with a total sample mean of 308.83 mu/L (54.90 SEM). There was a non-significant increase in prolactin plasma concentration compared to Week 6 (17.67 mu/L, p=0.52).

5.8.5 Hair cortisol concentration

HCC by chemiluminescence in the celecoxib augmentation group at Week 12 (n=18) found a mean concentration of 7.44 pg/mg (SEM 4.44) (normal range 1-30 pg/mg), which was negatively correlated with mean HCC at Week 6 (p=0.77). There was a non-significant change from Week 6 to Week 12 of -1.24 pg/mg (p=0.80). HCC in the treatment as usual group (n=15) was 8.22 pg/mg (SEM 3.60). There was a non-significant increase in HCC from Week 6 to Week 12, of 1.72 pg/mg (p=0.13).

5.9 Interpretation of findings

The mean scores on the HADS-A at Week 6, 13.70 (SEM 0.73, Range 17) indicate that participating patients were troubled by substantial symptoms. Over three-quarters of the patient participants were found to have sexual dysfunction (as determined by ASEX criteria) at Week 6: sex drive and ability to reach orgasm were particularly affected. Analysis of inflammatory markers found low levels of IL-2 but high levels of TNF-α. HCC at Week 6 was within the normal range, albeit lower than at Week 0 (Baseline).

Longitudinal analysis found that ASEX mean scores increased from Week 0 (Baseline) to Week 6, with significantly worsening in sexual drive and ability to reach orgasm. Patients who received SSRI treatment had significantly worsened sexual drive and orgasm satisfaction. Patients who underwent SNRI treatment had significantly worsened sex drive and arousal. Regression analysis found a positive predictability of

ASEX total score at Week 6 from ASEX total score at Week 0 (Baseline). There were no significant changes in HCC, serum prolactin, or inflammatory markers, from Week 0 (Baseline) to Week 6.

At Week 12, there was a significant change in psychometric scores in the celecoxib augmentation group, reflecting improved sexual dysfunction (ASEX); improved mental well-being (WEMWBS); reduced anxiety (HADS-A); reduced depression (HADS-D); less reduction in positive emotions (OQUESA-RP); and attribution of antidepressants as cause (OQUESA-AC). There was a significant improvement in sexual drive; ability to reach orgasm; orgasm satisfaction; with a reduction of 4.06 in mean ASEX total score, in the celecoxib augmentation group. Changes in rating scale scores in the non-augmentation group from Week 6 were non-significant. ASEX scores changes in the non-augmentation ('treatment as usual' group) were found to be non-significant. There were no significant changes in inflammatory markers' concentrations, HCC or plasma prolactin in either the celecoxib augmentation group or the 'treatment as usual' group.

Chapter 6 Discussion

6.1 Rationale for study methods

Many studies have explored the relationship between sexual dysfunction, depressive illness and treatment with antidepressant drugs (Baldwin et al., 2013). By contrast, little is known about the prevalence of sexual dysfunction in patients with anxiety disorders, or its association with demographic and other clinical factors: and the relationships between anxiety disorders, sexual dysfunction and dissatisfaction and treatment with psychotropic drugs have not been explored extensively.

Panic disorder appears to be characterized by an elevation in urinary cortisol levels (Bandelow et al., 1997; Lopez et al., 1990; Kathol et al., 1989; Kathol et al., 1988), by a decline in cortisol levels with successful pharmacological treatment (Herran et al., 2005; Abelson et al., 1996; Lopez et al., 1990; Fava et al., 1989), and by non-suppression following dexamethasone administration, in a proportion greater than that in healthy controls (Judd et al., 1987) but less than that in depressed patients (Faludi et al., 1986; Goldstein et al., 1987). GAD appears to be characterized by a decline in cortisol levels with successful psychological or pharmacological treatment (Rosnick et al., 2013; Lenze et al., 2011; Pomara et al., 2005; Tafet et al., 2005; Roy-Byrne et al., 1991; Tiller et al., 1988). Specific phobia appears characterized by cortisol levels which rise during experimental exposure to feared objects or situations (Alpers et al., 2003; Abelson et al., 1989; Nesse et al., 1985; Fredrikson et al., 1985), but which decline with successful exposure therapy (Lass-Hennemann et al., 2014; Brand et al., 2011). Social anxiety disorder is possibly characterized by cortisol levels that rise during psychological challenge (Furlan et al., 2001; Van West et al., 2008). There is no unifying disturbance of HPA axis function across these anxiety disorders. In panic disorder, there continues to be much uncertainty about whether it is characterized by chronically elevated cortisol levels, whether cortisol levels fall following psychological challenge, and whether the anxiety response to 'panicogenic' challenges is accompanied by changes in endocrine function. It is uncertain whether GAD is characterized by elevated cortisol levels prior to treatment. Review of published studies found that, within

each disorder, the findings of investigations using similar methodology have produced inconsistent findings (Elnazer et al., 2014).

The number of investigations of HPA function in panic disorder and GAD is reasonably extensive, but there have been few studies in specific (simple) phobia or social anxiety disorder (social phobia). The association of sexual dysfunction in anxiety disorders with endocrine disturbance (including HPA disturbance) remains an under-researched area.

Published evidence indicates that symptoms of anxiety are associated with decreased levels of CRB, IL-1b, TNF-α, IL-6, IL-8 and neurotrophins (Fluitman et al., 2010; Koh et al., 2004; Denys et al., 2004). By contrast, a comparatively large study (n=1037) found no correlation between anxiety symptoms and inflammatory markers, after adjusting for environmental and health factors (Baune et al., 2012).

Published evidence found that six weeks' augmentation with celecoxib, when compared to placebo, led to significant improvement in HADS scores in patients with MDD (n=40) who underwent treatment with reboxetine (Müller et al., 2006). Augmentation with celecoxib led to significantly improved quality of life, as measured by the Quality of Life scale (QOL), in patients with gastric carcinoma receiving chemotherapy (n=120), when compared to controls ($p < 0.05$) (Guo et al., 2019; Guo et al., 2017). Patients with non-muscle-invasive bladder cancer (n=410) who received celecoxib augmentation had significantly improved quality of life scores on the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) ($p<0.001$), when compared to controls. Celecoxib augmentation was also found to improve sexual function in men more than in women ($p<0.001$) (Blazeby et al., 2014). Published evidence indicates that pharmacological modulation of the peripheral inflammatory process related to the physical illness is associated with improvement in anxiety symptoms in some but not all studies: and it is not clear whether this applies to anxiety symptoms in the absence of chronic physical health conditions.

The possible association of sexual dysfunction in anxiety disorders with inflammatory markers has yet to be explored. Investigation of this area may lead to potentially innovative pharmacological approaches such as treatment with non-steroidal anti-inflammatory drugs.

The current study was designed to obtain cross-sectional data to ascertain the prevalence of sexual dysfunction in patients with anxiety disorders at Baseline; treatment emergent sexual dysfunction after six weeks of treatment; and after a further six weeks of either 'treatment as usual' or augmentation with a COX-2 inhibitor (celecoxib). This design allowed for longitudinal analysis of change from Baseline to Week 6 post-treatment and after further six weeks of celecoxib augmentation or treatment as usual.

The validity of the assessment tools used in the current study is well established. Warwick-Edinburgh Mental Well-Being Scale (WEMWBS), has good content validity; Cronbach's α 0.91; a high correlation with mental health and well-being but lower correlations with overall health. It discriminated between population groups in a way that is largely consistent with the results of other population surveys. Test-retest reliability at one week was high (0.83). Social desirability bias was lower or similar to that of comparable scales. The Hospital Anxiety and Depression Scale (HADS) has good internal consistency (Cronbach's α for HADS-A is 0.83 and 0.82 for HADS-D). The sensitivity and specificity for both HADS-A and HADS-D is approximately 0.80. HADS has a good positive correlation (0.49-0.83), with other widely used anxiety and depression scales with established validity (BDI; GHQ-28; SCI; STAI; SCL-90 and MADRS). Oxford Questionnaire of Emotional Side Effects of Antidepressants (OQuESA), has good internal consistency (Cronbach's α, 0.87 for ED; 0.88 for GR, 0.86 for PR and 0.87 for NC; 0.89 for the subtotal ED-GR; for PR-NC and 0.93 for the total score and 0.80 for each of the dimensions, subtotals, and the total score). OQuESA appears sensitive to change. ED and GR are weakly positively correlated (0.22) with BDI-II scores; with Kendall's tau-b. PR and NC were moderately positively correlated (0.54). Clinical Global Impression (CGI) ratings are positively correlated with self-reported and clinician-administered measures in patients with social anxiety. The CGI-I was found to be highly correlated (r=0.71) with measures of change from Health of the Nation Outcomes Scales (HONOS), the Michigan Hand Outcomes Questionnaire

(MHQ,) and with Depression Anxiety Stress Scales (DASS-2). CGI is a short scale with poor distribution properties and, presumably, a restricted property of recognising significance of rating change.

The Emotional Quality of the Relationship Scale (EQR) has high internal consistency (Cronbach's α=0.85). EQR is significantly and moderately correlated with the: Sexual Behaviour Scale (r=0.45); HADS (r=-0.38) and the Quality of Life Visual Analog Scale (r=0.37). No cut-points or normative data have been established. Sexual Activity and Satisfaction Scales (SAS), has high internal consistency (Cronbach's α =0.87). SAS is positively correlated with EQRS (r=0.57). No cut-points or normative data have been established.

Preclinical studies have found that measurement of hair cortisol is a valid method of evaluating stress over long periods in wild chipmunk populations (*Tamias striatus*), providing valuable information on the response to environmental changes (Mastromonaco et al., 2014). Endogenous cortisol levels follow a diurnal pattern and therefore the timing of collection is critical. Hair cortisol is a reliable measure of the total retrospective activity of the HPA axis in humans over the preceding weeks, with a minimal burden to participants (Wright et al., 2015). Published evidence found hair cortisol concetration to be a valid and successful method for detection of Cushing syndrome (Hodes et al., 2018). The current study used enzyme-linked immunosorbent assay, which is an established and sensitive method for detecting hair cortisol levels, the lower limits of quantification of this assay method were below 0.1 pg cortisol per mg hair. The reported median coefficient of variation (CV) of all replicates was 4.9% (interquartile range: 1.3–13.9%).

To determine levels of inflammatory markers, the current study used the Luminex multi-analyte profiling (xMAP) technology, which employs proprietary bead sets which are distinguishable under flow cytometry. The kit was reportedly validated following a fit-for-purpose principles and MSD design control procedures. V-PLEX assay components go through an extensive critical reagents program to ensure that the reagents are controlled and well characterised. Prior to the release of each V-PLEX panel, at least three independent kit lots are produced. Using results from multiple runs (typically greater than 50) and

multiple operators, these lots were used to establish production specifications for sensitivity, specificity, accuracy, and precision.

6.2 Sexual function

The ASEX has excellent internal consistency and scale reliability (Cronbach's α=0.9055) and strong test–retest reliability (for patients, r=0.801, p<0.01; for controls, r=0.892, p<0.01). Analyses of variance (ANOVAs) showed significant differences in total ASEX scores between patients and controls (for males F=18.1, p<0.000; for females F=31.71, p<0.000) and between females and males (for patients F=5.22, p=0.026; for controls F=5.05, p=0.031). My review indicates that the ASEX appears useful in a range of clinical situations including patients with primary sexual dysfunction (n=7), specific psychiatric disorders (n=9), specific physical illnesses (n=44) and treatment emergent sexual dysfunction (n=42). Higher ASEX scores in populations with treatment emergent dysfunction are associated with the 5-HT2A receptor -1438 AA genotype, and CYP2D6 poor metabolic status phenotype in female patients. The ASEX appears to be a reliable clinical instrument for identifying and quantifying sexual dysfunction across a range of populations in various clinical settings. Prior to the current study little was known about either the utility of ASEX in patients with anxiety disorders or possible relationships between ASEX scores and potential biological markers.

The additional, systematic review conducted within this study, demonstrated that ASEX is a reliable and valid measure for investigating sexual dysfunction in clinical samples. The current study demonstrated that ASEX is a reliable method to determine sexual function at baseline, and treatment-emergent sexual dysfunction in a UK clinical population with a diagnosis of anxiety disorders.

6.3 Principal cross-sectional findings

At Baseline, the ASEX mean score was 17.40 (SEM 1.21) and 57.1% (n=20) of patients with a diagnosis of an anxiety disorder had sexual dysfunction. Mean Item scores were: item 1 (sex drive), 3.57 (SEM 0.27); item 2 (arousal), 3.57 (SEM 0.28); item 3 (erection/vaginal lubrication), 3.34 (SEM 0.27); item 4 (ability to reach orgasm), 3.63 (SEM 0.25) and item 5 (orgasm satisfaction), 3.40 (SEM 0.28). At Week 0 (Baseline), the differing ASEX criteria for delineating sexual dysfunction were as follows: a total score of 19 (criterion 1) or more was met 8 times; a single item score of 5 (criterion 2) or more was met 14 times; and any three items with a score of 4 (criterion 3) or more was met 15 times. Fourteen patients met more than one ASEX criteria of sexual dysfunction: both Criteria 1 and 2 were fulfilled 10 times; all Criteria were fulfilled 8 times; both Criteria 2 and 3 combined were fulfilled 9 times; and both Criteria 3 and 1 combined were fulfilled 10 times.

At Week 6, 75.1% (n=26) of the participants were found to have sexual dysfunction. The ASEX criterion of sexual dysfunction as a total score of 19 (criterion 1) or more was met 19 times; any single item with a score of 5 (criterion 2) or more was met 25 times; and any three items with a score of 4 (criteria 3) or more was met 22 times. Twenty-three patients met more than one ASEX criterion of sexual dysfunction. Criteria 1 and 2 combined were fulfilled 18 times; criteria 1, 2 and 3 combined were fulfilled 19 times; criteria 2 and 3 combined were fulfilled 23 times, and criteria 3 and 1 combined were fulfilled 20 times. At Week 12, 39.3% (n=13) of the participants were found to have sexual dysfunction. ASEX criteria of sexual dysfunction as, total score of 19 (criteria 1) or more was fulfilled 13 times; any single item with a score of 5 (criteria 2) or more was fulfilled 12 times and any three items with a score of 4 (criteria 3) or more was fulfilled 13 times. Ten patients met more than one ASEX criterion of sexual dysfunction. Criteria 1 and 2 combined were met 11 times; criteria 1, 2 and 3 combined were fulfilled 11 times; criteria 2 and 3 combined were fulfilled 11 times; and criteria 3 and 1 combined were fulfilled 12 times.

At Week 0 (Baseline), mental wellbeing (WEMWBS) was found to be significantly inversely correlated with sexual dysfunction (ASEX) (Pearson's correlation=- 0.87) with WEMWBS mean score (p=0.00). At Week 6, mental wellbeing (WEMWBS) was found to be significantly inversely correlated with sexual dysfunction

(ASEX) (Pearson's correlation=-0.44, p=0.01). At Week 12 in the celecoxib augmentation group, mental wellbeing (WEMWBS) was not correlated with sexual dysfunction (ASEX) (Pearson's correlation=0.04, p=0.86), but was significantly inversely correlated with sexual dysfunction (ASEX) (Pearson's correlation= -0.79, p=0.01) in the non-augmentation group.

6.4 Principal longitudinal findings

The current study found worsening sexual function at Week 6 and predictability of ASEX total score at Week 6 from ASEX total score at Week 0 (Baseline). Most patients with sexual dysfunction met more than one ASEX criterion at every time point. Participants continued to be troubled by significant anxiety symptoms at Week 6, having a mean HADS-A score of 13.70 (SEM 0.73), less than the score at Week 0 (Baseline) (HADS-A 15.42 [SEM 0.88]). Patient quality of life improved from Week 0 (Baseline) (WEMWBS 27 [SEM 1.8]) to Week 6 (WEMWBS 33.30 [SEM 1.75]). At Week 12, the current study found that patients who underwent augmentation with celecoxib had significant improvement in sexual function (ASEX-total 4.06 reduction [SEM 0.98, p=0.00]); quality of life (WEMWBS 7.50 increase [SEM 2.63, p=0.01]); and a significant improvement in anxiety symptoms (HADS-A 3.17 reduction [SEM 0.52, p=0.00]). Patients who underwent a further 6 weeks of 'treatment as usual' showed no significant changes from Week 6.

6.5 Principal limitations of study findings

The study findings are limited by the small sample size. This was found to be due to potential participants' time constraints and the lack of financial compensation (29%); potential participants feeling too unwell to participate (22%); and the sensitivity of the subject (sexual dysfunction) (10%). Relatively small numbers of patients provided both blood and hair samples. This could be a further limiting factor of the conclusions which can be drawn about the relationships between HPA function, inflammatory markers and severity of anxiety symptoms.

Other potential weaknesses of the current study include the lack of randomisation; the 'open' approach to celecoxib augmentation (allocation bias and selection bias): and the lack of blindness to treatment

group (assessment bias). A randomised control design would have required a vast sample size, which can be challenging for the reasons above and would require more resources.

6.6 Implications for future research

The current study screened 170 referrals from primary care or secondary care mental health services of patients who expressed an interest in being contacted about the study. Of these, 79% (135 patients) dropped out following the initial explanation of the study, most of whom were females (61%). The most common reason for non-consent to participation in referred patients was feeling too unwell to participate at baseline (22%). Concerns about time commitment (15%), lack of financial compensation (14%). and the sensitivity of the subject (10%), were also cited as reasons for not consenting. These findings provide useful guidance for future research designs to take into consideration and attempt to mitigate these potential hurdles for recruitment.

The study provides evidence of a correlation between mental wellbeing and sexual function. The findings also provide some evidence for the potential benefit of augmenting antidepressant treatment with celecoxib in patients with anxiety disorders in improving mental wellbeing, reducing anxiety symptoms and ameliorating sexual function. These preliminary findings justify further research work in this area to explore these associations in a larger scale.

The current study found evidence of beneficial effects of augmentation with celecoxib in patients with anxiety disorders. Most participants who received celecoxib gave positive free-text feedback. *Verbatim* participants' comments are shown in Table 6.2. Further studies could help to explore the effects of novel pharmacological interventions for sexual dysfunction associated with anxiety disorders, and improve our understanding of the molecular mechanisms associated with the disorders and potentially new anxiolytic treatments.

6.7 Implications for clinical practice

This systematic review contained within this thesis demonstrates that the ASEX is a reliable clinical measure of sexual dysfunction in patients with a diagnosis of anxiety disorders. The empirical study shows that patients with anxiety disorders who suffer sexual dysfunction are likely to struggle with dysfunction in more than one sexual domain. Sexual dysfunction was correlated with the severity of anxiety symptoms and findings from the current study provide evidence of a correlation between anxiety symptoms and mental wellbeing.

Investigating sexual dysfunction in this patient group, as an integral part of overall clinical assessment, can provide the patient with a better opportunity for effective management of their anxiety symptoms; sexual function and enhancing their overall wellbeing. Augmentation with celecoxib may improve anxiety symptoms and sexual dysfunction, in at least some patients.

Table 6.1 **Participants' reports of experiences in augmentation phase**

Patient 1. 48-year-old male. Diagnosis OCD. Celecoxib concordance 30%.
No difference.
Participant's comment: "I felt no difference in the first two weeks so I stopped it".

Patient 2. 48-year-old male. Diagnosis panic disorder with agoraphobia. Celecoxib concordance 50%.
No difference.
Participant's comment: "it didn't do anything".

Patient 3. 24-year-old female. Diagnosis panic disorder with agoraphobia. Celecoxib concordance 100%.
Improved mood, remission of panic attacks.
Participant's comment: "much better", "I'm back to work", "I enjoy my life", "planning for my wedding in the summer".

Patient 5. 20-year-old female. Diagnosis social phobia. Celecoxib concordance 100%.
Improved mood and social function. Patient decided to seek further treatment with celecoxib from her GP.
Participant's comment: "I was wondering if I could partake in the anti-inflammatory medication trial again? I found that it made quite a big difference in my mental health and moods now that I'm no longer taking them!"

Patient 6. 21-year-old female. Diagnosis panic disorder with agoraphobia. Celecoxib concordance 100%.
No qualitative data available. No comments volunteered by the participant.

Patient 8. 23-year-old female. Diagnosis social phobia and panic disorder. Celecoxib concordance 100%.
Improved mood and level of function.
Participant's comment: "I feel better, I started a new job too"

Patient 9. 29-year-old female. Diagnosis: Panic disorder with agoraphobia. Celecoxib concordance 100%.
No qualitative data available. No comments volunteered by the participant.

Patient 12. 21-year-old female. Diagnosis panic disorder with agoraphobia. Celecoxib concordance 100%.
Improved level of function.
Participant's comment: "less stressed, I started a new job".

Patient 14. 27-year-old male. Diagnosis: OCD. Celecoxib concordance 100%.
Improved levels of anxiety. Patient has been engaging better with leisure activities.
Participant's comment: "I am well and don't seem to be having any side effects. Although I have noticed after about a week of taking them I am more active and no longer ache the day after a gym session, even know I'm still doing the Same run in miles and the Same weight routine I no longer have achy legs or a sore stomach from sit-ups".

Patient 16. 22-year-old female. Diagnosis panic disorder with agoraphobia. Celecoxib concordance 100%.
No qualitative data available. No comments volunteered by the participant.

Patient 21. 26-year-old female. Diagnosis GAD. Celecoxib concordance 100%
Patient was less anxious with augmentation.
Participant's comment: "I think they work quiet well; I like them in combination with the sertraline"

Patient 22. 24-year-old male. Diagnosis social phobia, some symptoms of panic disorder. Celecoxib concordance 100%.
Augmentation didn't change the patient's mood, but seem to have alleviated his anhedonia. And seems to have improved positive cognitive bias. He also mentioned that the augmentation had enabled him to go on a holiday with others, which he had not done for some time.
Participant's comment: "it didn't change my depression, but I'm able to enjoy things that I didn't used to", "it took edge off the anxiety", positive feelings are not dull anymore", "I was not consistently better but I was able to enjoy certain moments a lot better", "I'm more able to pick up on the positives".

Patient 31. 60-year-old male. Diagnosis generalised anxiety disorder, some limited symptoms of panic attach and past manic episode. Celecoxib concordance 0 days less the 6 weeks course.
Much improved levels of anxiety; interest in activities and energy levels. Patient has been more at ease to discuss sexual difficulties with partner. Patient decided to approach his GP for further treatment with celecoxib.
Participant's comment: "I am more interested in doing more"; "there has been a significant decrease in avoiding instead of stagnation".

Patient 32. 24-year-old female. Diagnosis social phobia. Celecoxib concordance 5 days less the 6 weeks course, as she missed 10 night doses.
Minimally improved levels of anxiety, but appeared to had improved her levels of activity and her ability to enjoy. Patient started seeking change of job for another which involved more interaction with people. She appeared more able to challenge the status-quo in her life. Which she had previously expressed lack of satisfaction towards, i.e., relationship and moving home. These were steady for 3 years, which she didn't feel that she was able to challenge.
Participant's comment: "I can't say I noticed a difference"; "I feel I need a more stimulating job, may be the charity sector".

Patient 33. 58-year-old female. Diagnosis social phobia and generalised anxiety disorder. Celecoxib concordance 0 days less the 6 weeks course.
Noticeable improved levels of anxiety and sexual function. Improved mood; energy levels and interest in activities. Improved sexual drive and overall sexual function. Patient was able to re-instate sexual activity which had been on hold for many months.
Participant's comments: "I think I have noticed I haven't been anxious as much. I noticed a definite difference in the spiking of my anxiety. I had only one occasion of spike of anxiety over the last 6 weeks. Before so, I had 8 a month". "I feel I am getting my sense of humour back, nothing else changed in my life, it must be the medication. I am laughing more and messing about more". "I have more feelings, more drive. Once I week I have sexual thoughts, this is a massive change". "I feel hopeful, I can put up with physical things, this is to me is a big improvement".

Patient 34. 48-year-old male. Diagnosis panic disorder; generalised anxiety disorder and recurrent major depressive disorder. Celecoxib concordance 0 days less the 6 weeks course.
Noticeable improved levels of anxiety and reduced number of panic attacks. Improved mood; energy levels and interest in activities.
Participant's comments: "people around me said I look more relaxed. In 2, 3 weeks my anxiety sever attacks went, it took the edge off, these were less frequent. My baseline anxiety is less severe". "I had a massive increase of activity, I started going to the gym and cleated the garden".

Patient 35. 51-year-old female. Diagnosis diagnoses of generalised anxiety disorder, panic disorder, and recurrent major depressive disorder. Celecoxib concordance 8 days less the 6 weeks course.
Some improvement levels of anxiety.
Participant's comments: "I am not sure if it helped, but maybe, I want to take it for a longer period as it might help me".

6.8 Conclusion

The current study found a statistically significant correlation between sexual dysfunction scores (ASEX) and psychometric scores (HADS and CGS). These findings support rejection of the null hypothesis, for hypothesis 1 (H0: no statistically significant correlation between sexual dysfunction psychometrics scores and anxiety disorders psychometric scores). The current study found no statistically significant difference between mean cortisol levels in patients with symptoms of anxiety disorders and reference normal range laboratory values for hair cortisol. These findings support the null hypothesis, for hypothesis 2 (H0: no difference between cortisol levels in patients with symptoms of anxiety disorders and reference normal range lab values for hair cortisol). The current study found a Baseline low IL-12p70 in GAD, high TNF-α in panic disorder; GAD and social phobia, low IFN-γ in panic disorder, low IL-1β in GAD, low IL-6 in panic disorder, low IL-13 in GAD, and low IL-2 in GAD and social phobia. The study also found a significant correlation between HADS-A and IL-6. These findings support rejection of the null hypothesis, for hypothesis 3 (H0: no statistically significant correlation between levels of inflammatory makers and anxiety disorders psychometric scores). The current study found a statistically significant difference/change in anxiety psychometric scores (HADS-A) after celecoxib treatment. These findings support rejection of the null hypothesis, for hypothesis 4 (H0: no statistically significant difference/change in anxiety disorders psychometric scores after celecoxib treatment).

In conclusion, the work contained within this thesis provides evidence for the importance of investigating sexual dysfunction in this patient group; the significant correlation between some inflammatory markers and specific anxiety disorders; and the potential utility of augmentation in some patients with anxiety disorders. A relationship between anxiety symptoms and hair cortisol in this patient group was found, but this did not meet statistical significance. The relatively limited numbers of patients who provided blood

and hair samples, is a limiting factor regarding the conclusions that can be drawn about the relationship between HPA function, inflammatory markers and anxiety disorders. This study provides preliminary results given the small total number of participants and limitation of analysis methods and further research is needed in this area. Further research is needed to examine the effectiveness and acceptability of celecoxib augmentation in a larger clinical sample.

Appendix A Summary of vignette for each patient participant

Patient 1. A 48-year-old, unemployed, heterosexual man who was not in a relationship at the time of enrolment. Assessment of sexual function was based on solitary sexual activity. He first developed obsessive-compulsive symptoms in his early thirties. He later developed panic symptoms and social avoidance. He had not worked for almost 6 years due to the severity of anxiety symptoms. He had no significant medical or surgical history. His BMI was 36 (overweight). Interview with MINI generated DSM-5 diagnoses of current panic disorder with agoraphobia, and current obsessive-compulsive disorder. At Week 0, prior to treatment, he was found to have no sex drive; no arousal; was never able to get and keep an erection; and could never reach orgasm. Scale total scores were ASEX 30; SAS 3 and CGI-S 6.

At Week 6, he had undergone treatment with the combination of mirtazapine, pregabalin and clomipramine. Reassessment revealed some improvement of sexual function: he reported no sex drive; very difficult to get aroused, very difficult to achieve and maintain erection, and very difficult to reaching orgasm, but orgasms were somewhat satisfying. Assessment scores were WEMWBS 28; HADS-A 17; HADS-D 14; ASEX 25; CGI-S 5; CGI-I 2; OQUESA-GR 19; OQUESA-RP 22; OQUESA-ED 11; OQUESA-NC 23; and OQUESA-AC 19. At Week 12, he had undertaken six weeks' augmentation with celecoxib. Tablet count found 14 days less than the prescribed treatment course. Reassessment found some improvement in sexual function. He was found to have, very weak sex drive; very difficult to get aroused; somewhat difficult to achieve and maintain erection; somewhat difficult to reach orgasm and somewhat unsatisfying orgasm. Scale total scores were WEMWBS 30; HADS-A 15; HADS-D 11; ASEX 21; CGI-S 4; CGI-ICGI-I 3; OQUESA-GR 22; OQUESA-RP 22; OQUESA-ED 16; OQUESA-NC 19; and OQUESA-AC 16.

Patient 2. A 48-year-old, unemployed, heterosexual father of two children, in a stable heterosexual relationship at enrolment. He first developed anxiety symptoms in his early twenties. He was unemployed due to the severity of his anxiety symptoms. He had a history of bilateral knee replacement and essential hypertension, treated with a stable dosage of anti-hypertensive treatment for many years. His BMI was 44.9 (overweight). Interview with MINI generated DSM-5 diagnoses of lifetime panic disorder with current agoraphobia, and antisocial personality disorder. At Week 0, prior to treatment, he was found to have an extremely strong sex drive; extremely easy to get aroused; very easy able to get and keep an erection; very easy to reach orgasm and extremely satisfying orgasm. Total scale scores were ASEX 7; SAS 3; and EQRS 7.

At Week 6, after combination treatment with fluoxetine and trazodone, augmented with pregabalin, reassessment of sexual function found, no sex drive; very difficult to get aroused; very difficult to achieve and maintain erection; very difficult to reach orgasm and very unsatisfying orgasms. Scale total scores were WEMWBS 36; HADS-A 12; HADS-D 11; SAS 11; EQRS 22; ASEX 26; CGI-S 6; CGI-I 1; OQUESA-GR 15; OQUESA-RP 22; OQUESA-ED 10; OQUESA-NC 12; and OQUESA-AC 9. At Week 12, he had undertaken six weeks' augmentation with celecoxib, though a tablet count found 21 days less than the prescribed treatment course. Reassessment of sexual function found no change in sexual function. Scale total scores were WEMWBS 34; HADS-A 13; HADS-D 11; SAS 8; EQRS 27; ASEX 26; CGI-S 5; CGI-I 2; OQUESA-GR 19; OQUESA-RP 21; OQUESA-ED 17; OQUESA-NC 17; and OQUESA-AC 9.

Patient 3. A 24-year-old female University student, in a stable heterosexual relationship. She developed anxiety symptoms about a year prior to participation. She had no significant medical or surgical history. Her BMI was 21 (healthy). Interview with MINI generated a DSM-5 diagnosis of lifetime panic disorder. At Week 0, prior to treatment, she was found to have, a somewhat strong sex drive; somewhat easy to get aroused; extremely easy able to get vaginal lubrication; very easy

to reach orgasm and extremely satisfying orgasm. Scale total scores were WEMWBS 32; HADS-A 13; HADS-D 12; SAS 14; EQRS 28; ASEX 10; CGI-S 5; OQUESA-GR 17; OQUESA-RP 21; OQUESA-ED 21 and OQUESA-NC 21.

At Week 6, she had undergone six weeks of treatment with mirtazapine. Reassessment found worsened sexual function, though scores remained under ASEX thresholds for sexual dysfunction. She was found to have somewhat weak sex drive; somewhat easy to get aroused; very easily able to get vaginal lubrication; somewhat easy to reach orgasm and very satisfying orgasm. Scale total scores were WEMWBS 32; HADS-A 14; HADS-D 12; SAS 15; EQRS 23; ASEX 14; CGI 3; CGI-I 3; OQUESA-GR 16; OQUESA-RP 20; OQUESA-ED 19; OQUESA-NC 16 and OQUESA-AC 18. At Week 12, she had undergone six weeks of augmentation with celecoxib. Tablet count indicated full treatment adherence. Reassessment found an improvement in sexual function. She was found to have somewhat strong sex drive; very easy to get aroused; very easily able to get vaginal lubrication; very easy to reach orgasm and very satisfying orgasm. Scale total scores were WEMWBS 39; HADS-A 13; HADS-D 11; SAS 14; EQRS 28; ASEX 11; CGI-S 2; CGI-I 1; OQUESA-GR 16; OQUESA-RP 18; OQUESA-ED 20; OQUESA-NC 18; and OQUESA-AC 6.

Patient 4. A 23-year-old female University student in a stable heterosexual relationship. She developed anxiety symptoms about a year prior to participation. She had no significant medical or surgical history. She had a BMI of 20.9 (healthy). Interview with MINI generated a DSM-5 diagnosis of generalised social phobia. At Week 0, prior to treatment, she was found to have, a somewhat strong sex drive; somewhat difficult to get aroused; finding it somewhat difficult to get vaginal lubrication; somewhat difficult to reach orgasm and somewhat satisfying orgasm. Total scores were WEMWBS 23; HADS-A 16; HADS-D 14; SAS 6; EQRS 22; ASEX 18; CGI-S 5; OQUESA-GR 16; OQUESA-RP 25; OQUESA-ED 6 and OQUESA-NC 22.

At Week 6, she had undergone 6 weeks' treatment with CBT. Reassessment of sexual function found worsened sexual function. She was found to have somewhat weak sex drive; somewhat easy to get aroused; very easily able to get vaginal lubrication; somewhat difficult to reach orgasm and very unsatisfying orgasm. Scale total scores were WEMWBS 25; HADS-A 10; HADS-D 15; SAS 6; EQRS 19; ASEX 20; CGI 3; CGI-I 3; OQUESA-GR 15; OQUESA-RP 24; OQUESA-ED 17 and OQUESA-NC 13. At Week 12, she had undergone a further six weeks of CBT. Reassessment found an improvement in total sexual function, though she met criteria for sexual dysfunction in some domains. She was found to have somewhat strong sex drive; somewhat easy to get aroused; somewhat difficult to get vaginal lubrication; somewhat difficult to reach orgasm and somewhat satisfying orgasm. Total scores were WEMWBS 35; HADS-A 12; HADS-D 12; SAS 7; EQRS 18; ASEX 17; CGI-S 4; CGI-I 3; OQUESA-GR 21; OQUESA-RP 22; OQUESA-ED 9 and OQUESA-NC 13.

Patient 5. A 20-year-old female University student in a stable homosexual relationship. She developed anxiety symptoms about five years previously, received sertraline and escitalopram to poor effect, and then stopped all pharmacological treatments. She had no significant medical or surgical history. Her BMI was 25 (healthy). Interview with MINI generated the DSM-5 diagnosis of non-generalised social phobia. At Week 0, prior to treatment, she was found to have, a somewhat strong sex drive; very easily to get aroused; very easily to get vaginal lubrication; somewhat easily to reach orgasm and somewhat unsatisfying orgasm. Total scores were SAS 7; EQRS 22; ASEX 14 and CGI-S 2.

At Week 6, the relationship with her former partner had ended, and she had started another homosexual relationship. She had undergone 6 weeks' treatment with fluoxetine. Reassessment found an improvement in overall sexual function, apart from a worsened sexual drive. She was found to have very weak sex drive; extremely easy to get aroused; extremely easy to get vaginal lubrication; somewhat easily to reach orgasm and very satisfying orgasm. Total scores were

WEMWBS 36; HADS-A 13; HADS-D 10; SAS 8; EQRS 19; ASEX 12; CGI 2; CGI-I 4; OQUESA-GR 11; OQUESA-RP 10; OQUESA-ED 9; OQUESA-NC 14 and OQUESA-AC 15. At Week 12, she had undertaken six weeks' augmentation with celecoxib, tablet count indicating full treatment adherence. Reassessment found an improvement in total sexual function, with the overall score not meeting the threshold for sexual dysfunction. She was found to have somewhat weak sex drive; extremely easy to get aroused; extremely easy to get vaginal lubrication; very easily to reach orgasm and somewhat satisfying orgasm. Total scores were WEMWBS 40; HADS-A 10; HADS-D 5; SAS 11; EQRS 24; ASEX 11; CGI-S 2; CGI-I 2; OQUESA-GR 14; OQUESA-RP 13; OQUESA-ED 10; OQUESA-NC 15 and OQUESA-AC 12.

Patient 6. A 21-year old transgender (female to male) musician, who identified as asexual though in a relationship with a female at the time of enrolment. He was awaiting surgical gender reassignment referral at the time of enrolment, and was being prescribed depot testosterone. He had history of anxiety symptoms for the past year. He had no significant medical or surgical history. His BMI was 17.6 (underweight). Interview with MINI generated the DSM-5 diagnosis of panic disorder with agoraphobia. At Week 0, prior to treatment, he was found to have, no sex drive; no arousal; no vaginal lubrication; not able to reach orgasm. Total scores were SAS 3; EQRS 24; ASEX 30 and CGI-S 4.

At Week 6, he had undergone 6 weeks' treatment with fluoxetine. Reassessment found no change in overall sexual function. Total scores were WEMWBS 41; HADS-A 11; HADS-D 8; SAS 3; EQRS 24; ASEX 30; CGI 4; CGI-I 3; OQUESA-GR 17; OQUESA-RP 12; OQUESA-ED 14; OQUESA-NC 12 and OQUESA-AC 12. At Week 12, he had undergone six weeks of augmentation with celecoxib, a tablet count indicating full treatment adherence. Reassessment found no change in sexual function. Total scores were WEMWBS 47; HADS-A 9; HADS-D 7; SAS 3; EQRS 18; ASEX 30; CGI-S 3; CGI-I 2; OQUESA-GR 13; OQUESA-RP 11; OQUESA-ED 12; OQUESA-NC 11 and OQUESA-AC 9.

Patient 7. A 27-year-old female student nurse, heterosexual but not in a current relationship. She had a history of depression, and had struggled with anxiety symptoms for approximately one year. She had no significant medical or surgical history. Her BMI was 24.6 (healthy). Interview with MINI generated DSM-5 diagnoses of panic disorder and generalised social phobia. At Week 0, prior to treatment, she was found to have, somewhat weak sex drive; somewhat easy to get aroused; somewhat easily able to get vaginal lubrication; very difficult to reach orgasm and somewhat satisfying orgasm. Total scores were SAS 6; EQRS 19; ASEX 18 and CGI-S 5.

At Week 6, she had undergone 6 weeks of treatment with duloxetine, augmented with quetiapine in the later stages. Reassessment found, worsened sex drive and arousals. Total scores were WEMWBS 24; HADS-A 17; HADS-D 12; SAS 3; ASEX 21; CGI 5; CGI-I 3; OQUESA-GR 19; OQUESA-RP 21; OQUESA-ED 7; OQUESA-NC 23 and OQUESA-AC 12. At Week 12, following continued combination treatment with duloxetine and quetiapine, reassessment of sexual function found worsened arousal and vaginal lubrication. Total scores were WEMWBS 24; HADS-A 21; HADS-D 12; SAS 3; ASEX 24; CGI-S 5; CGI-I 4; OQUESA-GR 16; OQUESA-RP 19; OQUESA-ED 8; OQUESA-NC 15 and OQUESA-AC 15.

Patient 8. A 23-year-old female administrative officer in a stable heterosexual relationship. She had a history of major depressive disorder, which had been in remission. She had experienced anxiety symptoms for almost three years and would only occasionally use cannabis (once a month). She had no significant medical or surgical history. Her BMI was 26.8 (overweight). Interview with MINI generated DSM-5 diagnoses of generalised social phobia and lifetime limited symptoms panic disorder. At Week 0, prior to treatment, she was found to have somewhat weak sex drive; somewhat easy to get aroused; somewhat difficult to get vaginal lubrication; somewhat difficult to

reach orgasm can't reach orgasm. Scale total scores were WEMWBS 27; HADS-A 15; HADS-D 16; SAS 13; ASEX 20; CGI-S 4; OQUESA-GR 12; OQUESA-RP 21; OQUESA-ED 43 and OQUESA-NC 118.

At Week 6, she had broken-up with her partner. She had undergone treatment with venlafaxine. Reassessment, based on solitary sexual activity, found worsened sex drive but improved orgasm satisfaction. Scale total scores were WEMWBS 39; HADS-A 8; HADS-D 7; ASEX 21; CGI 5; CGI-I 3; CGI-I 2; OQUESA-GR 18; OQUESA-RP 14; OQUESA-ED 16; OQUESA-NC 14 and OQUESA-AC 14. At Week 12, she had undertaken six weeks of augmentation with celecoxib, tablet count indicating full treatment adherence. Reassessment, based on solitary sexual activity, found worsened arousal and vaginal lubrication. Scale total scores were WEMWBS 48; HADS-A 5; HADS-D 6; ASEX 11; CGI-S 3; CGI-I 2; OQUESA-GR 13; OQUESA-RP 13; OQUESA-ED 12; OQUESA-NC 13 and OQUESA-AC 9.

Patient 9. A 29-year-old unemployed woman in a stable heterosexual relationship. She had a history of depression, then in remission, but had suffered anxiety symptoms for almost one year. She had no significant medical or surgical history, apart from chronic neuropathic pain for which she was receiving pregabalin. Her BMI was 20.3 (healthy). Interview with MINI generated DSM-5 diagnoses of panic disorder with agoraphobia and non-generalised social phobia. At Week 0, prior to treatment, she was found to have, a very weak sex drive; somewhat difficult arousal; somewhat easy to get vaginal lubrication; somewhat difficult to reach orgasm and somewhat unsatisfying orgasm. Scale total scores were SAS 9; EQRS 26; ASEX 20 and CGI-S 5.

At Week 6, she had undergone treatment with vortioxetine and pregabalin. Reassessment found improved overall sexual function, apart from sexual drive, which remained the same. She was found to have very weak sex drive; extremely easy to get aroused; extremely easy to get vaginal lubrication; somewhat easily to reach orgasm and very satisfying orgasm. Scale total scores were WEMWBS 31; HADS-A 14; HADS-D 13; SAS 13; EQRS 27; ASEX 21; CGI 5; CGI-I 3; OQUESA-GR 15;

OQUESA-RP 22; OQUESA-ED 5; OQUESA-NC 19 and OQUESA-AC 19. At Week 12, she had undertaken six weeks' augmentation with celecoxib, tablet count indicating full adherence. Reassessment found an improvement in ability to reach orgasm and orgasm satisfaction. She was found to have somewhat weak sex drive; extremely difficult to get aroused; somewhat easy to get vaginal lubrication; somewhat difficult to reach orgasm and somewhat unsatisfying orgasm. Scale total scores were WEMWBS 37; HADS-A 9; HADS-D 8; SAS 9; EQRS 22; ASEX 19; CGI-S 3; CGI-I 2; OQUESA-GR 11; OQUESA-RP 17; OQUESA-ED 5; OQUESA-NC 16 and OQUESA-AC 13.

Patient 10. A 24-year-old female nursing student, in a "casual" relationship. She had a diagnosis of epilepsy and was stabilised on topiramate and clobazam. Her BMI was 25.3 (overweight). Interview with MINI generated DSM-5 diagnoses of panic disorder with agoraphobia and social phobia. At Week 0, prior to treatment, she was found to have a somewhat strong sex drive; somewhat easy arousal; somewhat easy to get vaginal lubrication; very difficult to reach orgasm and very satisfying orgasm. Scale total scores were SAS 13; EQRS 15; ASEX 16 and CGI-S 5.

At Week 6, she was no longer in that relationship, but had started another. She had undergone 6 weeks' treatment with citalopram. Reassessment found, worsened overall sexual function, in all domains. She was found to have no sex drive; very difficult to get aroused; very difficult to get vaginal lubrication; never reach orgasm. Scales' total scores were WEMWBS 22; HADS-A 13; HADS-D 14; SAS 8; ASEX 28; CGI 5; CGI-I 6; OQUESA-GR 15; OQUESA-RP 22; OQUESA-ED 5; OQUESA-NC 19 and OQUESA-AC 19. She did not attend the Week 12 assessment.

Patient 11. A 48-year-old unemployed man in a "casual" relationship. He had experienced mobility problems related to a hip injury for eight years. His BMI was 25.9 (overweight). Interview with MINI generated the DSM-5 diagnosis of generalised anxiety disorder. At Week 0, prior to treatment, he

was found to have, a somewhat weak sex drive; somewhat easy to get aroused; somewhat difficult to get and keep erection; somewhat easy to reach orgasm and somewhat satisfying orgasm. Scale total scores were SAS 7; ASEX 17 and CGI-S 3.

At Week 6, he had undertaken six weeks of sertraline treatment. Reassessment found improved overall sexual function. He was found to have very strong sex drive; very easy to get aroused; extremely easy to get and keep erection; extremely easy to reach orgasm and extremely satisfying orgasm. Scale total scores were WEMWBS 76; HADS-A 4; HADS-D 0; SAS 4; ASEX 7; CGI 2; CGI-I 1; OQUESA-GR 13; OQUESA-RP 5; OQUESA-ED 5; OQUESA-NC 5 and OQUESA-AC 6. At Week 12, he had undergone six further weeks of sertraline treatment. Reassessment found improvement of sex drive. He was found to have extremely strong sex drive; very easy to get aroused; extremely easy to get and keep an erection; extremely easy to reach orgasm and extremely satisfying orgasm. Scale total scores were WEMWBS 69; HADS-A 1; HADS-D 1; SAS 11; ASEX 6; CGI-S 2; CGI-I 1; OQUESA-GR 10; OQUESA-RP 5; OQUESA-ED 6; OQUESA-NC 5 and OQUESA-AC 6.

Patient 12. A 21-year-old female restaurant manager in a long-term homosexual relationship, who described her sexual preference as bisexual. She had a history of major depressive disorder and described blood phobia. She had no significant medical or surgical history. Her BMI was 37.3 (overweight). Interview with MINI generated DSM-5 diagnoses of panic disorder with agoraphobia and generalised anxiety disorder. At Week 0, prior to treatment, she was found to have, a very strong sex drive; extremely easy to get aroused; extremely easy to get vaginal lubrication; somewhat easy to reach orgasm and very satisfying orgasm. Scale total scores were WEMWBS 32; HADS –A 21; HADS-D 11; SAS 10; EQRS 17; ASEX 9 and CGI-S 5.

At Week 6, she had undergone six weeks of combination treatment with sertraline and quetiapine. Reassessment found worsened overall sexual function, although did not meet the threshold of

sexual dysfunction. She was found to have very strong sex drive; extremely easy to get aroused; extremely easy to get vaginal lubrication; somewhat difficult to reach orgasm and somewhat unsatisfying orgasm. Scale total scores were WEMWBS 28; HADS-A 21; HADS-D 11; SAS 11; EQRS 18; ASEX 13; CGI 5; CGI-I 3; OQUESA-GR 22; OQUESA-RP 18; OQUESA-ED 11; OQUESA-NC 15 and OQUESA-AC 28. At Week 12, she had undertaken six weeks of augmentation with celecoxib. Tablet count indicated complete treatment adherence. Reassessment found improvement in arousal; ability to get lubrication; ability to reach orgasm and orgasm satisfaction. She was found to have very strong sex drive; extremely easy to get aroused; extremely easy to get vaginal lubrication; very easy to reach orgasm and very satisfying orgasm. Scales' total scores were WEMWBS 44; HADS-A 17; HADS-D 9; SAS 10; EQRS 18; ASEX 8; CGI-S 4; CGI-I 1; OQUESA-GR 22; OQUESA-RP 18; OQUESA-ED 11; OQUESA-NC 26 and OQUESA-AC 23.

Patient 13. A 20-year-old transgender health professional, undergoing female-to-male gender reassignment, and currently awaiting surgery: his sexual preference was male but he was not in a stable relationship. Assessment of sexual function was based on casual relationships. He was receiving testosterone depot injection. He had no significant medical or surgical history. His BMI was 18.2 (underweight). Interview with MINI generated DSM-5 diagnoses of panic disorder with agoraphobia and generalised anxiety disorder. At Week 0, prior to treatment, he was found to have a somewhat strong sex drive; somewhat easy arousal; somewhat difficult to get vaginal lubrication; somewhat difficult to reach orgasm and somewhat unsatisfying orgasm. Scale total scores were WEMWBS 29; HADS –A 19; HADS-D 10; SAS 6; ASEX 18 and CGI-S 3.

At Week 6, he had undergone six weeks of CBT. Reassessment found improved overall sexual function. He was found to have very strong sex drive; very easy to get aroused; somewhat easy to get vaginal lubrication; somewhat easy to reach orgasm and somewhat satisfying orgasm. Scale total scores were WEMWBS 40; HADS-A 15; HADS-D 9; SAS 10; EQRS 26; ASEX 13; CGI 3; CGI-I 4;

OQUESA-GR 15; OQUESA-RP 18; OQUESA-ED 10 and OQUESA-NC 13. At Week 12, he had undertaken six further weeks of CBT. Reassessment found no change in his sexual function. He was found to have very strong sex drive; very easy to get aroused; somewhat easy to get vaginal lubrication; somewhat easy to reach orgasm and somewhat satisfying orgasm. Scale total scores were WEMWBS 37; HADS-A 15; HADS-D 9; SAS 10; EQRS 26; ASEX 13; CGI 3; CGI-I 4; OQUESA-GR 15; OQUESA-RP 16; OQUESA-ED 11 and OQUESA-NC 14.

Patient 14. A 27-year-old male engineer in a stable heterosexual relationship. He had experienced anxiety symptoms over the prior year. He underwent hernia surgery when 22-years old. His BMI was 54.7 (overweight). Interview with MINI generated the DSM-5 diagnosis of obsessive-compulsive disorder. At Week 0, prior to treatment, he was found to have, extremely strong sex drive; somewhat easy to get aroused; extremely easy to get and keep erection; extremely easy to reach orgasm and extremely satisfying orgasm. Scale total scores were SAS 12; EQRS 24; ASEX 7 and CGI-S 4.

At Week 6, he had undergone six weeks of sertraline treatment. Reassessment found worsened overall sexual function. He was found to have somewhat weak sex drive; somewhat difficult to get aroused; extremely easy to get and keep erection; very difficult to reach orgasm and extremely satisfying orgasm. Scale total scores were WEMWBS 29; HADS-A 11; HADS-D 2; SAS 11; ASEX 15; CGI 4; CGI-I 2; OQUESA-GR 13; OQUESA-RP 6; OQUESA-ED 5; OQUESA-NC 5 and OQUESA-AC 6. At Week 12, he had undertaken six weeks of augmentation with celecoxib. Tablet count found complete treatment adherence. Reassessment found improvement overall sexual function apart from worsened ability to reach orgasm. He was found to have somewhat strong sex drive; very easy to get aroused; extremely easy to get and keep an erection; very difficult to reach orgasm and extremely satisfying orgasm. Scale total scores were WEMWBS 51; HADS-A 9; HADS-D 4; SAS 13;

EQRS 25; ASEX 12; CGI-S 1; CGI-I 1; OQUESA-GR 5; OQUESA-RP 9; OQUESA-ED 17; OQUESA-NC 11 and OQUESA-AC 14.

Patient 15. A 22-year-old female chef, in a stable heterosexual relationship. She had no significant medical or surgical history. Her BMI was 22.3 (healthy). Interview with MINI generated the DSM-5 diagnosis of generalised anxiety disorder. At Week 0, prior to treatment, she was found to have, somewhat strong sexual drive; very difficult to get aroused; somewhat difficult to get vaginal lubrication; very difficult to reach orgasm and very unsatisfying orgasm. Scale total scores were SAS 7; EQRS 14; ASEX 22 and CGI-S 5.

At Week 6, she had undergone six weeks of sertraline treatment. Reassessment found worsened her overall sexual function, apart from no change in sex drive and improved arousal. She was found to somewhat strong sex drive; somewhat difficult to get aroused; somewhat difficult to get vaginal lubrication; and never able reach orgasm. Scale total scores were WEMWBS 16; HADS-A 19; HADS-D 13; SAS 8; EQRS 17; ASEX 23; CGI 5 and CGI-I 3. At week 12, she had undertaken a further six weeks of sertraline treatment. Reassessment found no change in overall sexual dysfunction, apart from improved ability to reach orgasm and orgasm satisfaction. She was found to somewhat strong sex drive; somewhat difficult to get aroused; somewhat difficult to get vaginal lubrication; very difficult to reach orgasm and very unsatisfying orgasm. Scales' total scores were WEMWBS 18; HADS-A 18; HADS-D 13; SAS 7; EQRS 15; ASEX 21; CGI-S 5 and CGI-I 4.

Patient 16. A 22-year-old female technician in a stable heterosexual relationship. She had one son from a previous relationship. She had struggled with anxiety symptoms for three months prior to participation. She had a history of recurrent depressive disorder, which was in remission at the time of enrolment. She had no significant medical or surgical history. Her BMI was 28.1 (overweight).

Interview with MINI generated DSM-5 diagnoses of panic disorder with agoraphobia and non-generalised social phobia. At Week 0, prior to treatment, she was found to have a very strong sex drive; somewhat easy to get aroused; very difficult to get vaginal lubrication; somewhat difficult to reach orgasm and somewhat satisfying orgasm. Scale total scores were SAS 10; EQRS 14; ASEX 17 and CGI-S 5.

At Week 6, she had undergone six weeks of treatment with duloxetine. Reassessment found worsened overall sexual function, but improved orgasm satisfaction. She was found to have somewhat strong sex drive; somewhat easy to get aroused; somewhat easy to get vaginal lubrication; somewhat difficult to reach orgasm and very satisfying orgasm. Scale total scores were WEMWBS 38; HADS-A 17; HADS-D 10; SAS 9; EQRS 18; ASEX 18; CGI-S 5; CGI-I 3; OQUESA-GR 5; OQUESA-RP 18; OQUESA-ED 9; OQUESA-NC 12 and OQUESA-AC 8. At Week 12, she had undertaken six weeks of augmentation with celecoxib, tablet count indicating full treatment adherence. Reassessment found improvement in the ability to get vaginal lubrication and ability to reach orgasm. She was found to have somewhat strong sex drive; somewhat easy to get aroused; somewhat easy to get vaginal lubrication; somewhat difficult to reach orgasm and very satisfying orgasm. Scale total scores were WEMWBS 42; HADS-A 13; HADS-D 9; SAS 9; EQRS 20; ASEX 15; CGI-S 4; CGI-I 2; OQUESA-GR 6; OQUESA-RP 16; OQUESA-ED 11; OQUESA-NC 13 and OQUESA-AC 6.

Patient 17. A 37-year-old male heterosexual married accountant. He began to experience anxiety symptoms four months prior to participation. He had no significant medical or surgical history. His BMI was 20.6 (healthy). Interview with MINI generated the DSM-5 diagnosis of generalised anxiety disorder. At Week 0, prior to treatment, he was found to have, very weak sex drive; never aroused; very difficult to get and keep erection; somewhat difficult to reach orgasm and very unsatisfying orgasm. Scale total scores were WEMWBS 20; HADS-A 17; HADS-D 17; SAS 4; EQRS 14; ASEX 25 and CGI-S 7; OQUESA-GR 8; OQUESA-RP 25; OQUESA-ED 10 and OQUESA-NC 15.

At Week 6, he had undergone six weeks of escitalopram treatment. Reassessment found an improvement in overall sexual function. He was found to somewhat weak sex drive; somewhat difficult to get aroused; somewhat difficult to get and keep erection; somewhat difficult to reach orgasm and somewhat unsatisfying orgasm. Scale total scores were WEMWBS 52; HADS-A 6; HADS-D 7; SAS 6; EQRS 19; ASEX 20; CGI 2; CGI-I 2; OQUESA-GR 18; OQUESA-RP 15; OQUESA-ED 8; OQUESA-NC 12 and OQUESA-AC 10. At Week 12, he had undergone six further weeks of escitalopram treatment. Reassessment found an improvement in overall sexual function. He was found to have somewhat strong sex drive; somewhat easy to get aroused; very easy to get and keep an erection; somewhat easy to reach orgasm and somewhat satisfying orgasm. Scale total scores were WEMWBS 63; HADS-A 3; HADS-D 0; SAS 11; EQRS 25; ASEX 14; CGI-S 1; CGI-I 1; OQUESA-GR 12; OQUESA-RP 9; OQUESA-ED 9; OQUESA-NC 9 and OQUESA-AC 7.

Patient 18. A 22-year-old female hospital administrator in a stable heterosexual relationship. She had no significant medical or surgical history. Her BMI was 19.8 (healthy). Interview with MINI generated DSM-5 diagnoses of OCD and social phobia. At Week 0, prior to treatment, she was found to have a very weak sex drive; very difficult to get aroused; very difficult to get vaginal lubrication and never reach orgasm. Scale total scores were SAS 6; EQRS 16; ASEX 27 and CGI-S 6.

At Week 6, she had undergone six weeks of citalopram treatment. Reassessment found improved overall sexual function, apart from sex drive, which remained the same. She was found to have very weak sex drive; somewhat difficult to get aroused; somewhat difficult to get vaginal lubrication; somewhat difficult to reach orgasm and somewhat satisfying orgasm. Scale total scores were WEMWBS 32; HADS-A 17; HADS-D 11; SAS 6; EQRS 16; ASEX 20; CGI-S 6; CGI-I 2; OQUESA-GR 21; OQUESA-RP 22; OQUESA-ED 13; OQUESA-NC 20 and OQUESA-AC 20. She did not attend the Week 12 assessment.

Patient 19. A 23-year-old female administrator in a stable heterosexual relationship. She developed anxiety symptoms eighteen months previously. She had no significant medical history apart from a road traffic accident with liver contusion that required emergency surgery. Her BMI was 20 (healthy). Interview with MINI generated the DSM-5 diagnosis of generalised social phobia. At Week 0, prior to treatment, she was found to have, a somewhat strong sex drive; somewhat easy to get aroused; somewhat difficult to get vaginal lubrication; somewhat difficult to reach orgasm and somewhat satisfying orgasm. Scale total scores were WEMWBS 30; HADS-A 12; HADS-D 12; SAS 7; EQRS 18; ASEX 17 and CGI-S 6; OQUESA-GR 20; OQUESA-RP 20; OQUESA-ED 9 and OQUESA-NC 11.

At Week 6, she had six weeks of treatment with propranolol. Reassessment of sexual function found worsened overall sexual function, apart from vaginal lubrication and ability to reach orgasm, which remained the same. She was found to have somewhat weak sex drive; somewhat difficult to get aroused; somewhat difficult to get vaginal lubrication; somewhat difficult to reach orgasm and very unsatisfying orgasm. Scale total scores were WEMWBS 35; HADS-A 10; HADS-D 12; SAS 8; EQRS 22; ASEX 21; CGI-S 6; CGI-I 3; OQUESA-GR 16; OQUESA-RP 22; OQUESA-ED 8; OQUESA-NC 13 and OQUESA-AC 11. At Week 12, she had stopped propranolol and changed to sertraline (4 weeks prior to the review). Reassessment found worsened drive and arousal. She was found to have very weak sex drive; very difficult to get aroused; somewhat difficult to get vaginal lubrication; somewhat difficult to reach orgasm and very unsatisfying orgasm. Scale total scores were WEMWBS 37; HADS-A 13; HADS-D 8; SAS 8; EQRS 17; ASEX 23; CGI-S 4; CGI-I 2; OQUESA-GR 20; OQUESA-RP 19; OQUESA-ED 8; OQUESA-NC 11 and OQUESA-AC 13.

Patient 20. A 23-year-old unemployed man in a stable heterosexual relationship. He had a past history of anxiety problems, which had been in remission for one year, reappearing one month prior to participation. He had no significant medical or surgical history. His BMI was 22.5 (healthy). Interview with MINI generated the DSM-5 diagnosis of generalised anxiety disorder. At Week 0, prior to treatment, he was found to have a somewhat weak sex drive; somewhat difficult arousal; very easy to get and maintain erection; very easy to reach orgasm and somewhat unsatisfying orgasm. Scale total scores were WEMWBS 22; HADS-A 16; HADS-D 10; SAS 6; EQRS 13; ASEX 16 and CGI-S 4; OQUESA-GR 14; OQUESA-RP 18; OQUESA-ED 13 and OQUESA-NC 17.

At Week 6, he had not undergone additional treatment. Reassessment found improved overall sexual function. He was found to have somewhat strong sex drive; somewhat easy to get aroused; extremely easy to get and maintain erection; somewhat easy to reach orgasm and somewhat satisfying orgasm. Scale total scores were WEMWBS 30; HADS-A 13; HADS-D 12; SAS 9; EQRS 15; ASEX 13; CGI-S 4; CGI-I 3; OQUESA-GR 13; OQUESA-RP 21; OQUESA-ED 17 and OQUESA-NC 21. At Week 12, he disclosed that he been drinking heavily for four weeks, and met the criteria for alcohol dependence: this condition is an exclusion criterion so his study participation ended.

Patient 21. A 26-year-old unemployed woman in a stable heterosexual relationship. She developed anxiety symptoms approximately four years prior to participation. She suffered a road accident two years previously, with a tibial fracture. She had no other significant medical or surgical history. Her BMI was 24.1 (healthy). Interview with MINI generated DSM-5 diagnoses of generalised anxiety disorder and antisocial personality disorder. At Week 0, prior to treatment, she was found to have a very strong sex drive; somewhat easy to get aroused; very easy to get vaginal lubrication; very easy to reach orgasm and very satisfying orgasm. Scale total scores were SAS 9; EQRS 20; ASEX 11 and CGI-S 2.

At Week 6, she had undergone six weeks of sertraline treatment. Reassessment found worsened overall sexual function, apart from lubrication and orgasm satisfaction, which remained the same. She was found to have a very weak sex drive; somewhat difficult to get aroused; very easy to get vaginal lubrication; somewhat difficult to reach orgasm and very satisfying orgasm. Scale total scores were WEMWBS 42; HADS-A 10; HADS-D 5; SAS 8; EQRS 18; ASEX 17; CGI-S 2; CGI-I 3; OQUESA-GR 13; OQUESA-RP 18; OQUESA-ED 8; OQUESA-NC 16; and OQUESA-AC 12. At Week 12, she had undertaken six weeks of augmentation with celecoxib, tablet count indicating complete treatment adherence. Reassessment found improvement in overall sexual function apart from lubrication and orgasm satisfaction, which remained unchanged. She was found to have a very strong sex drive; very easy to get aroused; very easy to get vaginal lubrication; very easy to reach orgasm and very satisfying orgasm. Scale total scores were WEMWBS 50; HADS-A 4; HADS-D 3; SAS 8; EQRS 19; ASEX 10; CGI-S 2; CGI-I 3; OQUESA-GR 10; OQUESA-RP 11; OQUESA-ED 9; OQUESA-NC 11 and OQUESA-AC 10.

Patient 22. A 24-year-old heterosexual man, an engineer who was not in a relationship at the time of enrolment. Sexual function was assessed based on solitary sexual activity. He had a depressive disorder 10 years prior to participation, treated at that time. Accidental concussion was followed by behavioural disturbance and suicidality, requiring hospital admission. He described four months of anxiety-related problems associated with work challenges, and lifelong blood-injury phobia. He had no other significant medical or surgical history. His BMI was 21.9 (healthy). Interview with MINI generated DSM-5 diagnosis of social phobia and of lifetime symptoms of panic disorder and agoraphobia. At Week 0, prior to treatment, he was found to have a very strong sex drive; extremely easy to get aroused; extremely easy to get and maintain erection; very easy to reach orgasm and somewhat satisfying orgasm. Scale total scores were WEMWBS 37; HADS-A 15; HADS-D 11; ASEX 9 and CGI-S 5; OQUESA-GR 15; OQUESA-RP 21; OQUESA-ED 8 and OQUESA-NC 20.

At Week 6, he had undergone six weeks of venlafaxine treatment. Reassessment found worsened overall sexual function. He was found to have somewhat weak sex drive; very easy to get aroused; very difficult to get and maintain erection; very difficult to reach orgasm and very unsatisfying orgasm. Scale total scores were WEMWBS 22; HADS-A 17; HADS-D 13; ASEX 21; CGI-S 5; CGI-I 5; OQUESA-GR 10; OQUESA-RP 22; OQUESA-ED 9; OQUESA-NC 20 and OQUESA-AC 15. At Week 12, he had undertaken six weeks of celecoxib augmentation, tablet count indicating full treatment adherence. Reassessment found improvement in his overall sexual function. He was found to have very strong sex drive; extremely easy to get aroused; somewhat easy to get and maintain erection; somewhat difficult to reach orgasm and somewhat satisfying orgasm. Scale total scores were WEMWBS 49; HADS-A 13; HADS-D 10; ASEX 13; CGI-S 3; CGI-I 1; OQUESA-GR 11; OQUESA-RP 13; OQUESA-ED 5; OQUESA-NC 24 and OQUESA-AC 11.

Patient 23. A 22-year-old female gallery assistant in a stable heterosexual relationship. She had been troubled by anxiety symptoms for twelve months. She had histories of surgical septoplasty and depression and was on a combined oral contraceptive pill. Her BMI was 22.2 (healthy). Interview with MINI generated DSM-5 diagnoses of generalised anxiety disorder and past major depressive disorder. At Week 0, prior to treatment, she was found to have a somewhat strong sex drive; somewhat easy to get aroused; very easy to get vaginal lubrication; somewhat easy to reach orgasm and somewhat satisfying orgasm. Scale total scores were SAS 11; EQRS 28; ASEX 14 and CGI-S 4.

At Week 6, she had undergone six weeks of citalopram treatment. Reassessment found worsened overall sexual function, apart from orgasm satisfaction, which remained the same. She was found to have no sex drive; very difficult to get aroused; very difficult to get vaginal lubrication; somewhat difficult to reach orgasm and somewhat satisfying orgasm. Scale total scores were WEMWBS 36; HADS-A 16; HADS-D 8; SAS 10; EQRS 28; ASEX 23; CGI-S 4; CGI-I 3; OQUESA-GR 24; OQUESA-RP 24;

OQUESA-ED 10; OQUESA-NC 18 and OQUESA-AC 30. At Week 12, she had undertaken 6 weeks of celecoxib augmentation, tablet count indicating full treatment adherence. Reassessment found improved overall sexual function. She was found to have somewhat strong sex drive; somewhat difficult to get aroused; somewhat easy to get vaginal lubrication; somewhat easy to reach orgasm and very satisfying orgasm. Scale total scores were WEMWBS 42; HADS-A 11; HADS-D 7; SAS 11; EQRS 27; ASEX 15; CGI-S 3; CGI-I 2; OQUESA-GR 21; OQUESA-RP 18; OQUESA-ED 6; OQUESA-NC 18 and OQUESA-AC 21.

Patient 24. A 23-year-old woman, a married travel agent. She had experienced anxiety symptoms for seven months. She had no significant medical or surgical history. Her BMI was 22 (healthy). Interview with MINI generated the DSM-5 diagnosis of generalised anxiety disorder. At Week 0, prior to treatment, she was found to have no sex drive; never aroused; never able to get vaginal lubrication and never able to reach orgasm. Scale total scores were SAS 3; EQRS 8; ASEX 30 and CGI-S 4.

At Week 6, she had undergone six weeks of sertraline treatment. Reassessment found no effect on overall sexual function. She was found to have no sex drive; never aroused; never able to get vaginal lubrication and never able to reach orgasm. Scales' total scores were WEMWBS 29; HADS-A 15; HADS-D 13; SAS 3; EQRS 28; ASEX 30; CGI-S 5; CGI-I 2; OQUESA-GR 16; OQUESA-RP 14; OQUESA-ED 14; OQUESA-NC 17 and OQUESA-AC 11. She did not attend the Week 12 assessment.

Patient 25. A 24-year-old unemployed man with no current sexual partner. Assessment of sexual function was based on solitary sexual activity. He been troubled by severe anxiety symptoms and social isolation for six months. His long-term partner died by suicide twelve months prior to participation. He had no significant medical or surgical history. His BMI was 17.8 (underweight).

Interview with MINI generated the DSM-5 diagnosis of generalised anxiety disorder. At Week 0, prior to treatment, he was found to have, a very strong sex drive; extremely easy to get aroused; very easy to get and maintain erection; somewhat easy to reach orgasm and extremely satisfying orgasm. Scale total scores were ASEX 9 and CGI-S 7.

At Week 6, he had undergone six weeks of combination treatment with sertraline and olanzapine. Reassessment found worsened overall sexual function, apart from the ability to get and maintain erection, which remained the same. He was found to have somewhat weak sex drive; somewhat easy to get aroused; very easy to get and maintain erection; somewhat easy to reach orgasm and somewhat satisfying orgasm. Scale total scores were WEMWBS 36; HADS-A 11; HADS-D 15; ASEX 15; CGI-S 7; CGI-I 2; OQUESA-GR 23; OQUESA-RP 24; OQUESA-ED 23; OQUESA-NC 24 and OQUESA-AC 27. He did not attend the Week 12 assessment.

Patient 26. A 56-year-old married heterosexual graphics designer with a history of recurrent depression. He was struggling with fluctuating levels of anxiety over the past year. He had a history of arrhythmia, type II diabetes, hypercholesterolemia and hypertension, and was taking clopidogrel, bisdoprolol, Ramipril, atorvastatin, lansoprazole and metformin. His physical health was stable at the time of enrolment, but he was unsuitable for the augmentation phase. His BMI was 31.4 (overweight). Interview with MINI generated a DSM-5 diagnosis of generalised anxiety disorder and some features of social phobia. At Week 0, prior to treatment, he was found to have no impairment of sexual function. This was associated with total scores of, SAS 14; EQRS 16; ASEX 7 and CGI-S 3.

At Week 6, he had undergone 6 weeks of treatment with duloxetine, which was augmented with pregabalin shortly afterwards. Reassessment of sexual function found worsened overall sexual function. He was found to have somewhat weak sex drive; somewhat difficult to get aroused;

somewhat easy to get and maintain erection and never able to reach orgasm. This was associated with total scores of, WEMWBS 25; HADS-A 20; HADS-D 15; SAS 12; EQRS 25; ASEX 19; CGI-S 3; CGI-I 3; OQUESA-GR 23; OQUESA-RP 23; OQUESA-ED 22; OQUESA-NC 23 and OQUESA-AC 16. At Week 12, he had continued treatment with duloxetine and pregabalin. Reassessment found no change in his overall sexual function. He was found to have somewhat weak sex drive; somewhat difficult to get aroused; somewhat difficult to get and maintain erection and never able to reach orgasm. Scale total scores were WEMWBS 22; HADS-A 19; HADS-D 19; SAS 12; EQRS 26; ASEX 24; CGI-S 3; CGI-I 4; OQUESA-GR 23; OQUESA-RP 23; OQUESA-ED 22; OQUESA-NC 23 and OQUESA-AC 16.

Patient 27. A 38-year-old unemployed man with no current sexual stable relationship. Assessment of sexual function was based on solitary sexual activity and occasional “casual”, heterosexual encounters. He described fluctuating anxiety symptoms for two years following the break-up of a long-term relationship, and had undergone multiple treatments (citalopram, mirtazapine and trazodone) all of which ended within three weeks due to unacceptable side effects. He used cannabis occasionally but did not meet criteria for substance dependence. At the time of enrolment, he had been free of drugs and prescribed medication for four months. He had no significant medical or surgical history. His BMI was 22.45 (healthy). Interview with MINI generated the DSM-5 diagnosis of panic disorder. At Week 0, prior to treatment, he was found to have, a very weak sex drive; somewhat difficult to get aroused; somewhat difficult to get and maintain erection; very easy to reach orgasm and somewhat satisfying orgasm. Scale total scores were WEMBWS 30; HADS-A 11; HADS-D 16; SAS 9; ASEX 18 and CGI-S 2; OQUESA-GR 21; OQUESA-RP 24; OQUESA-ED 10 and OQUESA-NC 23. He did not attend the Week 6 assessment.

Patient 28. A 38-year-old married heterosexual part-time teacher, the mother of a three-year-old daughter. She had experienced anxiety symptoms for three years, following childbirth. Her symptoms worsened one year prior to participation, following the sudden death of a family member. She had no significant medical or surgical history. Her BMI was 22.7 (healthy). Interview with MINI generated the DSM-5 diagnoses of OCD, specific phobia (illness phobia) and some features of panic disorder (non-generalised). At Week 0, prior to treatment, she was found to have a somewhat weak sex drive; somewhat difficult to get aroused; somewhat difficult to get vaginal lubrication; somewhat difficult to reach orgasm and somewhat satisfying orgasm. Scale total scores were SAS 10; EQRS 21; ASEX 15 and CGI-S 3.

At Week 6, she had undergone six weeks of combination treatment with fluoxetine and olanzapine. Reassessment found worsened overall sexual function. She was found to have no sex drive; very difficult to get aroused; very difficult to get vaginal lubrication; and never reach orgasm. Scale total scores were WEMWBS 20; HADS-A 20; HADS-D 17; SAS 5; EQRS 19; ASEX 28; CGI-S 3; CGI-I 4; OQUESA-GR 13; OQUESA-RP 24; OQUESA-ED 14; OQUESA-NC 19 and OQUESA-AC 10. She did not attend the Week 12 assessment.

Patient 29. A 42-year-old married heterosexual man, a research scientist. He had experienced anxiety for six months associated with intermittent but marked muscle stiffness and immobility. He had no significant medical or surgical history. His BMI was 26.78 (overweight). Interview with MINI generated the DSM-5 diagnosis of generalised anxiety disorder. At Week 0, prior to treatment, he was found to have a very weak sex drive; very difficult to get aroused; somewhat easy to get and maintain erection; somewhat easy to reach orgasm and very satisfying orgasm. Scales' total scores were SAS 8; EQRS 16; ASEX 18 and CGI-S 5.

At Week 6, he had undergone six weeks of sertraline treatment. Reassessment found no effect on his overall sexual function, apart from improved arousal. He was found to have a very weak sex drive; somewhat easy to get aroused; somewhat easy to get and maintain erection; somewhat easy to reach orgasm and very satisfying orgasm. Scale total scores were WEMWBS 48; HADS-A 8; HADS-D 9; SAS 6; EQRS 15; ASEX 16; CGI-S 5; CGI-I 5; OQUESA-GR 23; OQUESA-RP 16; OQUESA-ED 6; OQUESA-NC 14 and OQUESA-AC 6. At Week 12, he had stopped sertraline one week previously but had started a daily, intensive exercise regimen. Reassessment found worsened overall sexual function, apart from arousal, which was the same. He was found to have no sex drive; somewhat easy to get aroused; never able to get and maintain erection; never able to reach orgasm. Scale total scores were WEMWBS 43; HADS-A 7; HADS-D 11; SAS 7; EQRS 15; ASEX 23; CGI-S 4; CGI-I 5; OQUESA-GR 14; OQUESA-RP 13; OQUESA-ED 7 and OQUESA-NC 10.

Patient 30. A 49-year-old female married heterosexual care assistant with a 26-year-old son. She had no significant medical or surgical history. Her BMI was 20.3 (healthy). Interview with MINI generated the DSM-5 diagnosis of generalised anxiety disorder. At Week 0, prior to treatment, she was found to have, no sex drive; never aroused; very difficult to get vaginal lubrication and never reach orgasm. Scales' total scores were WEMWBS 14; HADS-A 18; HADS-D 17; SAS 4; EQRS 16; ASEX 29; CGI-S 5; OQUESA-GR 12; OQUESA-RP 25; OQUESA-ED 17 and OQUESA-NC 23. She did not attend the Week 6 assessment.

Patient 31. A 60-year-old retired, heterosexual married male hostel manager. Sexual activity was limited to solitary sexual activity. He described a 5-year history of anxiety symptoms. He suffered an accident 16 years prior to enrolment, which led to impaired mobility, and subsequent spinal surgery and physiotherapy. He took early retirement on ill health grounds. He had no other

significant medical or surgical history. His BMI was 27.3 (overweight). Interview with MINI, generated a DSM-5 diagnosis of generalised anxiety disorder, some limited symptoms of panic attach and past manic episode. At Week 0, prior to treatment, he was found to have, no sex drive; never aroused; somewhat easy to get and maintain erection; somewhat easy to reach orgasm and somewhat satisfying orgasm. Scales total scores were SAS 10; EQRS 21; ASEX 21 and CGI-S 5.

At Week 6, he had undergone 6 weeks of treatment with sertraline and quetiapine. Reassessment found no effect on his overall sexual function, apart from worsened orgasm satisfaction. He was found to have no sex drive; never aroused; somewhat easy to get and maintain erection; somewhat easy to reach orgasm and somewhat unsatisfying orgasm. Scales' total scores were WEMWBS 38; HADS-A 9; HADS-D 9; SAS 3; EQRS 23; ASEX 22; CGI-S 5; CGI-I 1; OQUESA-GR 13; OQUESA-RP 16; OQUESA-ED 7; OQUESA-NC 14 and OQUESA-AC 16.

At Week 12, he had undertaken 6 weeks of celecoxib augmentation, tablet count indicating full treatment adherence. Reassessment found no effect on his overall sexual function, apart from improved arousal but worsened ability to get and maintain erection. He was found to have no sex drive; somewhat difficult to get aroused; somewhat difficult to get and maintain erection; somewhat easy to reach orgasm and somewhat unsatisfying orgasm. Scales' total scores were WEMWBS 54; HADS-A 7; HADS-D 6; SAS 5; EQRS 22; ASEX 21; CGI-S 4; CGI-I 2; OQUESA-GR 13; OQUESA-RP 10; OQUESA-ED 7; OQUESA-NC 7 and OQUESA-AC 6.

Patient 32. A 24-year-old woman, an office administrator, in a stable heterosexual relationship at the time of enrolment. She developed anxiety symptoms about 18 months prior to participation. She disclosed that she had been subject to a sexually abusive relationship when she was 15 years old. She had no significant medical or surgical history. Her BMI was 22.5 (healthy). Interview with MINI generated a DSM-5 diagnosis of generalised social phobia. At Week 0, prior to treatment, she

was found to have a somewhat strong sex drive; somewhat difficult to get aroused; somewhat difficult to get vaginal lubrication; somewhat difficult to reach orgasm and somewhat satisfying orgasm. Scales' total scores were WEMBWS 28; HADS-A 12; HADS-D 10; SAS 7; EQRS 17 and ASEX 18.

At Week 6, she had received 6 weeks of treatment with citalopram and when-required propranolol. She was found to have no change in her overall sexual function, apart from worsened drive and orgasm satisfaction. On reassessment of sexual function, she was found to have very weak sexual drive; somewhat difficult to get aroused; somewhat difficult to get vaginal lubrication; somewhat difficult to reach orgasm and somewhat unsatisfying orgasm. This was associated with total scores of, WEMWBS 34; HADS-A 14; HADS-D 11; SAS 5; EQRS 14; ASEX 21; CGI-S 5; CGI-I 3; OQUESA-GR 20; OQUESA-RP 23; OQUESA-ED 9; OQUESA-NC 16 and OQUESA-AC 18.

At Week 12, she had stopped citalopram and had started fluoxetine 4 weeks before the review, because she felt "disconnected from the world and spaced out with the citalopram". She had also stated that she had separated from her partner; was looking into moving house and considering taking a different job. She explained that she felt she was keen on more "stimulating job". She had undertaken 6 weeks of augmentation with celecoxib, tablet count found 5 days less the course. Reassessment of sexual function, based on solitary sexual activity, found worsened overall sexual function apart from ability to reach orgasm, which was unchanged. She was found to have very weak sexual drive; very difficult to get aroused; very difficult to get vaginal lubrication; somewhat difficult to reach orgasm and very unsatisfying orgasm. This was associated with total scores of, WEMWBS 39; HADS-A 13; HADS-D 14; SAS 4; EQRS 16; ASEX 24; CGI-S 4; CGI-I 2; OQUESA-GR 18; OQUESA-RP 23; OQUESA-ED 7; OQUESA-NC 17 and OQUESA-AC 8.

Patient 33. A 58-year-old unemployed, married heterosexual woman. She stopped working 14 years prior to participation, following an accident which required spinal surgery and a period of hospitalisation. She developed anxiety symptoms approximately ten years prior to participation. She had a history of hypertension, which was well-controlled with candesartan. She also had a diagnosis of fibromyalgia. She received amitriptyline for neuropathic pain. Her BMI was 24.5 (healthy). Interview with MINI generated DSM-5 diagnoses of social phobia and generalised anxiety disorder. Assessment of sexual function was based on solitary sexual activity. At Week 0, prior to treatment, she was found to have no sex drive; never aroused; never able to get vaginal lubrication and never able reach orgasm. Scale total scores were SAS 3; EQRS 9; ASEX 30 and CGI-S 6.

At Week 6, she had undergone six weeks of fluoxetine treatment. Reassessment found improved, sex drive; arousal and lubrication. She was found to have a very weak sex drive; somewhat difficult to get aroused; somewhat difficult to get vaginal lubrication and never able to reach orgasm. Scale total scores were WEMWBS 39; HADS-A 16; HADS-D 11; SAS 6; EQRS 24; ASEX 25; CGI-S 4; CGI-I 1; OQUESA-GR 19; OQUESA-RP 22; OQUESA-ED 18; OQUESA-NC 19; OQUESA-AC 20. At Week 12, she had undertaken six weeks of augmentation with celecoxib, tablet count indicating complete treatment adherence. Reassessment found improvement in overall sexual function. She was found to have a somewhat strong sex drive; somewhat easy to get aroused; somewhat difficult to get vaginal lubrication; somewhat difficult to reach orgasm and somewhat satisfying orgasm. Scale total scores were WEMWBS 54; HADS-A 7; HADS-D 2; SAS 6; EQRS 25; ASEX 17; CGI-S 3; CGI-I 2; OQUESA-GR 7; OQUESA-RP 5; OQUESA-ED 7; OQUESA-NC 5 and OQUESA-AC 8.

Patient 34. A 48-year-old physiotherapist, heterosexual married man. He had a 3-year history of anxiety and low mood. He had type two diabetes mellitus, which was stable with the oral hypoglycaemias (metformin and gliclazide). He reported a history of sleep apnoea and insomnia. He had undergone haemorrhoidectomy one month prior to enrolment. His BMI was 27.3

(overweight). Interview with MINI generated DSM-5 diagnoses of panic disorder, generalised anxiety disorder and recurrent major depressive disorder. At Week 0, prior to treatment, he was found to have, extremely strong sex drive; very easy to get aroused; very easy to get and maintain erection; extremely easy to reach orgasm and extremely satisfying orgasm. Scales' total scores were SAS 10; EQRS 23; ASEX 7 and CGI-S 4.

At Week 6, he had undergone 6 weeks of treatment with venlafaxine and propranolol. Reassessment found worsened on his overall sexual function, apart from ability to get and maintain erection, which remained the same. He was found to have very weak sex drive; never aroused; very easy to get and maintain erection and never able to reach orgasm. Scales' total scores were WEMWBS 22; HADS-A 15; HADS-D 19; SAS 10; EQRS 21; ASEX 24; CGI-S 5; CGI-I 3; OQUESA-GR 16; OQUESA-RP 23; OQUESA-ED 8; OQUESA-NC 13 and OQUESA-AC 6. At week 12, he had undertaken six weeks of augmentation with celecoxib, tablet count indicating complete treatment adherence. Reassessment found improvement in overall sexual function. Reassessment of found improvement of his overall sexual function. He was found to have somewhat strong sexual drive; very easy to get aroused; somewhat easy to get and maintain erection; very easy to reach orgasm and an extremely satisfying orgasm. Scales' total scores were WEMWBS 27; HADS-A 13; HADS-D 10; SAS 10; EQRS 25; ASEX 11; CGI-S 3; CGI-I 1; OQUESA-GR 17; OQUESA-RP 13; OQUESA-ED 8; OQUESA-NC 8 and OQUESA-AC 8.

Patient 35. A 51-year-old unemployed married heterosexual woman. She developed anxiety symptoms approximately 5 years prior to participation. Her BMI was 25.1 (overweight). Interview with MINI generated DSM-5 diagnoses of generalised anxiety disorder, panic disorder, and recurrent major depressive disorder. At Week 0, prior to treatment, she was found to have somewhat strong sex drive; somewhat easily aroused; somewhat easy to get vaginal lubrication;

somewhat easy reach orgasm and somewhat satisfying orgasm. Scale total scores were SAS 10; EQRS 14; ASEX 15 and CGI-S 4.

At Week 6, she had undergone six weeks of mirtazapine and propranolol treatment. Reassessment found very weak sex drive; very difficult to get aroused; very difficult to get vaginal lubrication; very difficult to reach orgasm and a somewhat satisfying orgasm. Scale total scores were WEMWBS 27; HADS-A 19; HADS-D 9; SAS 6; EQRS 18; ASEX 24; CGI-S 5; CGI-I 3; OQUESA-GR 16; OQUESA-RP 24; OQUESA-ED 8; OQUESA-NC 23; OQUESA-AC 21. At Week 12, she had undertaken six weeks of augmentation with celecoxib, tablet count found 8 days less the prescribed treatment course. Reassessment found no change in her overall sexual function. She was found to have a very weak sex drive; very difficult to get aroused; very difficult to get vaginal lubrication; very difficult to reach orgasm and a somewhat satisfying orgasm. Scale total scores were WEMWBS 29; HADS-A 16; HADS-D 12; SAS 4; EQRS 11; ASEX 24; CGI-S 4; CGI-I 3; OQUESA-GR 21; OQUESA-RP 25; OQUESA-ED 7; OQUESA-NC 23 and OQUESA-AC 23.

Appendix B Raw data

B.1 Psychometrics' findings dataset

participant's code	diagnosis	BMI	age	gender (male/female)	WEMWBS-total W0	WEMWBS-total W6	WEMWBS-total W12	HADS-A W0	HADS-A W6	HADS-A W12	HADS-D W0	HADS-D W6	HADS-D W12	EQ6-Total W0	EQ6-Total W6	EQ6-Total W12	SAS-Total W0	SAS-Total W6	SAS-Total W12	ASEX-1 W0	ASEX-1 W6	ASEX-1 W12	ASEX-2 W0	ASEX-2 W6	ASEX-2 W12	ASEX-3 W0	ASEX-3 W6	ASEX-3 W12	ASEX-4 W0	ASEX-4 W6	ASEX-4 W12	ASEX-5 W0	ASEX-5 W6	ASEX-5 W12	ASEX-Total W0	ASEX-Total W6	ASEX-Total W12	CGI-1 W0	CGI-1 W6	CGI-1 W12	CGI-2 W6	CGI-2 W12	OQUESA-GR W0	OQUESA-GR W6	OQUESA-GR W12	OQUESA-RP W0	OQUESA-RP W6	OQUESA-RP W12	OQUESA-ED W0	OQUESA-ED W6	OQUESA-ED W12	OQUESA-NC W0	OQUESA-NC W6	OQUESA-NC W12	OQUESA-AC W6	OQUESA-AC W12	OQUESA-Total W6	OQUESA-Total W12
CKP02 *	300.3	36	48	1		28	30		17	15		14	11				3	3	8	6	6	5	6	5	5	6	5	4	6	5	4	6	4	3	30	25	21	6	5	4	2	3		19	22		22	22		11	16		23	19	18	16	93	95
CKP03 *	300.21	45	48	1		36	34		12	13		11	11	7	22	27	3	11	8	1	6	6	1	5	5	2	5	5	2	5	5	1	5	5	7	26	26		6	5	1	2		15	19		22	21		10	17		12	17	9	9	68	83
CKP06 *	300.21	21	24	2	32	32	39	13	14	13	12	12	11	28	23	28	14	15	14	3	4	3	3	3	2	1	2	2	2	3	2	1	2	2	10	14	11	5	3	2	3	1	17	16	16	21	20	18	21	19	20	21	16	18	18	6	89	78
CKP07	300.23	21	23	2	23	25	35	16	10	12	14	15	12	22	19	18	6	6	7	4	3	3	3	4	3	4	4	4	4	4	4	3	5	3	18	20	17	5	3	4	3	3	16	15	21	25	24	22	6	17	9	22	13	13				
CKP08 *	300.23	25	20	2		36	40		13	10		10	5	22	21	24	7	8	11	3	5	4	2	1	1	2	1	1	3	3	2	4	2	3	14	12	11	2	2	2	4	2		11	14		10	13		9	10		14	15	15	9	59	64
CKP09 *	300.21	18	21	2		41	47		11	9		8	7	24	18	18	3	3	3	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	30	30	30	4	4	3	3	2		17	13		12	11		14	12		12	11	12	9	67	57
CKP10	300.1	25	27	2		24	24		17	21		12	12	19			6	3	3	4	6	6	3	5	6	3	2	5	5	5	4	3	3	3	18	21	24	5	5	5	3	4		19	16		21	19		7	8		23	15	12	15	82	73
CKP11 *	300.23	27	23	2	27	39	48	15	8	5	16	7	6	15			13			3	5	3	3	4	2	4	4	2	4	4	2	6	4	2	20	21	11	4	3	3	2	2	12	18	13	21	14	13	43	16	12	18	17	13	14	9	79	60
CKP12 *	300.21	20	29	2		31	37		14	9		13	8	26	27	22	9	13	9	5	4	4	4	4	4	3	3	3	4	5	4	4	5	4	20	21	19	5	5	3	3	2		15	11		22	17		5	5		19	16	19	13	80	62
CKP14	300.21	25	24	2		22			13			14		15			13	8		3	6		3	5		3	5		5	6		2	6		16	28		5	5			6		16			20			9			19		6		70	
CKPO15	300.2	26	48	1		67	69		4	1		0	1				7	11	11	4	2	1	3	2	2	4	1	1	3	1	1	3	1	1	17	7	6	3	2	2	1	1		13	10		5	5		5	6		5	5	6	6	34	32
CKP16 *	300.21	37	21	2	32	28	4	21	21	17	11	11	9	17	18	18	10	11	10	2	2	2	1	2	1	1	1	1	3	4	2	2	4	2	9	13	8	5	5	4	3	1		22	22		22	18		12	11		15	26	28	23	99	100
CKP17	300.21	18	20	2	29	40	37	19	15	15	10	9	9		26	26	6	10	10	3	2	2	3	2	2	4	3	3	4	3	3	4	3	3	18	13	13	3	3	3	4	4	17	15	15	24	18	16	20	10	11	16	13	14				
CKP18 *	300.3	55	27	1		29	51		11	9		2	4	24	28	25	12	11	13	1	4	3	3	4	2	1	1	1	1	5	5	1	1	1	7	15	12	4	4	1	2	1		13	5		6	9		5	17		5	17	6	14	35	56
CKP19	300.02	22	22	2		16	18		19	18		13	13	14	17	15	7	8	7	3	3	3	5	4	4	4	4	4	5	6	5	5	6	5	22	23	21	5	5	5	3	4																
CKP20 *	300.21	28	22	2		38	42		17	13		10	9	14	18	20	10	9	9	2	3	3	3	3	3	5	5	3	4	5	4	3	2	2	17	18	15	5	5	4	3	2		5	6		18	16		9	11		12	13	8	6	52	52
NN01	300.02	21	37	1	20	52	63	17	6	3	17	7	0	14	19	25	4	6	11	5	4	3	6	4	3	5	4	2	4	4	3	5	4	3	25	20	14	7	2	1	2	1	8	18	12	25	15	9	10	8	9	15	12	9	10	7	63	46
NN02	300.3	20	22	2		32			17			11		16	16		6	6		5	5		5	4		5	4		6	4		6	3		27	20		6	6		3			21			22			13			20		20		96	
CKP21	300.23	20	23	2	30	35	37	12	10	13	12	12	8	18	22	17	7	8	8	3	4	5	3	4	5	4	4	4	4	4	4	3	5	5	17	21	23	6	6	4	3	2	20	16	20	20	22	19	9	8	8	11	13	11	11	13	70	71
CKP22	300.02	23	24	1	22	30		16	13		10	12		13	15		6	9		4	3		4	3		2	1		2	3		4	3		16	13		4	4		3		14			18			13			17						
CKP23 *	300.02	24	26	2		42	50		10	4		5	3	20	18	19	9	8	8	2	5	2	3	4	2	2	2	2	2	4	2	2	2	2	11	17	10	2	2	2	3	3		13	10		18	11		8	9		16	11	12	10	67	51
CKP24 *	300.23	22	24	1	37	22	49	15	17	13	11	13	10							2	4	2	1	2	1	1	5	3	2	5	4	3	5	3	9	21	13	5	5	3	5	1	15	10	11	21	22	13	8	9	5	20	20	24	15	11	76	64
CKP25 *	300.02	22	22	2		36	42		16	11		8	7	28	28	27	11	10	11	3	6	3	3	5	4	2	5	3	3	4	3	3	3	2	14	23	15	4	4	3	3	2					24	18		10	6		18	18	30	21	106	84
CKP26	300.02	22	23	2		29			15			13		8	8		3	3		6	6		6	6		6	6		6	6		6	6		30	30		5	5		2			16			14			14			17		11		72	
CKP27	300.02	18	24	1		36			11			15								2	4		1	3		2	2		3	3		1	3		9	15		7	7		2			23			24			23			24		27		121	
CKP28	300.02	31	56	1		25	17		20	20		15	19	25	25	18	14	12	11	1	4	5	1	4	5	1	3	4	2	6	6	2	6	6	7	19	26	3	3	3	3	4		23	25		23	25		22	25		23	24	16	16	115	107
CKP29	300.01	22	38	1	30			11			16						9			5			4			4			2			3			18			2					21			24			10			23						
CKP30	300.03	23	38	2		20			20			17		21	19		10	5		4	6		4	5		4	5		4	6		3	6		15	28		3	3		4			13			24			14			19		10		80	
CKP31	300.02	27	42	1		48	43		8	7		9	11	16	15	15	8	6	7	5	5	6	5	3	3	3	3	6	3	3	6	2	2	6	18	16	23	5	5	4	2	5		23	14		16	13		6	7		14	10	6		65	
CKP32	300.02	20	49	2	14			18			17			16			4			6			6			5			6			6			29			5					12			25			17			23						
CKP33 *	300.02	27	60	2		38	54		9	7		9	6	21	23	22	10	3	5	6	6	6	6	6	4	3	3	4	3	3		3	4	4	21	22	21	5	5	4	1	2		13	13		16	10		7	7		14	7	16	6	66	43
CKP34 *	300.23	23	24	2	28	34	39	12	14	13	10	11	14	17	14	16	7	5	4	3	5	5	4	4	5	4	4	5	4	4	4	3	4	5	18	21	24	6	5	4	3	2	19	20	18	20	23	23	9	9	7	12	16	17	18	8	86	73
CKP35 *	300.23	25	58	2		39	54		16	7		11	2	9	24	25	3	6	6	6	5	3	6	4	3	6	4	4	6	6	4	6	6	3	30	25	17	6	4	3	1	2		19	7		22	5		18	7		19	5	20	8	98	32
CKP36 *	300.01	37	48	1		22	44		15	13		19	10	23	21	25	10	10	10	1	5	2	2	5	2	2	2	3	1	6	2	1	6	1	7	24	11	4	5	3	3	1		16	17		23	13		8	8		13	8	6	8	66	54
CKP37 *	300.02	25	51	2		27	29		19	16		9	12	14	18	11	10	6	4	3	5	5	3	5	5	3	5	5	3	5	5	3	4	4	15	24	24	4	5	4	3	3		16	21		24	25		8	7		23	23	21	23	92	99

Key
Social phobia 300.23
Panic Disorder 300.01
Panic disorder with agoraphobia 300.21
GAD 300.02
OCD 300.3
male, 1 female, 2
* celecoxib augmentation

B.2 Correlations at Baseline

		ASEX-Total	CGI-1	HADS-A	HCC	prolctin	WEMWBS-total	HADS-D	EQRS-Total	SAS-Total	OQUESA-GR	OQUESA-RP	OQUESA-ED	OQUESA-NC	IFNγ	IL1βW6	IL10	IL12p70	IL13	IL2	IL4	IL6	IL8	TNFα
ASEX-Total	Pearson Correlation	1	.341*	.068	-.459	.262	-.868**	.689*	-.365	-.653**	-.484	.559	.114	.004	-.927**	.008	-.956**	.453	.049	-.869*	-.089	.122	-.973**	-.608
	Sig. (2-tailed)		.048	.834	.155	.570	.000	.013	.051	.000	.131	.074	.739	.990	.008	.968	.003	.367	.926	.025	.867	.818	.001	.201
	Sum of Squares and Cross-products	1748.400	103.588	13.750	-1152.684	912.000	-360.000	129.000	-414.069	-492.364	-107.000	79.000	68.000	1.000	-43.880	13.828	-15.101	.721	.170	-.866	-.032	.337	-61.443	-11.158
	Covariance	51.424	3.139	1.250	-115.268	152.000	-32.727	11.727	-14.788	-15.386	-10.700	7.900	6.800	.100	-8.776	.576	-3.020	.144	.034	-.173	-.006	.067	-12.289	-2.232
	N	35	34	12	11	7	12	12	29	33	11	11	11	11	6	25	6	6	6	6	6	6	6	6
CGI-1	Pearson Correlation	.341*	1	.049	.310	.658	-.192	.024	-.402*	-.338	-.387	-.070	-.286	-.484	.597	.283	.559	.189	-.135	.652	-.165	.176	.543	.582
	Sig. (2-tailed)	.048		.879	.354	.108	.549	.942	.034	.058	.239	.839	.394	.132	.211	.181	.249	.720	.798	.160	.754	.739	.265	.225
	Sum of Squares and	103.588	56.382	2.250	194.018	1075.714	-18.000	1.000	-67.107	-43.469	-21.364	-2.455	-42.727	-29.000	9.433	80.466	2.949	.100	-.157	.217	-.020	.162	11.448	3.568

	Cross-products																						
	Covariance	3.139	1.709	.205	19.402	179.286	-1.636	.091	-2.485	-1.402	-2.136	-.245	-4.273	-2.900	1.887	3.499	.590	.020	-.031	.043	-.004	.032	2.290	.714
	N	34	34	12	11	7	12	12	28	32	11	11	11	11	6	24	6	6	6	6	6	6	6	6
HADS-A	Pearson Correlation	.068	.049	1	-.131	.280	-.275	-.042	-.336	-.272	-.682*	.432	.178	.153	-.251	-.467	-.306	.054	-.404	-.239	.602	.788	-.253	-.083
	Sig. (2-tailed)	.834	.879		.701	.544	.387	.897	.377	.419	.021	.184	.601	.652	.631	.290	.556	.919	.427	.648	.206	.062	.629	.876
	Sum of Squares and Cross-products	13.750	2.250	102.917	-151.476	856.000	-58.000	-4.000	-36.889	-29.091	-69.455	28.182	49.091	17.000	-9.368	-140.736	-3.801	.067	-1.104	-.188	.171	1.712	-12.567	-1.201
	Covariance	1.250	.205	9.356	-15.148	142.667	-5.273	-.364	-4.611	-2.909	-6.945	2.818	4.909	1.700	-1.874	-23.456	-.760	.013	-.221	-.038	.034	.342	-2.513	-.240
	N	12	12	12	11	7	12	12	9	11	11	11	11	11	6	7	6	6	6	6	6	6	6	6
HCC	Pearson Correlation	-.459	.310	-.131	1	-.388	.302	-.062	.673	.476	-.150	-.100	.033	.163	.922**	-.146	.994**	-.145	.242	.880*	.119	-.209	.879*	.485
	Sig. (2-tailed)	.155	.354	.701		.390	.367	.857	.067	.164	.659	.771	.924	.631	.009	.755	.000	.784	.644	.021	.823	.691	.021	.329
	Sum of Squares and Cross-	-1152.684	194.018	-151.476	19446.969	-22290.036	847.148	-78.831	1160.789	672.537	-257.113	-109.000	151.557	304.024	715.737	-902.169	257.333	-3.786	13.779	14.387	.699	-9.459	909.750	146.019

	products																						
	Covariance	-115.268	19.402	-15.148	1944.697	-3715.006	84.715	-7.883	165.827	74.726	-25.711	-10.900	15.156	30.402	143.147	-150.362	51.467	-.757	2.756	2.877	.140	-1.892	181.950	29.204
	N	11	11	11	11	7	11	11	8	10	11	11	11	11	6	7	6	6	6	6	6	6	6	6
prolctin	Pearson Correlation	.262	.658	.280	-.388	1	-.480	-.612	-.319	-.755*	.086	-.087	-.469	-.640	-.312	.369	-.296	.053	-.741	-.306	.294	.482	-.195	-.193
	Sig. (2-tailed)	.570	.108	.544	.390		.276	.144	.601	.050	.855	.853	.288	.121	.609	.471	.629	.932	.152	.617	.632	.411	.753	.756
	Sum of Squares and Cross-products	912.000	1075.714	856.000	-22290.036	195157.714	-1495.286	-1686.571	-1128.000	-2728.571	277.714	-199.429	-6550.571	-3319.714	-648.308	6024.330	-210.181	3.064	-99.778	-13.233	4.515	47.051	-532.113	-107.071
	Covariance	152.000	179.286	142.667	-3715.006	32526.286	-249.214	-281.095	-282.000	-454.762	46.286	-33.238	-1091.762	-553.286	-162.077	1204.866	-52.545	.766	-24.945	-3.308	1.129	11.763	-133.028	-26.768
	N	7	7	7	7	7	7	7	5	7	7	7	7	7	5	6	5	5	5	5	5	5	5	5
WEMWBS-total	Pearson Correlation	-.868**	-.192	-.275	.302	-.480	1	-.549	.462	.691*	.578	-.406	-.020	-.134	.272	.328	.475	.104	.620	.186	.459	-.472	.201	-.342
	Sig. (2-tailed)	.000	.549	.387	.367	.276		.065	.211	.019	.063	.216	.953	.694	.602	.472	.341	.845	.189	.724	.360	.344	.702	.506
	Sum of Squares and	-360.000	-18.000	-58.000	847.148	-1495.286	432.000	-107.000	103.667	131.182	142.727	-64.091	-13.545	-36.000	14.599	140.402	8.514	.187	2.439	.211	.187	-1.477	14.390	-7.129

	Cross-products																						
	Covariance	-32.727	-1.636	-5.273	84.715	-249.214	39.273	-9.727	12.958	13.118	14.273	-6.409	-1.355	-3.600	2.920	23.400	1.703	.037	.488	.042	.037	-.295	2.878	-1.426
	N	12	12	12	11	7	12	12	9	11	11	11	11	11	6	7	6	6	6	6	6	6	6	6
HADS-D	Pearson Correlation	.689*	.024	-.042	-.062	-.612	-.549	1	-.175	-.100	-.473	.650*	.233	.443	-.356	.000	-.263	.626	.579	-.308	-.537	-.697	-.459	-.433
	Sig. (2-tailed)	.013	.942	.897	.857	.144	.065		.653	.770	.142	.031	.491	.173	.488	.999	.614	.184	.229	.553	.271	.124	.360	.391
	Sum of Squares and Cross-products	129.000	1.000	-4.000	-78.831	-1686.571	-107.000	88.000	-18.556	-9.636	-53.091	46.636	70.818	54.000	-13.286	.135	-3.276	.785	1.581	-.242	-.152	-1.514	-22.792	-6.260
	Covariance	11.727	.091	-.364	-7.883	-281.095	-9.727	8.000	-2.319	-.964	-5.309	4.664	7.082	5.400	-2.657	.022	-.655	.157	.316	-.048	-.030	-.303	-4.558	-1.252
	N	12	12	12	11	7	12	12	9	11	11	11	11	11	6	7	6	6	6	6	6	6	6	6
EQRS-Total	Pearson Correlation	-.365	-.402*	-.336	.673	-.319	.462	-.175	1	.538**	.486	.093	-.065	.375	.576	-.031	.769	-.052	.068	.526	.683	-.880	.624	-.095
	Sig. (2-tailed)	.051	.034	.377	.067	.601	.211	.653		.003	.222	.826	.878	.360	.424	.890	.231	.948	.932	.474	.317	.120	.376	.905
	Sum of Squares and Cross-	-414.069	-67.107	-36.889	1160.789	-1128.000	103.667	-18.556	887.448	288.586	67.750	8.875	-27.000	58.375	34.349	-41.424	16.689	-.123	.352	.601	.128	-2.403	53.649	-1.787

	products																						
	Covariance	-14.788	-2.485	-4.611	165.827	-282.000	12.958	-2.319	31.695	10.307	9.679	1.268	-3.857	8.339	11.450	-1.883	5.563	-.041	.117	.200	.043	-.801	17.883	-.596
	N	29	28	9	8	5	9	9	29	29	8	8	8	8	4	23	4	4	4	4	4	4	4	4
SAS-Total	Pearson Correlation	-.653**	-.338	-.272	.476	-.755*	.691*	-.100	.538**	1	.256	-.373	.629	.185	.552	-.079	.622	.494	.867*	.576	-.077	-.319	.308	.144
	Sig. (2-tailed)	.000	.058	.419	.164	.050	.019	.770	.003		.475	.289	.051	.608	.256	.706	.187	.319	.025	.232	.884	.538	.553	.785
	Sum of Squares and Cross-products	-492.364	-43.469	-29.091	672.537	-2728.571	131.182	-9.636	288.586	355.515	32.400	-29.800	210.200	25.200	27.535	-67.832	10.351	.828	3.171	.605	-.029	-.927	20.473	2.786
	Covariance	-15.386	-1.402	-2.909	74.726	-454.762	13.118	-.964	10.307	11.110	3.600	-3.311	23.356	2.800	5.507	-2.826	2.070	.166	.634	.121	-.006	-.185	4.095	.557
	N	33	32	11	10	7	11	11	29	33	10	10	10	10	6	25	6	6	6	6	6	6	6	6
OQUESA-GR	Pearson Correlation	-.484	-.387	-.682*	-.150	.086	.578	-.473	.486	.256	1	-.260	-.305	-.098	-.148	.571	.026	-.476	-.155	-.266	.085	-.702	.080	-.421
	Sig. (2-tailed)	.131	.239	.021	.659	.855	.063	.142	.222	.475		.439	.361	.775	.780	.181	.960	.340	.770	.610	.873	.120	.881	.406
	Sum of Squares and Cross-	-107.000	-21.364	-69.455	-257.113	277.714	142.727	-53.091	67.750	32.400	150.727	-25.091	-124.545	-16.000	-6.115	185.166	.364	-.662	-.470	-.232	.027	-1.694	4.390	-6.752

	products																						
	Covariance	-10.700	-2.136	-6.945	-25.711	46.286	14.273	-5.309	9.679	3.600	15.073	-2.509	-12.455	-1.600	-1.223	30.861	.073	-.132	-.094	-.046	.005	-.339	.878	-1.350
	N	11	11	11	11	7	11	11	8	10	11	11	11	11	6	7	6	6	6	6	6	6	6	6
OQUESA-RP	Pearson Correlation	.559	-.070	.432	-.100	-.087	-.406	.650*	.093	-.373	-.260	1	-.119	.468	-.594	-.232	-.354	.231	-.080	-.654	.237	-.578	-.456	-.847*
	Sig. (2-tailed)	.074	.839	.184	.771	.853	.216	.031	.826	.289	.439		.726	.147	.214	.616	.491	.660	.880	.159	.652	.230	.363	.033
	Sum of Squares and Cross-products	79.000	-2.455	28.182	-109.000	-199.429	-64.091	46.636	8.875	-29.800	-25.091	61.636	-31.182	49.000	-21.184	-66.360	-4.220	.277	-.209	-.492	.064	-1.201	-21.714	-11.721
	Covariance	7.900	-.245	2.818	-10.900	-33.238	-6.409	4.664	1.268	-3.311	-2.509	6.164	-3.118	4.900	-4.237	-11.060	-.844	.055	-.042	-.098	.013	-.240	-4.343	-2.344
	N	11	11	11	11	7	11	11	8	10	11	11	11	11	6	7	6	6	6	6	6	6	6	6
OQUESA-ED	Pearson Correlation	.114	-.286	.178	.033	-.469	-.020	.233	-.065	.629	-.305	-.119	1	.086	.097	-.289	.075	.750	.832*	.167	.217	.306	-.242	-.056
	Sig. (2-tailed)	.739	.394	.601	.924	.288	.953	.491	.878	.051	.361	.726		.802	.856	.530	.887	.086	.040	.752	.680	.555	.644	.916
	Sum of Squares and Cross-	68.000	-42.727	49.091	151.557	-6550.571	-13.545	70.818	-27.000	210.200	-124.545	-31.182	1104.909	38.000	17.190	-430.605	4.477	4.489	10.862	.627	.293	3.174	-57.483	-3.855

	products																						
	Covariance	6.800	-4.273	4.909	15.156	-1091.762	-1.355	7.082	-3.857	23.356	-12.455	-3.118	110.491	3.800	3.438	-71.768	.895	.898	2.172	.125	.059	.635	-11.497	-.771
	N	11	11	11	11	7	11	11	8	10	11	11	11	11	6	7	6	6	6	6	6	6	6	6
OQUESA-NC	Pearson Correlation	.004	-.484	.153	.163	-.640	-.134	.443	.375	.185	-.098	.468	.086	1	.034	-.607	.176	-.018	.042	.007	-.561	-.950**	.164	-.146
	Sig. (2-tailed)	.990	.132	.652	.631	.121	.694	.173	.360	.608	.775	.147	.802		.949	.149	.739	.973	.937	.990	.247	.004	.757	.783
	Sum of Squares and Cross-products	1.000	-29.000	17.000	304.024	-3319.714	-36.000	54.000	58.375	25.200	-16.000	49.000	38.000	178.000	1.335	-295.819	2.282	-.024	.121	.006	-.166	-2.155	8.498	-2.200
	Covariance	.100	-2.900	1.700	30.402	-553.286	-3.600	5.400	8.339	2.800	-1.600	4.900	3.800	17.800	.267	-49.303	.456	-.005	.024	.001	-.033	-.431	1.700	-.440
	N	11	11	11	11	7	11	11	8	10	11	11	11	11	6	7	6	6	6	6	6	6	6	6
IFNγ	Pearson Correlation	-.927**	.597	-.251	.922**	-.312	.272	-.356	.576	.552	-.148	-.594	.097	.034	1	-.226	.958**	-.257	.112	.990**	-.029	.068	.941**	.778
	Sig. (2-tailed)	.008	.211	.631	.009	.609	.602	.488	.424	.256	.780	.214	.856	.949		.715	.003	.623	.833	.000	.956	.898	.005	.069
	Sum of Squares and Cross-	-43.880	9.433	-9.368	715.737	-648.308	14.599	-13.286	34.349	27.535	-6.115	-21.184	17.190	1.335	36.556	-.102	11.692	-.316	.300	.763	-.008	.146	45.870	11.021

	products																						
	Covariance	-8.776	1.887	-1.874	143.147	-162.077	2.920	-2.657	11.450	5.507	-1.223	-4.237	3.438	.267	7.311	-.026	2.338	-.063	.060	.153	-.002	.029	9.174	2.204
	N	6	6	6	6	5	6	6	4	6	6	6	6	6	6	5	6	6	6	6	6	6	6	6
IL1βW6	Pearson Correlation	.008	.283	-.467	-.146	.369	.328	.000	-.031	-.079	.571	-.232	-.289	-.607	-.226	1	-.115	.187	-.354	-.213	-.441	-.719	-.066	-.188
	Sig. (2-tailed)	.968	.181	.290	.755	.471	.472	.999	.890	.706	.181	.616	.530	.149	.715		.854	.763	.559	.731	.457	.171	.916	.762
	Sum of Squares and Cross-products	13.828	80.466	-140.736	-902.169	6024.330	140.402	.135	-41.424	-67.832	185.166	-66.360	-430.605	-295.819	-.102	2566.246	-.018	.003	-.013	-.002	-.002	-.015	-.041	-.032
	Covariance	.576	3.499	-23.456	-150.362	1204.866	23.400	.022	-1.883	-2.826	30.861	-11.060	-71.768	-49.303	-.026	106.927	-.004	.001	-.003	.000	.000	-.004	-.010	-.008
	N	25	24	7	7	6	7	7	23	25	7	7	7	7	5	25	5	5	5	5	5	5	5	5
IL10	Pearson Correlation	-.956**	.559	-.306	.994**	-.296	.475	-.263	.769	.622	.026	-.354	.075	.176	.958**	-.115	1	-.177	.192	.925**	.088	-.125	.913*	.576
	Sig. (2-tailed)	.003	.249	.556	.000	.629	.341	.614	.231	.187	.960	.491	.887	.739	.003	.854		.737	.716	.008	.869	.814	.011	.231
	Sum of Squares and Cross-	-15.101	2.949	-3.801	257.333	-210.181	8.514	-3.276	16.689	10.351	.364	-4.220	4.477	2.282	11.692	-.018	4.071	-.073	.172	.238	.008	-.089	14.854	2.726

	products																						
	Covariance	-3.020	.590	-.760	51.467	-52.545	1.703	-.655	5.563	2.070	.073	-.844	.895	.456	2.338	-.004	.814	-.015	.034	.048	.002	-.018	2.971	.545
	N	6	6	6	6	5	6	6	4	6	6	6	6	6	6	5	6	6	6	6	6	6	6	6
IL12p70	Pearson Correlation	.453	.189	.054	-.145	.053	.104	.626	-.052	.494	-.476	.231	.750	-.018	-.257	.187	-.177	1	.695	-.178	.013	-.089	-.513	-.410
	Sig. (2-tailed)	.367	.720	.919	.784	.932	.845	.184	.948	.319	.340	.660	.086	.973	.623	.763	.737		.126	.735	.981	.866	.298	.419
	Sum of Squares and Cross-products	.721	.100	.067	-3.786	3.064	.187	.785	-.123	.828	-.662	.277	4.489	-.024	-.316	.003	-.073	.041	.063	-.005	.000	-.006	-.840	-.196
	Covariance	.144	.020	.013	-.757	.766	.037	.157	-.041	.166	-.132	.055	.898	-.005	-.063	.001	-.015	.008	.013	-.001	.000	-.001	-.168	-.039
	N	6	6	6	6	5	6	6	4	6	6	6	6	6	6	5	6	6	6	6	6	6	6	6
IL13	Pearson Correlation	.049	-.135	-.404	.242	-.741	.620	.579	.068	.867*	-.155	-.080	.832*	.042	.112	-.354	.192	.695	1	.143	.063	-.240	-.174	-.238
	Sig. (2-tailed)	.926	.798	.427	.644	.152	.189	.229	.932	.025	.770	.880	.040	.937	.833	.559	.716	.126		.787	.905	.647	.741	.650
	Sum of Squares and Cross-	.170	-.157	-1.104	13.779	-99.778	2.439	1.581	.352	3.171	-.470	-.209	10.862	.121	.300	-.013	.172	.063	.196	.008	.001	-.038	-.623	-.247

	products																						
	Covariance	.034	-.031	-.221	2.756	-24.945	.488	.316	.117	.634	-.094	-.042	2.172	.024	.060	-.003	.034	.013	.039	.002	.000	-.008	-.125	-.049
	N	6	6	6	6	5	6	6	4	6	6	6	6	6	6	5	6	6	6	6	6	6	6	6
IL2	Pearson Correlation	-.869*	.652	-.239	.880*	-.306	.186	-.308	.526	.576	-.266	-.654	.167	.007	.990**	-.213	.925**	-.178	.143	1	-.105	.114	.903*	.820*
	Sig. (2-tailed)	.025	.160	.648	.021	.617	.724	.553	.474	.232	.610	.159	.752	.990	.000	.731	.008	.735	.787		.843	.830	.014	.045
	Sum of Squares and Cross-products	-.866	.217	-.188	14.387	-13.233	.211	-.242	.601	.605	-.232	-.492	.627	.006	.763	-.002	.238	-.005	.008	.016	-.001	.005	.927	.245
	Covariance	-.173	.043	-.038	2.877	-3.308	.042	-.048	.200	.121	-.046	-.098	.125	.001	.153	.000	.048	-.001	.002	.003	.000	.001	.185	.049
	N	6	6	6	6	5	6	6	4	6	6	6	6	6	6	5	6	6	6	6	6	6	6	6
IL4	Pearson Correlation	-.089	-.165	.602	.119	.294	.459	-.537	.683	-.077	.085	.237	.217	-.561	-.029	-.441	.088	.013	.063	-.105	1	.362	-.057	-.376
	Sig. (2-tailed)	.867	.754	.206	.823	.632	.360	.271	.317	.884	.873	.652	.680	.247	.956	.457	.869	.981	.905	.843		.481	.915	.462
	Sum of Squares and Cross-	-.032	-.020	.171	.699	4.515	.187	-.152	.128	-.029	.027	.064	.293	-.166	-.008	-.002	.008	.000	.001	-.001	.002	.006	-.021	-.041

	products																						
	Covariance	-.006	-.004	.034	.140	1.129	.037	-.030	.043	-.006	.005	.013	.059	-.033	-.002	.000	.002	.000	.000	.000	.000	.001	-.004	-.008
	N	6	6	6	6	5	6	6	4	6	6	6	6	6	6	5	6	6	6	6	6	6	6	6
IL6	Pearson Correlation	.122	.176	.788	-.209	.482	-.472	-.697	-.880	-.319	-.702	-.578	.306	-.950**	.068	-.719	-.125	-.089	-.240	.114	.362	1	-.024	.376
	Sig. (2-tailed)	.818	.739	.062	.691	.411	.344	.124	.120	.538	.120	.230	.555	.004	.898	.171	.814	.866	.647	.830	.481		.965	.462
	Sum of Squares and Cross-products	.337	.162	1.712	-9.459	47.051	-1.477	-1.514	-2.403	-.927	-1.694	-1.201	3.174	-2.155	.146	-.015	-.089	-.006	-.038	.005	.006	.124	-.067	.311
	Covariance	.067	.032	.342	-1.892	11.763	-.295	-.303	-.801	-.185	-.339	-.240	.635	-.431	.029	-.004	-.018	-.001	-.008	.001	.001	.025	-.013	.062
	N	6	6	6	6	5	6	6	4	6	6	6	6	6	6	5	6	6	6	6	6	6	6	6
IL8	Pearson Correlation	-.973**	.543	-.253	.879*	-.195	.201	-.459	.624	.308	.080	-.456	-.242	.164	.941**	-.066	.913*	-.513	-.174	.903*	-.057	-.024	1	.760
	Sig. (2-tailed)	.001	.265	.629	.021	.753	.702	.360	.376	.553	.881	.363	.644	.757	.005	.916	.011	.298	.741	.014	.915	.965		.079
	Sum of Squares and Cross-products	-61.443	11.448	-12.567	909.750	-532.113	14.390	-22.792	53.649	20.473	4.390	-21.714	-57.483	8.498	45.870	-.041	14.854	-.840	-.623	.927	-.021	-.067	64.974	14.364

	Covariance	-12.289	2.290	-2.513	181.950	-133.028	2.878	-4.558	17.883	4.095	.878	-4.343	-11.497	1.700	9.174	-.010	2.971	-.168	-.125	.185	-.004	-.013	12.995	2.873
	N	6	6	6	6	5	6	6	4	6	6	6	6	6	6	5	6	6	6	6	6	6	6	6
TNFα	Pearson Correlation	-.608	.582	-.083	.485	-.193	-.342	-.433	-.095	.144	-.421	-.847*	-.056	-.146	.778	-.188	.576	-.410	-.238	.820*	-.376	.376	.760	1
	Sig. (2-tailed)	.201	.225	.876	.329	.756	.506	.391	.905	.785	.406	.033	.916	.783	.069	.762	.231	.419	.650	.045	.462	.462	.079	
	Sum of Squares and Cross-products	-11.158	3.568	-1.201	146.019	-107.071	-7.129	-6.260	-1.787	2.786	-6.752	-11.721	-3.855	-2.200	11.021	-.032	2.726	-.196	-.247	.245	-.041	.311	14.364	5.496
	Covariance	-2.232	.714	-.240	29.204	-26.768	-1.426	-1.252	-.596	.557	-1.350	-2.344	-.771	-.440	2.204	-.008	.545	-.039	-.049	.049	-.008	.062	2.873	1.099
	N	6	6	6	6	5	6	6	4	6	6	6	6	6	6	5	6	6	6	6	6	6	6	6

- Correlation is significant at the 0.05 level (2-tailed).

** Correlation is significant at the 0.01 level (2-tailed).

Correlations adjusted for age; diagnosis and gender

Control Variables			ASEX-Total	CGI-1	HADS-A	HCC	prolctin	WEMWBS-total	HADS-D	EQRS-Total	SAS-Total	OQUESA-GR	OQUESA-RP	OQUESA-ED	OQUESA-NC	IFNγ	IL1β	IL10	IL12p70	IL13	IL2	IL4	IL6	IL8	TNFα
age & diagnosis & gender	ASEX-Total	Correlation	1.000	.382	-.010	-.452	.270	-1.000	1.000	-.408	-.718	-.609	.648	-.012	-.007	-1.000	-1.000	-1.000	.494	-.099	-1.000	-.308	.320	-1.000	-.647
		Significance (2-tailed)	.	.034	.981	.261	.730	.000	.000	.038	.000	.109	.082	.977	.986	.000	.000	.000	.671	.937	.000	.801	.793	.000	.552
		df	0	29	7	6	2	7	7	24	28	6	6	6	6	1	1	1	1	1	1	1	1	1	1
	CGI-1	Correlation	.382	1.000	.072	.295	1.000	-.624	.223	-.423	-.341	-.500	.010	-.328	-.483	.619	.526	.568	.220	-.173	.690	-.279	.185	.567	.783
		Significance (2-tailed)	.034	.	.854	.478	.000	.073	.565	.035	.070	.207	.981	.428	.226	.575	.648	.616	.859	.889	.516	.820	.882	.616	.427
		df	29	0	7	6	2	7	7	23	27	6	6	6	6	1	1	1	1	1	1	1	1	1	1
	HADS-A	Correlation	-.010	.072	1.000	-.096	.589	-.262	-.270	-.345	-.287	-.749	.432	.134	.119	-.237	-.419	-.338	-.039	-.556	-.222	.726	1.000	-.228	.037
		Significance (2-tailed)	.981	.854	.	.821	.411	.495	.482	.503	.490	.033	.285	.752	.779	.848	.725	.780	.975	.625	.858	.483	.000	.854	.976
		df	7	7	0	6	2	7	7	4	6	6	6	6	6	1	1	1	1	1	1	1	1	1	1
	HCC	Correlation	-.452	.295	-.096	1.000	-.938	.314	.099	.680	.489	-.221	.012	.060	.256	.968	1.000	1.000	-.287	.315	.937	.136	-.439	.907	.576

	Significance (2-tailed)	.261	.478	.821	.	.062	.449	.816	.207	.265	.599	.977	.889	.541	.160	.000	.000	.815	.796	.227	.913	.711	.276	.610
	df	6	6	6	0	2	6	6	3	5	6	6	6	6	1	1	1	1	1	1	1	1	1	1
prolctin	Correlation	.270	1.000	.589	-.938	1.000	-1.000	-.246	.	-1.000	-.649	.661	-1.000	-.701	.	.	.	.	.	.	.	.	.	.
	Significance (2-tailed)	.730	.000	.411	.062	.	.000	.754	.	.000	.351	.339	.000	.299	.	.	.	.	.	.	.	.	.	.
	df	2	2	2	2	0	2	2	0	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0
WEMWBS-total	Correlation	-1.000	-.624	-.262	.314	-1.000	1.000	.376	.763	1.000	.564	.339	-.092	.499	.087	.877	.576	-.592	1.000	-.180	.518	-1.000	.134	-1.000
	Significance (2-tailed)	.000	.073	.495	.449	.000	.	.319	.078	.000	.145	.412	.828	.209	.944	.320	.610	.597	.000	.885	.654	.000	.915	.000
	df	7	7	7	6	2	0	7	4	6	6	6	6	6	1	1	1	1	1	1	1	1	1	1
HADS-D	Correlation	1.000	.223	-.270	.099	-.246	.376	1.000	-.165	-.146	-.291	.301	.540	.149	-.170	.014	-.066	1.000	1.000	-.006	-.546	-.492	-.526	-.406
	Significance (2-tailed)	.000	.565	.482	.816	.754	.319	.	.754	.729	.484	.469	.167	.724	.891	.991	.958	.000	.000	.996	.632	.672	.647	.734
	df	7	7	7	6	2	7	0	4	6	6	6	6	6	1	1	1	1	1	1	1	1	1	1
EQRS-Total	Correlation	-.408	-.423	-.345	.680	.	.763	-.165	1.000	.538	.490	.198	-.103	.478	.	.	.	.	.	.	.	.	.	.
	Significance (2-tailed)	.038	.035	.503	.207	.	.078	.754	.	.005	.402	.749	.870	.415	.	.	.	.	.	.	.	.	.	.

	df	24	23	4	3	0	4	4	0	24	3	3	3	3	0	0	0	0	0	0	0	0	0
SAS-Total	Correlation	-.718	-.341	-.287	.489	-1.000	1.000	-.146	.538	1.000	.272	-.499	.664	.221	.580	.693	.651	.907	.985	.619	-.125	-.503	.315	.185
	Significance (2-tailed)	.000	.070	.490	.265	.000	.000	.729	.005	.	.555	.254	.104	.634	.606	.513	.549	.276	.111	.575	.920	.665	.796	.882
	df	28	27	6	5	2	6	6	24	0	5	5	5	5	1	1	1	1	1	1	1	1	1	1
OQUESA-GR	Correlation	-.609	-.500	-.749	-.221	-.649	.564	-.291	.490	.272	1.000	-.067	-.480	.115	-.323	-.019	-.142	-1.000	-.262	-.499	-.194	-1.000	.035	-.671
	Significance (2-tailed)	.109	.207	.033	.599	.351	.145	.484	.402	.555	.	.874	.228	.787	.791	.988	.909	.000	.831	.667	.876	.000	.978	.532
	df	6	6	6	6	2	6	6	3	5	0	6	6	6	1	1	1	1	1	1	1	1	1	1
OQUESA-RP	Correlation	.648	.010	.432	.012	.661	.339	.301	.198	-.499	-.067	1.000	-.209	.290	-.544	-.179	-.308	.728	-.343	-.597	.611	-.244	-.413	-.962
	Significance (2-tailed)	.082	.981	.285	.977	.339	.412	.469	.749	.254	.874	.	.620	.486	.634	.886	.801	.481	.777	.593	.582	.843	.729	.176
	df	6	6	6	6	2	6	6	3	5	6	0	6	6	1	1	1	1	1	1	1	1	1	1
OQUESA-ED	Correlation	-.012	-.328	.134	.060	-1.000	-.092	.540	-.103	.664	-.480	-.209	1.000	.178	.077	-.089	-.031	.942	.850	.159	.011	.493	-.245	.119
	Significance (2-tailed)	.977	.428	.752	.889	.000	.828	.167	.870	.104	.228	.620	.	.673	.951	.943	.980	.217	.353	.898	.993	.672	.843	.924
	df	6	6	6	6	2	6	6	3	5	6	6	0	6	1	1	1	1	1	1	1	1	1	1
OQUESA-NC	Correlation	-.007	-.483	.119	.256	-.701	.499	.149	.478	.221	.115	.290	.178	1.000	.223	.484	.383	.387	.046	.224	-.522	-1.000	.293	-.045

	Significance (2-tailed)	.986	.226	.779	.541	.299	.209	.724	.415	.634	.787	.486	.673	.	.857	.678	.750	.747	.971	.856	.650	.000	.811	.972
	df	6	6	6	6	2	6	6	3	5	6	6	6	0	1	1	1	1	1	1	1	1	1	1
IFNγ	Correlation	-1.000	.619	-.237	.968	.	.087	-.170	.	.580	-.323	-.544	.077	.223	1.000	.966	.986	-.660	.214	.990	-.185	-.310	.952	.884
	Significance (2-tailed)	.000	.575	.848	.160	.	.944	.891	.	.606	.791	.634	.951	.857	.	.167	.105	.541	.863	.089	.882	.799	.198	.310
	df	1	1	1	1	0	1	1	0	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1
IL1β	Correlation	-1.000	.526	-.419	1.000	.	.877	.014	.	.693	-.019	-.179	-.089	.484	.966	1.000	.995	-.901	.153	.923	-.146	-.534	.979	.758
	Significance (2-tailed)	.000	.648	.725	.000	.	.320	.991	.	.513	.988	.886	.943	.678	.167	.	.063	.286	.902	.251	.907	.641	.130	.452
	df	1	1	1	1	0	1	1	0	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1
IL10	Correlation	-1.000	.568	-.338	1.000	.	.576	-.066	.	.651	-.142	-.308	-.031	.383	.986	.995	1.000	-.843	.169	.954	-.150	-.448	.980	.810
	Significance (2-tailed)	.000	.616	.780	.000	.	.610	.958	.	.549	.909	.801	.980	.750	.105	.063	.	.361	.892	.194	.904	.704	.127	.399
	df	1	1	1	1	0	1	1	0	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1
IL12p70	Correlation	.494	.220	-.039	-.287	.	-.592	1.000	.	.907	-1.000	.728	.942	.387	-.660	-.901	-.843	1.000	.772	-.536	-1.000	-.227	-.876	-.204

	Significance (2-tailed)	.671	.859	.975	.815	.	.597	.000	.	.276	.000	.481	.217	.747	.541	.286	.361	.	.439	.640	.000	.854	.321	.869
	df	1	1	1	1	0	1	1	0	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1
IL13	Correlation	-.099	-.173	-.556	.315	.	1.000	1.000	.	.985	-.262	-.343	.850	.046	.214	.153	.169	.772	1.000	.269	-.171	-.079	-.077	.087
	Significance (2-tailed)	.937	.889	.625	.796	.	.000	.000	.	.111	.831	.777	.353	.971	.863	.902	.892	.439	.	.827	.890	.950	.951	.944
	df	1	1	1	1	0	1	1	0	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1
IL2	Correlation	-1.000	.690	-.222	.937	.	-.180	-.006	.	.619	-.499	-.597	.159	.224	.990	.923	.954	-.536	.269	1.000	-.317	-.305	.916	.936
	Significance (2-tailed)	.000	.516	.858	.227	.	.885	.996	.	.575	.667	.593	.898	.856	.089	.251	.194	.640	.827	.	.795	.803	.262	.230
	df	1	1	1	1	0	1	1	0	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1
IL4	Correlation	-.308	-.279	.726	.136	.	.518	-.546	.	-.125	-.194	.611	.011	-.522	-.185	-.146	-.150	-1.000	-.171	-.317	1.000	.443	-.076	-.415
	Significance (2-tailed)	.801	.820	.483	.913	.	.654	.632	.	.920	.876	.582	.993	.650	.882	.907	.904	.000	.890	.795	.	.708	.952	.727
	df	1	1	1	1	0	1	1	0	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1
IL6	Correlation	.320	.185	1.000	-.439	.	-1.000	-.492	.	-.503	-1.000	-.244	.493	-1.000	-.310	-.534	-.448	-.227	-.079	-.305	.443	1.000	-.364	-.050
	Significance (2-tailed)	.793	.882	.000	.711	.	.000	.672	.	.665	.000	.843	.672	.000	.799	.641	.704	.854	.950	.803	.708	.	.763	.968
	df	1	1	1	1	0	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1

IL8	Correlation	-1.000	.567	-.228	.907	.	.134	-.526	.	.315	.035	-.413	-.245	.293	.952	.979	.980	-.876	-.077	.916	-.076	-.364	1.000	.802
	Significance (2-tailed)	.000	.616	.854	.276	.	.915	.647	.	.796	.978	.729	.843	.811	.198	.130	.127	.321	.951	.262	.952	.763	.	.407
	Df	1	1	1	1	0	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1
TNFα	Correlation	-.647	.783	.037	.576	.	-1.000	-.406	.	.185	-.671	-.962	.119	-.045	.884	.758	.810	-.204	.087	.936	-.415	-.050	.802	1.000
	Significance (2-tailed)	.552	.427	.976	.610	.	.000	.734	.	.882	.532	.176	.924	.972	.310	.452	.399	.869	.944	.230	.727	.968	.407	.
	df	1	1	1	1	0	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0

Appendix B

Correlations adjusted for age; diagnosis; gender; EQRS and SAS

Control Variables			ASEX-Total	CGI-1	HADS-A	HCC	WEMWBS-total	HADS-D	OQUESA-GR	OQUESA-RP	OQUESA-ED	OQUESA-NC	IFNγ	IL1β	IL10	IL12p70	IL13	IL2	IL4	IL6	IL8	TNFα
age & diagnosis & gender & EQRS-Total & SAS-Total	ASEX-Total	Correlation	1.000	.207	-.343	-.175	.	1.000	-.665	.656	1.000	.266	.	.	.	.	.	.	.	.	.	.
		Significance (2-tailed)	.	.343	.657	.888	.	.000	.537	.544	.000	.828	.	.	.	.	.	.	.	.	.	.
		df	0	21	2	1	2	2	1	1	1	1	0	0	0	0	0	0	0	0	0	0
	CGI-1	Correlation	.207	1.000	-.108	.934	.	.163	-.373	-.006	-.557	-.365	.	.	.	.	.	.	.	.	.	.
		Significance (2-tailed)	.343	.	.892	.232	.	.837	.757	.996	.624	.762	.	.	.	.	.	.	.	.	.	.
		df	21	0	2	1	2	2	1	1	1	1	0	0	0	0	0	0	0	0	0	0
	HADS-A	Correlation	-.343	-.108	1.000	.234	.	-.366	-.713	.666	.423	.341	.	.	.	.	.	.	.	.	.	.
		Significance (2-tailed)	.657	.892	.	.850	.	.634	.495	.536	.722	.778	.	.	.	.	.	.	.	.	.	.
		df	2	2	0	1	2	2	1	1	1	1	0	0	0	0	0	0	0	0	0	0
	HCC	Correlation	-.175	.934	.234	1.000	.	.313	-.887	-.036	.011	-.100	.	.	.	.	.	.	.	.	.	.
		Significance (2-tailed)	.888	.232	.850	.	.	.798	.306	.977	.993	.936	.	.	.	.	.	.	.	.	.	.
		Df	1	1	1	0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0

Control variables		ASEX - Total	CGI-1	HADS -A	HCC	WEMWBS -total	HADS -D	OQUESA -GR	OQUESA -RP	OQUESA -ED	OQUESA -NC	IFNγ	IL1β	IL10	IL12p70	IL13	IL2	IL4	IL6	IL8	TNFα
WEMWBS -total	Correlation	.	.	.	.	1.000	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
	Significance (2-tailed)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
	df	2	2	2	1	0	2	1	1	1	1	0	0	0	0	0	0	0	0	0	0
HADS-D	Correlation	1.000	.163	-.366	.313	.	1.000	-.244	.434	1.000	.261	.	.	.	.	.	.	.	.	.	.
	Significance (2-tailed)	.000	.837	.634	.798	.	.	.843	.714	.000	.832	.	.	.	.	.	.	.	.	.	.
	df	2	2	2	1	2	0	1	1	1	1	0	0	0	0	0	0	0	0	0	0
OQUESA-GR	Correlation	-.665	-.373	-.713	-.887	.	-.244	1.000	-.270	-.983	-.156	.	.	.	.	.	.	.	.	.	.
	Significance (2-tailed)	.537	.757	.495	.306	.	.843	.	.826	.118	.900	.	.	.	.	.	.	.	.	.	.
	df	1	1	1	1	1	1	0	1	1	1	0	0	0	0	0	0	0	0	0	0
OQUESA-RP	Correlation	.656	-.006	.666	-.036	.	.434	-.270	1.000	1.000	.282	.	.	.	.	.	.	.	.	.	.
	Significance (2-tailed)	.544	.996	.536	.977	.	.714	.826	.	.000	.818	.	.	.	.	.	.	.	.	.	.
	Df	1	1	1	1	1	1	1	0	1	1	0	0	0	0	0	0	0	0	0	0

Control variables		ASEX - Total	CGI-1	HADS -A	HCC	WEMWBS -total	HADS -D	OQUESA -GR	OQUESA -RP	OQUESA -ED	OQUESA -NC	IFNγ	IL1β	IL10	IL12p70	IL13	IL2	IL4	IL6	IL8	TNFα
OQUESA-ED	Correlation	1.000	-.557	.423	.011	.	1.000	-.983	1.000	1.000	.587	.	.	.	.	.	.	.	.	.	.
	Significance (2-tailed)	.000	.624	.722	.993	.	.000	.118	.000	.	.601	.	.	.	.	.	.	.	.	.	.
	df	1	1	1	1	1	1	1	1	0	1	0	0	0	0	0	0	0	0	0	0
OQUESA-NC	Correlation	.266	-.365	.341	-.100	.	.261	-.156	.282	.587	1.000	.	.	.	.	.	.	.	.	.	.
	Significance (2-tailed)	.828	.762	.778	.936	.	.832	.900	.818	.601	.	.	.	.	.	.	.	.	.	.	.
	df	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0
IFNγ	Correlation	.	.	.	.	.	.	.	.	.	.	1.000	.	.	.	.	.	.	.	.	.
	Significance (2-tailed)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
	df	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
IL1β	Correlation	.	.	.	.	.	.	.	.	.	.	.	1.000	.	.	.	.	.	.	.	.
	Significance (2-tailed)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
	Df	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Control variables		ASEX - Total	CGI-1	HADS -A	HCC	WEMWBS -total	HADS -D	OQUESA -GR	OQUESA -RP	OQUESA -ED	OQUESA -NC	IFNγ	IL1β	IL10	IL12p70	IL13	IL2	IL4	IL6	IL8	TNFα
IL10	Correlation	.	.	.	.	.	.	.	.	.	.	.	.	1.000	.	.	.	.	.	.	.
	Significance (2-tailed)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
	df	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
IL12p70	Correlation	.	.	.	.	.	.	.	.	.	.	.	.	.	1.000	.	.	.	.	.	.
	Significance (2-tailed)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
	df	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
IL13	Correlation	.	.	.	.	.	.	.	.	.	.	.	.	.	.	1.000	.	.	.	.	.
	Significance (2-tailed)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
	df	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
IL2	Correlation	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	1.000	.	.	.	.
	Significance (2-tailed)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
	Df	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Control variables		ASEX - Total	CGI-1	HADS -A	HCC	WEMWBS -total	HADS -D	OQUESA -GR	OQUESA -RP	OQUESA -ED	OQUESA -NC	IFNγ	IL1β	IL10	IL12p70	IL13	IL2	IL4	IL6	IL8	TNFα
IL4	Correlation	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	1.000	.	.	.
	Significance (2-tailed)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
	df	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
IL6	Correlation	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	1.000	.	.
	Significance (2-tailed)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
	df	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
IL8	Correlation	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	1.000	.
	Significance (2-tailed)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
	df	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
TNFα	Correlation	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	1.000
	Significance (2-tailed)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
	df	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

highlight indicates significant correlation (p≤0.05).

Appendix C Study documents

C.1 Study protocol

Sexual functioning in patients with anxiety disorders: an investigation of the potential influence of neuroinflammatory and endocrine factors (V.5.2; 17/08/2017)

1. The need for this study

This is an educational study towards a Doctor of Medicine degree for Dr Hesham Elnazer under supervision of Professor David Baldwin and Dr Anthony Sampson, Faculty of Medicine, University of Southampton.

Many studies have explored the relationship between sexual dysfunction, depressive illness and treatment with antidepressant drugs. However the relationship between anxiety disorders, sexual dysfunction and dissatisfaction and treatment with psychotropic drugs has not been explored extensively. Little is known about the prevalence of sexual dysfunction in patients with anxiety disorders, or its association with demographic and other clinical factors, and the optimal management of sexual dysfunction in patients with anxiety disorders who are undergoing psychotropic drug treatment remains uncertain. Treatment with an antidepressant drug – particularly a selective serotonin reuptake inhibitor (SSRI) - is the main pharmacological approach in patients with anxiety disorders (Baldwin et al. 2014). However randomised placebo-controlled trials have consistently shown that antidepressant drugs can be associated with either the development or worsening of sexual dysfunction. Sexual difficulties during antidepressant treatment of depressed patients may persist over long periods, and can reduce self-esteem and affect mood and relationships adversely. Sexual dysfunction during antidepressant treatment is typically associated with many possible causes, but the risk of dysfunction varies between

antidepressants, and should be considered when selecting an antidepressant (Baldwin et al. 2013). Reduction of depressive symptoms through successful antidepressant treatment of depressed patients is sometimes accompanied by reported improvements in sexual desire and satisfaction, but it is not known whether this phenomenon is also seen in patients with anxiety disorders.

Recent studies into the potential pathophysiology of anxiety disorders have included investigations of salivary cortisol levels and concentrations of cortisol in hair. For example, an investigation involving serial saliva sampling found the cortisol awakening response to be less elevated in patients with generalised anxiety disorder (GAD) than in patients with panic disorder, with neither group showing more dexamethasone non-suppression than in matched controls (Vreeburg et al. 2010). A case–control study of cortisol concentrations in hair, which may provide a better reflection of cortisol levels over time, found significantly lower cortisol levels among patients with GAD than in controls (Steudte et al. 2011). The association of sexual dysfunction in anxiety disorders with endocrine disturbance (including hypothalamic pituitary axis disturbance) remains an under-researched area (Elnazer et al. 2014). Although some investigations of inflammatory markers in patients with anxiety disorders have been performed (Hou et al. 2012), the possible association of sexual dysfunction in anxiety disorders with inflammatory markers has yet to be explored. Investigation of this area may lead to potential innovative pharmacological approaches such as treatment with non-steroidal anti-inflammatory drugs.

2. Study aims

The overall aims of the proposed programme of research are to establish:

- the point prevalence of sexual difficulties in patients with anxiety disorders, prior to staring antidepressant treatment;
- the incidence of 'treatment-emergent sexual dysfunction' (i.e. the emergence of new sexual

problems or worsening of pre-existing sexual difficulties) in patients with anxiety disorders undergoing six weeks of antidepressant treatment;

- the influence of endocrine factors on the risk and severity of sexual difficulties, through investigation of cortisol and prolactin levels;
- the influence of inflammatory factors markers on the risk and severity of sexual difficulties, through investigation of circulating inflammatory cytokines and c-reactive protein.
- the potential efficacy of six weeks augmentation of an antidepressant with an anti-inflammatory drug (celecoxib) in reducing reported sexual difficulties in patients with anxiety disorders.

3. Proposed study design and procedures

Referrals of potential participants would be invited, for patients with a diagnosis of an anxiety disorder in accordance with the DSM-5 criteria. Study participants would be invited to a screening process using the Mini International Neuropsychiatric Interview (MINI) (Sheehan *et al*., 1998).

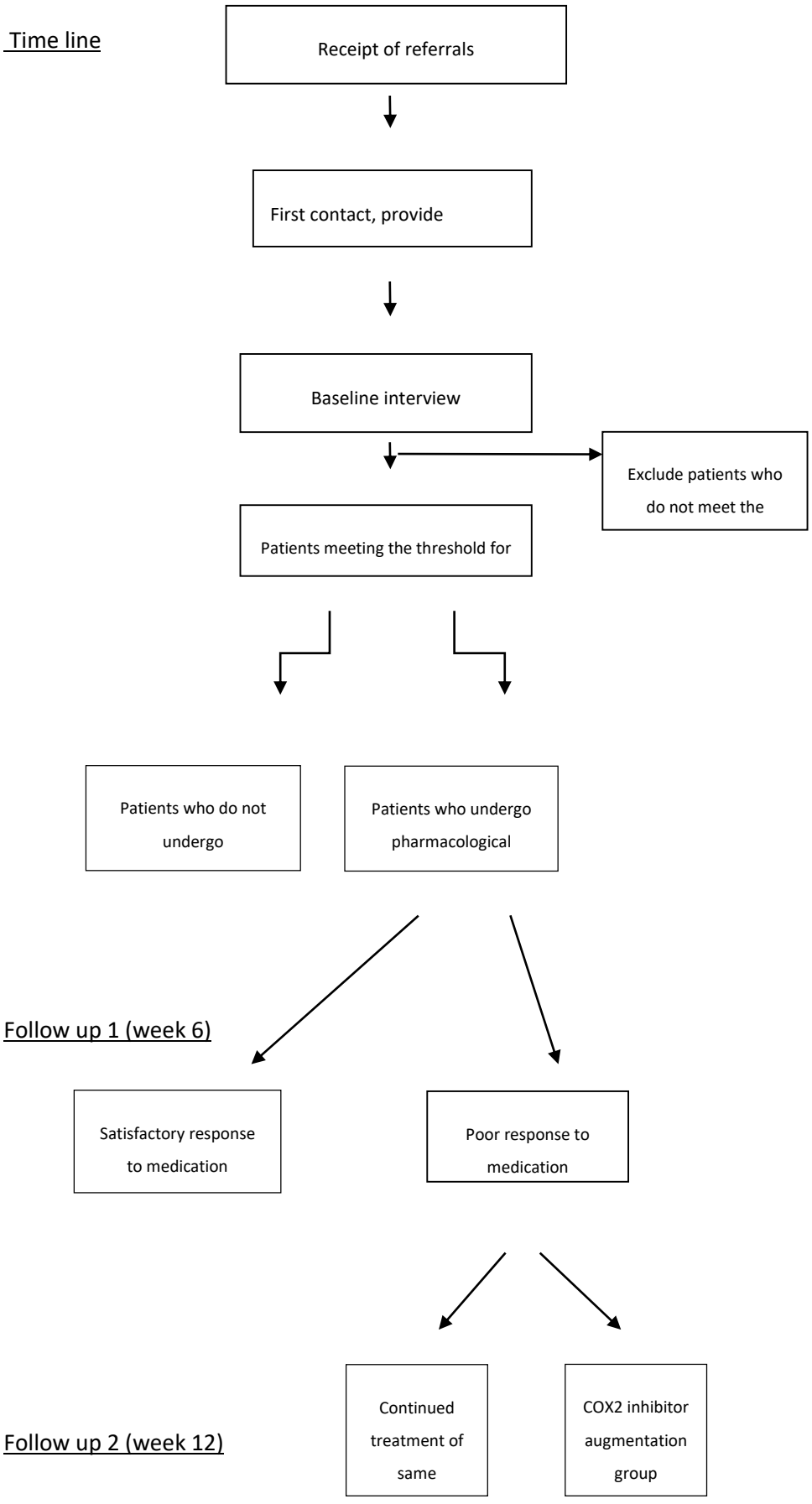
Potentially eligible patients who meet threshold criteria for an anxiety disorder would be included in a cross-sectional investigation of the relationships between the presence of an anxiety disorder and sexual difficulties. The following assessment measures would be used:

- Arizona Sexual Experiences Scale (ASEX) (McGahuey et al, 2000)
- Warwick- Edinburgh Mental Well-Being Scale (WEMWEBS) (Tennant et al 2007)
- Hospital Anxiety and Depression Scale (HADS) (Zigmond et al, 1983)
- Oxford Questionnaire of Emotional Side Effects of Antidepressants (OQuESA) (Price et al, 2012)
- Clinical Global Impression of Illness Severity (CGI-S) (Guy W et al, 1976)
- Emotional Quality of the Relationship Scale (EQR) (Kreuter M et al, 1996)

To determine the incidence of treatment-emergent sexual difficulties, the above assessments would be repeated after 6 weeks for patients in whom new treatment is been contemplated to compare with baseline data. Treatment adherence would be determined by patient report.

To determine the potential influence of endocrine factors, scalp hair samples from the vertex area (3cm in length) would be collected from participants at baseline and after 6 weeks. Descriptive sub-group analysis would include consideration of cortisol levels in differing anxiety disorders, and the influence of medication.

To determine the potential influence of interleukins and tumour necrotic factor alpha, venous blood samples would be collected from participants at baseline and after 6 weeks. Sub-group analysis would include consideration of differing anxiety disorders, and the influence of concomitant medication.


Time line
Receipt of referrals
First contact, provide
Baseline interview
Exclude patients who do not meet the
Patients meeting the threshold for
Patients who do not undergo
Patients who undergo pharmacological
Follow up 1 (week 6)
Satisfactory response to medication
Poor response to medication
Follow up 2 (week 12)
Continued treatment of same
COX2 inhibitor augmentation group

4. Recruitment of the study sample

Patients would be recruited from among current and future outpatients attending outpatient mental health services. In addition, letters with an information sheet would be sent to local general practitioners and consultant psychiatrists working within Southern Health NHS Foundation Trust, Sussex Partnership NHS Foundation and Northamptonshire Healthcare NHS Foundation Trust; inviting the referral of potentially suitable patients who meet the study criteria. Identified patients would be sent a letter with the participant information sheet, consent form and stamped addressed envelope. They would be provided with the contact details for the research team and have an opportunity to ask any questions about the study aims and procedures. If a consent form is returned, the research assistant (holder of an honorary contract with Southern Health Foundation Trust and full clinical contract with Sussex Partnership NHS Foundation Trust or Northamptonshire Healthcare NHS Foundation Trust or an affiliated research assistant, would contact the potential patient to make an appointment for confirmation of continued consent and the study baseline assessment.

Patients would only be eligible for the study if they met the following criteria:

- aged 18-70 years inclusive;
- diagnosis of an anxiety disorder according to DSM-5 criteria;
- competent to provide written, informed consent.

All eligible patients who are not currently receiving any pharmacological treatment for an anxiety disorder would be included in the assessment of the point prevalence of sexual dysfunction in anxiety disorders.

Patients who are not receiving pharmacological treatment for anxiety disorder at the time of referral will be treated with usual evidence-based treatment (after considering patients

preference). Patients who have been already started on a pharmacological treatment by their GP will be assessed to be expedited to follow up 1.

Patients who subsequently underwent pharmacological treatment would be potentially suitable for participation in the follow-up phase of the study.

Patients would be excluded from the study if they met the following criteria:

- outside the age range 18-65 years;
- the primary diagnosis is not an anxiety disorder;
- unable to provide written, informed consent;
- clinically significant alcohol or substance use in the previous three months;
- physical illness that is unlikely to be stable over the course of the study.
- pregnancy and breast feeding.
- exclusion criteria for augmentation phase;
    - medical contra indication for celecoxib; history of hypersensitivity to NSAID, patient with cardiac impairment, thromboembolic disease, renal impairment, hepatic impairment or history of recurrent gastro-intestinal ulceration.
    - concomitant use of NSAIDS, ciclosporins, cumarins, dabigatran, ketorolac, lithium, methotrexate, phenindione, quinolones and sulfonylureas.

Prospective evidence of treatment-emergent sexual dysfunction (prospective phase):

Assessment of patient participants who had started treatment for an anxiety disorder in the preceding 6 weeks. Enquiries about treatment history and current treatment status would be made. Assessment of sexual dysfunction would be obtained by sensitive interviewing and through using the measures shown in section 3. The degree of adherence to the prescribed medication would be assessed by sensitive questioning. Endocrine factors would be assessed through sampling hair for

cortisol levels and blood for prolactin levels. Inflammatory markers would be assessed using venous blood sampling. Samples will be spun quickly and at 4 degree, and that serum and plasma are frozen at –80.

Non-steroidal anti-inflammatory drug (celecoxib) treatment phase (augmentation phase):

Assessment of patient participants who had started augmentation treatment 6 weeks previously. Enquiries about treatment history and current treatment status would be made. Assessment of sexual dysfunction would be obtained by sensitive interviewing and through using the measures shown in section 3. The degree of adherence to the prescribed medication would be assessed by sensitive questioning. Endocrine factors would be assessed through sampling hair for cortisol levels and blood for prolactin levels. Inflammatory markers would be assessed using venous blood sampling.

Dose Schedule

The dose to be used is 200 mg twice daily. Previous studies suggested effective SSRI augmentation in patients with depression at a dose of 400 mg daily/200mg Bd (Akhondzadeh et al 2009, Abbasi et al 2012, Nery et al 2008).

Treatment withdrawal criteria

As per patient's information sheet; participants will be reminded of their right to withdraw their consent and from the study at any point. The treatment will be stopped immediately for patient who experience any of the following serious adverse events (occurred in <0.1% of patients) and the patient will be excluded from the augmentation phase. Where appropriate patient will be advised to seek medical help from their GP.

Cardiovascular:	Syncope, congestive heart failure, ventricular fibrillation, pulmonary embolism, cerebrovascular accident, peripheral gangrene, thrombophlebitis, vasculitis, deep venous thrombosis
Gastrointestinal:	Intestinal obstruction, intestinal perforation, gastrointestinal bleeding, colitis with bleeding, oesophageal perforation, pancreatitis, ileus
Liver and biliary:	Cholelithiasis, hepatitis, jaundice, liver failure
Hemic and lymphatic:	Thrombocytopenia, agranulocytosis, aplastic anaemia, pancytopenia, leucopoenia
Metabolic:	Hypoglycaemia, hyponatremia
Nervous:	Ataxia, aggravated suicidal thoughts, aseptic meningitis, ageusia, anosmia, fatal intracranial haemorrhage.
Renal:	Acute renal failure, interstitial nephritis
Skin:	Erythema multiform, exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis drug rash with eosinophilia and systemic symptoms (DRESS, or hypersensitivity syndrome)

General:	Sepsis, sudden death, anaphylactoid reaction, angioedema.
	Patients on Warfarin, Aspirin, ACE-inhibitors and Angiotensin II antagonists, Fluconazole, Furosemide, concomitant use of other NSAIDs.

Patients will be advised to get emergency help right away if they have any of the following symptoms:

- shortness of breath or trouble breathing
- chest pain
- weakness in one part or side of your body
- slurred speech
- swelling of the face or throat

Patients will be advised to stop Celecoxib and call their Gp immediately if they have any of the following symptoms:

- nausea
- more tired or weaker than usual
- itching
- your skin or eyes look yellow
- stomach pain
- flu-like symptoms
- vomit blood
- there is blood in your bowel movement or it is black and sticky like tar
- skin rash or blisters with fever
- unusual weight gain
- swelling of the arms and legs, hands and feet

5. Sample size and statistical aspects

Based on current referral patterns we expect around 120 patients to be referred over the course of 1 year across the study sites. Of these we anticipate that around 100 patients would be potentially suitable for the study, and that approximately 80 patients would provide consent. Based on typical

treatment responses with an SSRI, we anticipate that around 40 patients would respond to treatment but around 40 would still be troubled by anxiety symptoms of at least moderate intensity. These non-responding patients would then be approached about potential participation in the open label celecoxib augmentation phase: in which 20 participants would be allocated to active treatment and 20 participants as a control group.

6. Tolerability of treatment and reporting of adverse events

During the celecoxib augmentation phase, tolerability assessments would be based on an open-ended question relating to any potential adverse events during treatment. Adverse events would be recorded and reported in the conventional way, noting whether the adverse event was mild, moderate or severe; its duration; any intervention which was needed; and its likelihood of being related to the study interventions. All 'serious' adverse events (according to conventional categorisations) would be characterised similarly, and categorised as expected or unexpected, and reported to the study sponsor (University of Southampton Research Governance Office), host (Southern Health NHS Foundation Trust Research and Outcomes office), the MHRA, National Research Ethics Service, and the manufacturers of celecoxib, within 24 hours of the research team becoming aware of their existence.

6.1 Categorisation of adverse events occurring during the investigation

Professor Baldwin (Chief Investigator) would be responsible for reporting adverse events to the Sponsor, the Medicines and Healthcare Products Regulatory Agency (MHRA), the Research Ethics Committee (REC) and Southern Health NHS Trust R & D Office, within agreed timelines. Reporting of adverse events would include an assessment of the seriousness, expectedness, and presumed causality with regard to the study medication.

a. Adverse Event (AE). An 'adverse event' would be any untoward medical occurrence in a trial participant administered the study medication, which does not necessarily have a causal relationship with the medication. An adverse event could therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of trial medication, whether or not considered related to the trial medication.

b. Adverse Reaction (AR). An 'adverse reaction' would be any untoward and unintended response in a trial participant administered the study medication, which is related to any dose administered to that individual.

c. Serious Adverse Event (SAE). An adverse event, adverse reaction or unexplained adverse reaction would be categorised as 'serious' if it: (i) results in death, (ii) is life-threatening, (iii) requires hospitalisation or prolongation of existing hospitalisation, (iv) results in persistent or significant disability of incapacity, or (v) consists of a congenital anomaly or birth defect.

d. Suspected Unexpected Serious Adverse Reaction (SUSAR). All adverse events that are suspected to be related to the study medication and are both unexpected and serious are considered to be SUSARs. All SUSARS that are life threatening or fatal require would be reported to the MHRA and other bodies within 24 hours of becoming aware of their existence.

e. Adverse Incidents (AIs). An adverse incident would be defined as 'an event or circumstance that could have or did lead to unintended or unexpected harm, loss or damage'. Adverse incidents would be reported separately, and in accordance with the Southern Health NHS Foundation Trust Adverse procedures.

6.2 Assessment and reporting of adverse events

a. Serious adverse events. As part of the recording process on the **Adverse Event Record Sheet**, assessment as to whether the adverse event was serious is required, indicated by responding 'yes' or 'no'. When the adverse event is assessed to be serious, a **Serious Adverse Event Form** would be completed and faxed to relevant authorities within 24 hours. Where the information available is incomplete at that time, as much information as can be ascertained would be sent to ensure timely reporting, and additional information would be provided as soon as it was known. Additional information received for an event (follow-up or corrections to the original event data) would be detailed on a new **Serious Adverse Event Reporting Form.** It would be left to clinical judgement whether or not an adverse event was of sufficient severity to require the participant's removal from the study. A participant could of course voluntarily withdraw from the study due to what he or she perceives as an intolerable adverse event.

b. Non serious AR/AEs. Events that are judged as not 'serious' are categorised as Adverse Events. An **Adverse Event Record Sheet** would be completed, with an assessment of the likelihood of the adverse event being related to the study medication is required.

c. Assessment of potential causality. Assessment of the likelihood of the adverse event being related to the study medication is judged according to the definitions below:

	Relationship	**Description**
1	**Unrelated**	No evidence of any causal relationship.
2	**Unlikely**	Little evidence to suggest a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).

3	**Possible**	Some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).
4	**Probable**	Evidence to suggest a causal relationship and the influence of other factors is unlikely.
5	**Definitely**	Clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

d. Assessment of severity. Severity relates to the intensity of the adverse event, and is not synonymous with seriousness. As part of the recording process on a study-specific Adverse Event Record Sheet, the event would be judged as 'mild', 'moderate', or 'severe'.

e. Expectedness. As part of the recording process on a study-specific Adverse Event Record Sheet, a judgement would be made on the likelihood of the adverse event being one of the recognised undesirable effects of the study medication, indicated by responding either 'expected' or 'unexpected'. Expected adverse effects for antidepressant drugs and celecoxib are listed in provided in their respective SmPCs and the British National Formulary.

f. Suspected Unexpected Serious Adverse Reactions (SUSARs). Where the event is not listed in the known side effects of the anxyiolytic or NSIAD drug, or where the nature and/or severity are not consistent with what might be expected, the event would be considered an 'unexpected' reaction. The event would be reported on the SAE form within 24 hours of being notified of the event, the Chief Investigator taking appropriate action in assessing and expediting the SUSAR to the relevant authorities.

g. Follow-up of adverse events

All adverse events would be followed-up until symptoms cease or the condition becomes stable. A study-specific Adverse Event Record Sheet would be completed, rating the adverse event as either 'resolved', 'resolved with sequelae', 'persisting', 'worsened', 'fatal', or 'not assessable'. Where an adverse event is not initially considered serious but subsequently becomes serious, the reporting protocol for a serious adverse event would be followed at that stage.

7. Ethical considerations

No particular ethical problems are anticipated, as the schedule of study visits is not onerous (3 assessments over12 weeks) and accords with recommended clinical practice. Sexual difficulties would be reported by participants using questionnaires which can avoid embarrassment when describing any sexual concerns. All treatments would either be licensed for the treatment of an anxiety disorder or available for routine clinical use (celecoxib). The study protocol and associated documentation would be submitted for approval to the National Research Ethics Service, to the University of Southampton, and to the Research and Outcomes office of Southern Health NHS Foundation Trust. Standard indemnity arrangements with the Trust and University would apply.

8. Anticipated recruitment and progress through the study

On the basis of previous research findings, it is reasonable to assume that a total of 100 patients would need to provide baseline data, for there to be 80 patients suitable for the follow up phase and 40 for the non- steroidal anti-inflammatory drug augmentation phase.

9. Funding of the study

The study has not currently received external support. Dr Elnazer is a postgraduate research student in the Faculty of Medicine at the University of Southampton.

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Appendix C

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	First contact	Baseline interview (week 0)	Follow up 1 (week 6)	Follow up 2 (week 12)
Provide information and forms	**√**			
Obtain consent		**√**		
Mini International Neuropsychiatric Interview (MINI) and treatment history		**√**		
Hair sample (cortisol)		**√**	**√**	**√**
Blood sample (prolactin level)		**√**	**√**	**√**
Blood sample (inflammatory markers)		**√**	**√**	**√**
Arizona Sexual Experiences Scale		**√**	**√**	**√**

Warwick- Edinburgh Mental Well-Being Scale		√	√	√
Hospital Anxiety and Depression Scale		√	√	√
Oxford Questionnaire of Emotional Side Effects of Antidepressants		√	√	√
Clinical Global Impression of Illness Severity		√	√	√
Emotional Quality of the Relationship Scale		√	√	√
Compliance with treatment check (questioning)		√	√	√

Dr Hesham Elnazer, DM student.

Prof. David Baldwin, Professor of Psychiatry and Honorary Consultant Psychiatrist.

Dr Anthony Sampson, Reader in Pharmacology.

August 2017

C.2 Patient information sheet

Sexual functioning in patients with anxiety disorders: an investigation of the potential influence of neuroinflammatory and endocrine factors: information sheet. Version 5.1 Dated 17/08/2017

Principal Investigator: Dr Hesham Elnazer, University of Southampton Faculty of Medicine.

This is an educational study towards a medical doctorate under supervision of Professor David Baldwin and Dr Anthony Sampson, University of Southampton.

Information for potential participants

Invitation

You are being invited to take part in a research project designed to evaluate the potential influence of neuroinflammatory and endocrine factors in sexual dysfunction in patients with anxiety disorders. The principal aim of the proposed study is to investigate relationships between neuroinflammatory markers, cortisol levels, prolactin levels and sexual dysfunction associated with anxiety disorders. The study will also look at the possible therapeutic effect of an anti-inflammatory drug on neuroinflammatory markers and sexual dysfunction associated with anxiety disorders.

Terms:

Anti-inflammatory drug - a drug used to reduce the process of inflammation

Neuroinflammatory markers - a group of chemical substances the neural tissue generates in response to an inflammation.

Cortisol a hormone secreted by the supra adrenal gland that is known to be closely associated with stress.

Prolactin a hormone secreted by the pituitary gland that can be associated with sexual dysfunction if in excess.

Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. *Part 1 of this information sheet tells you the purpose of the study and what would happen to you if you took part. Part 2 gives you more detailed information about the evaluation of the group.* Take time to decide whether or not you wish to take part. Thank you for reading this.

Part 1

What is the purpose of the study?

Many studies have explored the relationship between sexual dysfunction, depressive illness and treatment with antidepressant drugs. However the relationship between anxiety disorders, sexual dysfunction and dissatisfaction and treatment with psychotropic drugs has not been explored extensively. Little is known about the prevalence of sexual dysfunction in patients with anxiety disorders, or its association with demographic and other clinical factors, and the optimal management of sexual dysfunction in patients undergoing psychotropic drug treatment remains uncertain. Treatment with an antidepressant drug – particularly a selective serotonin reuptake

inhibitor (SSRI) - is the main pharmacological approach in patients with anxiety disorders. However many studies have consistently shown that antidepressant drugs can be associated with the development or worsening of sexual dysfunction.
Recent investigations into anxiety disorders have included investigation of on salivary cortisol levels and concentrations of cortisol in hair. But the association of sexual dysfunction in anxiety disorders with endocrine disturbance (including cortisol levels) remains an under-researched area, and the influence of inflammation is an area yet to be explored. This may lead to further potential possibilities for the novel use of licensed pharmacological agents such as non-steroidal anti-inflammatory drugs.

Why have I been invited?
You have been invited as your GP [name]/ Psychiatric Consultant [name] thought you might be interested in hearing more about the study. The GP believes you have the diagnosis of an anxiety disorder. Your GP [name]/ Psychiatric Consultant [name] will provide you with the participant's information sheet, the consent form and patient's invitation letter. If you are interested to participate, we request you to return the opt-in reply slip directly to the research team indicating your preferred method of contact; post, email or telephone. After receiving the relevant details from you, members of the research team would contact you to discuss potential participation in the study.

Who cannot take part?
Patients would be excluded from the study if they met the following criteria:
outside the age range 18-70 years;
the primary diagnosis is not an anxiety disorder;
unable to provide written, informed consent;
clinically significant alcohol or substance use in the previous three months;
physical illness that is unlikely to be stable over the course of the study;
Pregnant and breast feeding women;concomitant use of NSAIDS, ciclosporins, cumarins, dabigatran, ketorolac, lithium, methotrexate, phenindione, quinolones and sulfonylureas.
Exclusion criteria for augmentation phase:
medical contra indication for celecoxib; history of hypersensitivity to NSAID, patient with cardiac impairment, thromboembolic disease, renal impairment, hepatic impairment or history of recurrent gastro-intestinal ulceration.

Do I have to take part?
No. It is up to you to decide whether or not to take part. If you decide to take part you would be given this information sheet to keep and would be asked to sign a consent form. If you decide to take part, you would be free to withdraw from the treatment at any time, without giving a reason. This would not affect any standard of the continuing care that you would receive.

What would happen to me if I decide to take part
We would arrange an initial appointment with you to be held in the clinic in *(study site)*. This interview could take up to two hours. We would ask a detailed set of questions about anxiety and sexual dysfunction symptoms. We would also need to get some background information from you about your consumption of alcohol-containing drinks or use of illicit drugs, as patients with primary substance use disorders cannot take part in the study. You would also be asked to complete standard number of questionnaires, some of which could be completed at home. In total, the questionnaires could take up to 30 minutes to complete. If after this initial appointment you were considered potentially suitable and were still interested in taking part, you would have the opportunity to ask further questions. We would ask you to provide a blood sample and a hair sample. If you were suitable and consent to participate in the study, we would follow you up 6

weeks to re-evaluate your symptoms using a set of standarised questionnaires and repeat the blood tests. If your anxiety symptoms had not reduced in severity you would be asked whether you wanted to augment current treatment with an anti-inflammatory drug. We would follow you up again after another six weeks, regardless of whether or not you underwent this augmentation.

Where would the interview take place and for how long?
The assessments would take place at College Keep (4-12 Terminus Terrace, Southampton SO14 3DT).
What would I be agreeing to do?
The treatment itself and the evaluation of the treatment involve a considerable commitment from participants and staff, so it is important that you think carefully about whether or not you are willing and able to make this commitment.

In the first part of the study you would be assessed at baseline (week 1), using questionnaires to assess the anxiety disorder and sexual dysfunction. You will also be requested to consent to blood sampling and hair sampling (Scalp hair 3 cm in length).

The same process will be repeated on weeks 6 and 12. We would be interested to know whether you are taking any anti-inflammatory drugs by week 12.

Please remember that although you are agreeing to take part in the study -
you can decide to stop any interview at any point;
you need not answer questions that you do not wish to;
anything you tell us will be absolutely confidential;
it will not be possible to identify anyone from our reports on the study.

Adherence to medication
If you decide to take part in the study, it is important that you take the prescribed medication in all phases of the trial, according to instructions from your prescriber. It is also important that you tell the members of the research team at your next visit if you have not taken any of the prescribed study medication, for any reason.

Please note that if you do not take the study medication as advised, you would not be able to continue taking part in the study. However your normal treatment would not be affected by your early withdrawal from the study.
The last phase of the study (non-steroidal anti-inflammatory augmentation stage) is optional. You can choose to augment or not to augment the current treatment with celecoxib, which is a nonsteroidal anti-inflammatory drug (NSAID). It works by reducing inflammation and pain in the body, and and has has also been effective in reducing symptoms of depression when taken alongside SSRIs. As some reports have described an increase in the risk of a heart attack or stroke if celecoxib is used over the long term or in high doses, you could not take part in augmentation if you have a history of heart disease, a history of hypersensitivity to NSAID, or a history of recurrent gastro-intestinal ulceration: or current cardiac impairment, thromboembolic disease, renal impairment, hepatic impairment
The research group will discuss and consider the safety and suitability of being included in this phase. You would only be considered for augmentation with celecoxib if the research team thought it was not inadvisable and if you agreed to this.

More information about the research and treatment is given here

Part 2

Will my GP be contacted?
If you are interested in taking part in the study and the assessments suggest that you are likely to be suitable we would contact your GP to say that you are taking part. This is so that your GP is aware of your involvement in the study and could take this into account when planning other treatment for you. We would seek your consent to share information with your GP In case of any incidental or unexpected findings which were found during the research process

Who is in the research team?
This study is run by the Clinical and Experimental Sciences (CNS and Psychiatry) within theFaculty of Medicine. This study is led by Professor David Baldwin and Dr Anthony Sampson, study assessments being undertaken by Dr Hesham Elnazer. Other research assistants may help with the study.

What are the possible risks and benefits of taking part?
In the prospective phase of the study, we will be able to determine the presence of sexual dysfunction. Also we will be able to determine if there is an association between the markers investigated and the severity of the problem. In the augmentation phase we would be able to determine the possible benefit from anti-inflammatory drugs in improving sexual difficulties associated with anxiety disorder.

The Research Team can be contacted on: 02380 718 520.

What would happen if I withdrew from the study?
You are free to withdraw from the study at any time, simply by telling a member of the research team. If you withdrew from the study, we would still wish to use the data collected up to the point of your withdrawal. Withdrawing from the study would not affect the nature or standard of your continuing care.

What if there is a problem?
If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions: prof. David Baldwin, telephone 023 8071 8520.
In the unlikely event that something does go wrong and you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service and University of Southampton complaints mechanisms are available to you.

Feedback of the study findings. Feedback of the study findings would be available upon request.

Address: Research Governance Office
Room 4047/Building 37
University of Southampton
Tel. 023 8059 5058; 023 8059 5781 (fax); Email: rgoinfo@soton.ac.uk

NHS Complaints

Tel. 0845 4647;
http://www.nhs.uk/choiceintheNHS/Rightsandpledges/complaints/Pages/AboutNHScomplaints.aspx

Would my taking part in this study be kept confidential?
Yes. All information that would be collected about you during the course of the study would be kept strictly confidential within the limits of the law. Any information about you would be coded with a number, which would not have your name on it, and so you could not be recognised from it. Regulations require that any data will have to be stored for 10 years, but this would only be accessed by the study team and would be destroyed after this time. The only situation in which confidentiality would be breached would be in the very rare circumstance in which it was judged that someone was at immediate risk of serious harm (for example if someone was seriously planning to end their life) or if we had concerns about harm to others. In these circumstances we would only disclose information to a third party (normally your consultant or GP) that was essential for the safety of the person at risk.

What would happen to the results of the research?
If the findings from the study were used as part of a later research publication you would not be identifiable individually. If you wanted to have a copy of the published results, we would be pleased to send them to you when they became available. Simply let one of the research team know if this is the case.

Who is funding the study?
The study is supported by the University of Southampton, Faculty of Medicine.

Who has reviewed the study?
The protocol for this study has been reviewed by independent experts in anxiety disorders and their treatment and has also been approved by the local research ethics committee.

Contact for Further Information
If you have any further questions about this research, please feel free to speak to one of the facilitators or research team on 02380 718 520, or e-mail Dr Hesham Elnazer, the Principal Investigator for the study, on hye1c13@soton.ac.uk.

Thank you for taking the time to read this information sheet and considering whether to take part in this research. You will be given a copy of this information sheet and a signed consent form to keep if you do take part. Feel free to show it to any health professional involved in your care.

'Wet copy' for participant, one copy for medical notes and one copy for CRF*

C.3 Consent form

UNIVERSITY OF Southampton

Southern Health NHS
NHS Foundation Trust

CONSENT TO RESEARCH FORM (V. 3; 27/04/2016)
Research Ethics Committee number: 16/SC/0038.

Title of project: Sexual functioning in anxiety disorders: influence of neuroinflammatory and endocrine factors
Name of Researcher: Dr Hesham Elnazer *(on behalf of research team)* University Department of Psychiatry, College Keep, 4-12 Terminus Terrace, Southampton SO14 3DT.
Please initial the box that accompanies each statement.

1. I confirm that I have read and understand the patient information sheet Version 5.1 Dated 17/08/2017for the above study. I have had the opportunity to consider the information, ask questions and have had these questions answered satisfactorily. ☐

I understand my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that relevant sections of my medical notes and data collected during the course of the study may be looked at by individuals from the University of Southampton, from the NHS Trust, or from regulatory authorities, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4. I agree to my GP being informed of my participation in this study. In case of incidental or unexpected findings, I give permission for the research team to share information with my GP. ☐

5. I agree to take part in the above study. ☐

_____	_____	_____
Name of patient	Date	Signature
_____	_____	_____
Name of person taking consent	Date	Signature

Appendix C

C.4 Invitation letter for clinicians

Date

Dear Dr

Sexual functioning in patients with anxiety disorders: an investigation of the potential influence of neuroinflammatory and endocrine factors: a research study

This treatment study in patients with anxiety disorders has received approval from a local research ethics committee and Southern Health NHS Foundation Trust (REC reference 16/SC/0038).

I hope it would be possible for you to pass on to potentially suitable patients the provided participant information sheet, the consent form and patient's invitation letter. We request interested patients to contact the research team directly to indicating their preferred method of contact; post, email or telephone. After receiving the relevant details, members of the research team would contact you to discuss potential participation in the study.

The study consists of three phases. First, a baseline interview to confirm the presence of an anxiety disorder. Second, a 6-week prospective treatment phase in which patients who meet the threshold for diagnosis would be offered treatment as usual, and then grouped according to their treatment response. Third, non-responding patients would be offered participation in a treatment phase involving augmentation of current psychotropic drug treatment with the COX-2 inhibitor celecoxib for a period of 6 weeks.

Appendix C

Patients would be excluded from the study if they met any of the following criteria:

- outside the age range 18-70 years;
- unable to provide written, informed consent;
- clinically significant alcohol or substance use in the previous three months;
- physical illness that is unlikely to be stable over the course of the study;
- Pregnant or breast feeding;
- Exclusion criteria for augmentation phase;
    - medical contra-indication for celecoxib;
    - history of hypersensitivity to NSAID;
    - patient with cardiac impairment, thromboembolic disease, renal impairment, hepatic impairment or history of recurrent gastro-intestinal ulceration.

I enclose the study information sheet and would be happy to discuss the rationale and design of the study with you, should you need further information.

Many thanks for reading this letter.

Yours sincerely

David S Baldwin MA DM FRCPsych

Professor of Psychiatry and Head of Mental Health Group
Faculty of Medicine, Clinical and Experimental Sciences Academic Unit
Honorary Consultant Psychiatrist, Mood and Anxiety Disorders Service, Southern Health NHS Foundation Trust

(V4.1; 17/08/2017)

University Department of Psychiatry

Academic Centre, College Keep, 4-12 Terminus Terrace, Southampton, SO14 3DT, United Kingdom

Tel: +44 (0)23 8071 8520 Fax: +44 (0)23 8071 8532 Email: dsb1@soton.ac.uk

Appendix D Psychometric instruments

D.1 Arizona Sexual Dysfunction Scale (ASEX)

Arizona Sexual Experiences Scale (ASEX)

For each item, please indicate your **OVERALL** level during the **PAST WEEK**, including **TODAY**.

1. How strong is your sex drive?

1	2	3	4	5	6
extremely strong	very strong	somewhat strong	somewhat weak	very weak	no sex drive

2. How are you sexually aroused (turned on)?

1	2	3	4	5	6
extremely easily	very easily	somewhat easily	somewhat difficult	very difficult	never aroused

FOR MALE ONLY

3. Can you easily get and keep an erection?

1	2	3	4	5	6
extremely easily	very easily	somewhat easily	somewhat difficult	very difficult	never

FOR FEMALE ONLY

3. How easily does your vagina become moist or wet during sex?

1	2	3	4	5	6
extremely easily	very easily	somewhat easily	somewhat difficult	very difficult	never

If you have had any sexual activity in the past week, please also answer the following two questions. If not, leave questions 4, and 5 blank.

No Sexual activity in past week ..... ☐

4. How easily can you reach an orgasm?

1	2	3	4	5	6
extremely easily	very easily	somewhat easily	somewhat difficult	very difficult	never reach orgasm

5. Are your orgasms satisfying?

1	2	3	4	5	6
extremely satisfying	very satisfying	somewhat satisfying	somewhat unsatisfying	very unsatisfying	can't reach orgasm

COMMENTS:

Appendix D

D.2 Hospital Anxiety and Depression Scale (HADS)

Hospital Anxiety and Depression Scale (HADS)

Tick the box beside the reply that is closest to how you have been feeling in the past week.
Don't take too long over you replies: your immediate is best.

D	A		D	A	
		I feel tense or 'wound up':			**I feel as if I am slowed down:**
	3	Most of the time	3		Nearly all the time
	2	A lot of the time	2		Very often
	1	From time to time, occasionally	1		Sometimes
	0	Not at all	0		Not at all
		I still enjoy the things I used to enjoy:			**I get a sort of frightened feeling like 'butterflies' in the stomach:**
0		Definitely as much		0	Not at all
1		Not quite so much		1	Occasionally
2		Only a little		2	Quite Often
3		Hardly at all		3	Very Often
		I get a sort of frightened feeling as if something awful is about to happen:			**I have lost interest in my appearance:**
	3	Very definitely and quite badly	3		Definitely
	2	Yes, but not too badly	2		I don't take as much care as I should
	1	A little, but it doesn't worry me	1		I may not take quite as much care
	0	Not at all	0		I take just as much care as ever
		I can laugh and see the funny side of things:			**I feel restless as I have to be on the move:**
0		As much as I always could		3	Very much indeed
1		Not quite so much now		2	Quite a lot
2		Definitely not so much now		1	Not very much
3		Not at all		0	Not at all
		Worrying thoughts go through my mind:			**I look forward with enjoyment to things:**
	3	A great deal of the time	0		As much as I ever did
	2	A lot of the time	1		Rather less than I used to
	1	From time to time, but not too often	2		Definitely less than I used to
	0	Only occasionally	3		Hardly at all
		I feel cheerful:			**I get sudden feelings of panic:**
3		Not at all		3	Very often indeed
2		Not often		2	Quite often
1		Sometimes		1	Not very often
0		Most of the time		0	Not at all
		I can sit at ease and feel relaxed:			**I can enjoy a good book or radio or TV program:**
	0	Definitely	0		Often
	1	Usually	1		Sometimes
	2	Not Often	2		Not often
	3	Not at all	3		Very seldom

Please check you have answered all the questions

Scoring:
Total score: Depression (D) _____ Anxiety (A) _____
0-7 = Normal
8-10 = Borderline abnormal (borderline case)
11-21 = Abnormal (case)

Appendix D

D.3 Oxford Questionnaire of Emotional Side Effects of Antidepressants (OQuESA)

This questionnaire asks about your emotional experiences during the past week. There are three sections to this questionnaire - please complete each section.

SECTION 1

Please read each statement carefully. Then, place a tick in the box corresponding to the answer which best describes your experience *during the past week.* Please give an answer for every question. Do not spend too long on each question – your first impressions are probably best.

		Disagree	Disagree a little	Neither agree nor disagree	Agree a little	Agree
1	All my emotions, both 'pleasant' and 'unpleasant', are 'toned down'	☐	☐	☐	☐	☐
2	I don't fully enjoy things that should give me pleasure, such as beautiful places or things or music	☐	☐	☐	☐	☐
3	I care less about other people's feelings than I think I should	☐	☐	☐	☐	☐
4	Because I don't care so much about things, I'm having problems at home	☐	☐	☐	☐	☐
5	Unpleasant emotions, such as sadness, disappointment, and upset, feel toned down or different in some way	☐	☐	☐	☐	☐
6	I don't look forward to things with eager anticipation	☐	☐	☐	☐	☐

7	I don’t have much sympathy for people	☐	☐	☐	☐	☐
8	I feel ‘spaced out’ and distant from the world around me	☐	☐	☐	☐	☐
9	My emotions lack intensity	☐	☐	☐	☐	☐
10	I don’t have the passion and enthusiasm for life that I should	☐	☐	☐	☐	☐
11	Other people being upset doesn’t affect me	☐	☐	☐	☐	☐
12	Because I don’t care so much about things, I’m having problems at work or college	☐	☐	☐	☐	☐

SECTION 2

The following questions ask you to *compare* your experiences *during the past week* to your experiences *before you developed your illness / problem*. Again, read each statement carefully. Then, place a tick in the box corresponding to the answer which best describes your experience. Remember, do not spend too long on each question – your first impressions are probably best.

		Disagree	Disagree a little	Neither agree nor disagree	Agree a little	Agree
1	Day to day life just doesn't have the same emotional impact on me that it did before my illness / problem	☐	☐	☐	☐	☐
2	I don't experience <u>pleasant</u> emotions as much as I did before I developed my illness/problem	☐	☐	☐	☐	☐
3	I don't react to other people's emotions (such as their sadness, anger or upset) as much as I did before my illness / problem	☐	☐	☐	☐	☐
4	I don't care as much about my day to day responsibilities as I did before I developed my illness / problem	☐	☐	☐	☐	☐
5	My emotions are numbed / dulled / flattened compared to before I developed my illness / problem	☐	☐	☐	☐	☐

6	I don't get as much of a 'high' from good things in my life as I did before my illness / problem	☐	☐	☐	☐	☐
7	I don't have as much sympathy for other people as I did before my illness / problem	☐	☐	☐	☐	☐
8	I just don't care about things as much as I did before my illness / problem	☐	☐	☐	☐	☐

SECTION 3

If you are not currently prescribed antidepressants for your illness / problem, please tick this box ☐, and do not answer any more questions.

If you are currently prescribed antidepressants for your illness / problem, please answer the following questions. Remember, the questions refer to your experiences *during only the past week.*

		Disagree	Disagree a little	Neither agree nor disagree	Agree a little	Agree
1	The antidepressant is preventing me from feeling my emotions in some way	☐	☐	☐	☐	☐
2	The antidepressant seems to make me just not care about things that should matter to me	☐	☐	☐	☐	☐
3	The antidepressant seems to make me feel emotionally disconnected from people around me	☐	☐	☐	☐	☐
4	The antidepressant is preventing me from feeling pleasant emotions	☐	☐	☐	☐	☐
5	The antidepressant changes the way that I experience my emotions in a way that is unhelpful (not helpful) to me at the moment	☐	☐	☐	☐	☐
6	I have considered stopping (or have already stopped) my antidepressant because of its emotional side-effects	☐	☐	☐	☐	☐

Appendix D

SCORING

All items are scored as follows:

Disagree = 1 Disagree a little = 2

Neither agree nor disagree = 3 Agree a little = 4

Agree = 5

Four dimensions can then be scored:

GR =	*General reduction in emotions*	= 1:01 + 1:05 + 1:09 + 2:01 + 2:05
RP =	*Reduction in positive emotions*	= 1:02 + 1:06 + 1:10 + 2:02 + 2:06
ED =	*Emotional detachment from others*	= 1:03 + 1:07 + 1:11 + 2:03 + 2:07
NC =	*Not caring*	= 1:04 + 1:08 + 1:12 + 2:04 + 2:08

If required, a further attributional dimension can be scored:

AC = Antidepressant as cause = 3:01 + 3:02 + 3:03 + 3:04 + 3:05 + 3:06 Missing data can be imputed from data that is present.

Total

Total = GR + RP + ED + NC

Subtotals

Validation data suggest that two of the four dimensions (RP & NC) may be closely related to the phenomenon of depression as well as to the phenomenon of antidepressant-associated emotional blunting, whereas the two remaining dimensions (GR & ED) are less closely related to depression. It is therefore recommended that the following two sub-totals are calculated:

RP-NC = RP + NC

GR-ED = GR + ED

D.4 Warwick-Edinburgh Mental Well-Being Scale (WEMWBS)

The Warwick-Edinburgh Mental Well-being Scale (WEMWBS)

Below are some statements about feelings and thoughts.

Please tick the box that best describes your experience of each over the last 2 weeks

STATEMENTS	None of the time	Rarely	Some of the time	Often	All of the time
I've been feeling optimistic about the future	1	2	3	4	5
I've been feeling useful	1	2	3	4	5
I've been feeling relaxed	1	2	3	4	5
I've been feeling interested in other people	1	2	3	4	5
I've had energy to spare	1	2	3	4	5
I've been dealing with problems well	1	2	3	4	5
I've been thinking clearly	1	2	3	4	5
I've been feeling good about myself	1	2	3	4	5
I've been feeling close to other people	1	2	3	4	5
I've been feeling confident	1	2	3	4	5
I've been able to make up my own mind about things	1	2	3	4	5
I've been feeling loved	1	2	3	4	5
I've been interested in new things	1	2	3	4	5
I've been feeling cheerful	1	2	3	4	5

Warwick-Edinburgh Mental Well-Being Scale (WEMWBS)

D.5 Clinical Global Impression (CGI)

Clinical Global Impression Scales

Clinical Global Impression of Severity of Illness

Considering your total clinical experience with this particular population, how ill is this patient at this time?

- ◯ 1. Normal, not at all ill
- ◯ 2. Borderline ill
- ◯ 3. Mildly ill
- ◯ 4. Moderately ill
- ◯ 5. Markedly ill
- ◯ 6. Severely ill
- ◯ 7. Among the most extremely ill patients

Clinical Global Impression of Improvement

Compared to the patient's condition at baseline, how much has the patient changed?

Rate total improvement whether or not, in your judgement, it is due entirely to treatment.

- ◯ 1. Very much improved
- ◯ 2. Much improved
- ◯ 3. Minimally improved
- ◯ 4. No change
- ◯ 5. Minimally worse
- ◯ 6. Much worse
- ◯ 7. Very much worse

Appendix E Ethical approvals

E.1 Research ethics committee approval

Health Research Authority
South Central - Hampshire B Research Ethics Committee
Level 3 Block B
Whitefriars Lewins Mead
Bristol BS1 2NT

Telephone: 0207 104 8052

17 May 2016

Professor David Baldwin University of Southampton
University Department of Psychiatry, College Keep 4-12 Terminus Terrace SO14 3DT

Dear Professor Baldwin

Study title: Sexual functioning in patients with anxiety disorders: an investigation of the potential influence of neuroinflammatory and endocrine factors
REC reference: 16/SC/0038
Protocol number: submission ID-15345
EudraCT number: 2016-000337-48
IRAS project ID: 170365

Thank you for your letter of , responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact the REC Manager, Mrs Siobhan Bawn, nrescommittee.southcentral-hampshireb@nhs.net .
Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Appendix E

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).
Guidance on applying for NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to contest the need for registration they should contact Catherine Blewett (catherineblewett@nhs.net), the HRA does not, however, expect exceptions to be made.
Guidance on where to register is provided within IRAS.

Clinical trial authorisation must be obtained from the Medicines and Healthcare products Regulatory Agency (MHRA).

The sponsor is asked to provide the Committee with a copy of the notice from the MHRA, either confirming clinical trial authorisation or giving grounds for non-acceptance, as soon as this is available.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites listed in the application, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

The Committee has not yet completed any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. We will write to you again as soon as an SSA application(s) has been reviewed. In the meantime no study procedures should be initiated at non-NHS sites.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	Version	Date
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [UoS insurance letter]		
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only)		29 September 2015
GP/consultant information sheets or letters	Referrer information sheet	27 April 2016
GP/consultant information sheets or letters	4	17 May 2016
Letter from sponsor [Sponsorship letter]		
Letters of invitation to participant [Participants invitation letter]	3	17 May 2016
Other [CGI questionnaire]		
Other [ASEX questionnaire]		
Other [HADS questionnaire]		
Other [ODQ questionnaire]		
Other [SAS questionnaire]		
Other [WEMWBS questionnaire]		
Other [Celebrex SmPC]		
Other [Celebrex PIL]		
Other [Response letter to REC]		27 April 2016
Other [Response letter to REC]		17 May 2016
Participant consent form [Consent form]	3	27 April 2016

Appendix E

Participant consent form [CONSENT TO SHARE INFORMATION WITH RESEARCH TEAM] 1 27 April 2016
Participant information sheet (PIS) [Patient's information sheet] 5 17 May 2016

REC Application Form [REC_Form_10022016] 10 February 2016
Referee's report or other scientific critique report
Research protocol or project proposal [Revised Protocol] 4 27 April 2016
Summary CV for Chief Investigator (CI) 27 April 2016
Summary CV for student [H Elnazer CV]

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document “After ethical review – guidance for researchers” gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

Notifying substantial amendments
Adding new sites and investigators
Notification of serious breaches of the protocol
Progress and safety reports
Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at
http://www.hra.nhs.uk/hra-training/

With the Committee's best wishes for the success of this project. Yours sincerely

Professor Ron King Chair

Email: nrescommittee.southcentral-hampshireb@nhs.net

Enclosures: "After ethical review – guidance for researchers"

Copy to: Ms Diana Galpin
Ms Penny Bartlett, Southern Healthcare Foundation NHS Trust

E.2 Health research authority approval

Health Research Authority

Professor David Baldwin University of Southampton
University Department of Psychiatry, College Keep 4-12 Terminus Terrace
SO14 3DT
Email: hra.approval@nhs.net

01 November 2016 Dear Professor Baldwin

Letter of HRA Approval for a study processed through pre-HRA Approval systems

Study title: Sexual functioning in patients with anxiety disorders: an investigation of the potential influence of neuroinflammatory
and endocrine factors
IRAS project ID: 170365
Sponsor University of Southampton

Thank you for your request for HRA Approval to be issued for the above referenced study.

I am pleased to confirm that the study has been given HRA Approval. This has been issued on the basis that the study is compliant with the UK wide standards for research in the NHS.

The extension of HRA Approval to this study on this basis allows the sponsor and participating NHS organisations in England to set-up the study in accordance with HRA Approval processes, with decisions on study set-up being taken on the basis of capacity and capability alone.

If you have submitted an amendment to the HRA between 23 March 2016 and the date of this letter, this letter incorporates the HRA Approval for that amendment, which may be implemented in accordance with the amendment categorisation email (e.g. not prior to REC Favourable Opinion, MHRA Clinical Trial Authorisation etc., as applicable). If the submitted amendment included the addition of a new NHS organisation in England, the addition of the new NHS organisation is also approved and should be set up in accordance with HRA Approval processes (e.g. the organisation should be invited to assess and arrange its capacity and capability to deliver the study and confirm once it is ready to do so).

Participation of NHS Organisations in England

Appendix E

Please note that full information to enable set up of participating NHS organisations in England is not provided in this letter, on the basis that activities to set up these NHS organisations is likely to be underway already.

The sponsor should provide a copy of this letter, together with the local document package and a list of the documents provided, to participating NHS organisations in England that are being set up in accordance with HRA Approval Processes. It is for the sponsor to ensure that any documents provided to participating organisations are the current, approved documents.

For non-commercial studies the local document package should include an appropriate Statement of Activities and HRA Schedule of Events. The sponsor should also provide the template agreement to be used in the study, where the sponsor is using an agreement in addition to the Statement of Activities. Participating NHS organisations in England should be aware that the Statement of Activities and HRA Schedule of Events for this study have not been assessed and validated by the HRA. Any changes that are appropriate to the content of the Statement of Activities and HRA Schedule of Events should be agreed in a pragmatic fashion as part of the process of assessing, arranging and confirming capacity and capability to deliver the study. If subsequent NHS organisations in England are added, an amendment should be submitted to the HRA..

It is critical that you involve both the research management function (e.g. R&D office and, if the study is on the NIHR portfolio, the LCRN) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details and further information about working with the research management function for each organisation can be accessed from www.hra.nhs.uk/hra-approval.

After HRA Approval
In addition to the document, “After Ethical Review – guidance for sponsors and investigators”, issued with your REC Favourable Opinion, please note the following:
HRA Approval applies for the duration of your REC favourable opinion, unless otherwise notified in writing by the HRA.
Substantial amendments should be submitted directly to the Research Ethics Committee, as detailed in the After Ethical Review document. Non-substantial amendments should be submitted for review by the HRA using the form provided on the HRA website, and emailed to hra.amendments@nhs.net.
The HRA will categorise amendments (substantial and non-substantial) and issue confirmation of continued HRA Approval. Further details can be found on the HRA website.

Scope
HRA Approval provides an approval for research involving patients or staff in NHS organisations in England.

If your study involves NHS organisations in other countries in the UK, please contact the relevant national coordinating functions for support and advice. Further information can be found at http://www.hra.nhs.uk/resources/applying-for-reviews/nhs-hsc-rd-review/.

If there are participating non-NHS organisations, local agreement should be obtained in accordance with the procedures of the local participating non-NHS organisation.

User Feedback
The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please email the HRA at hra.approval@nhs.net. Additionally, one of our staff would be happy to call and discuss your experience of HRA Approval.

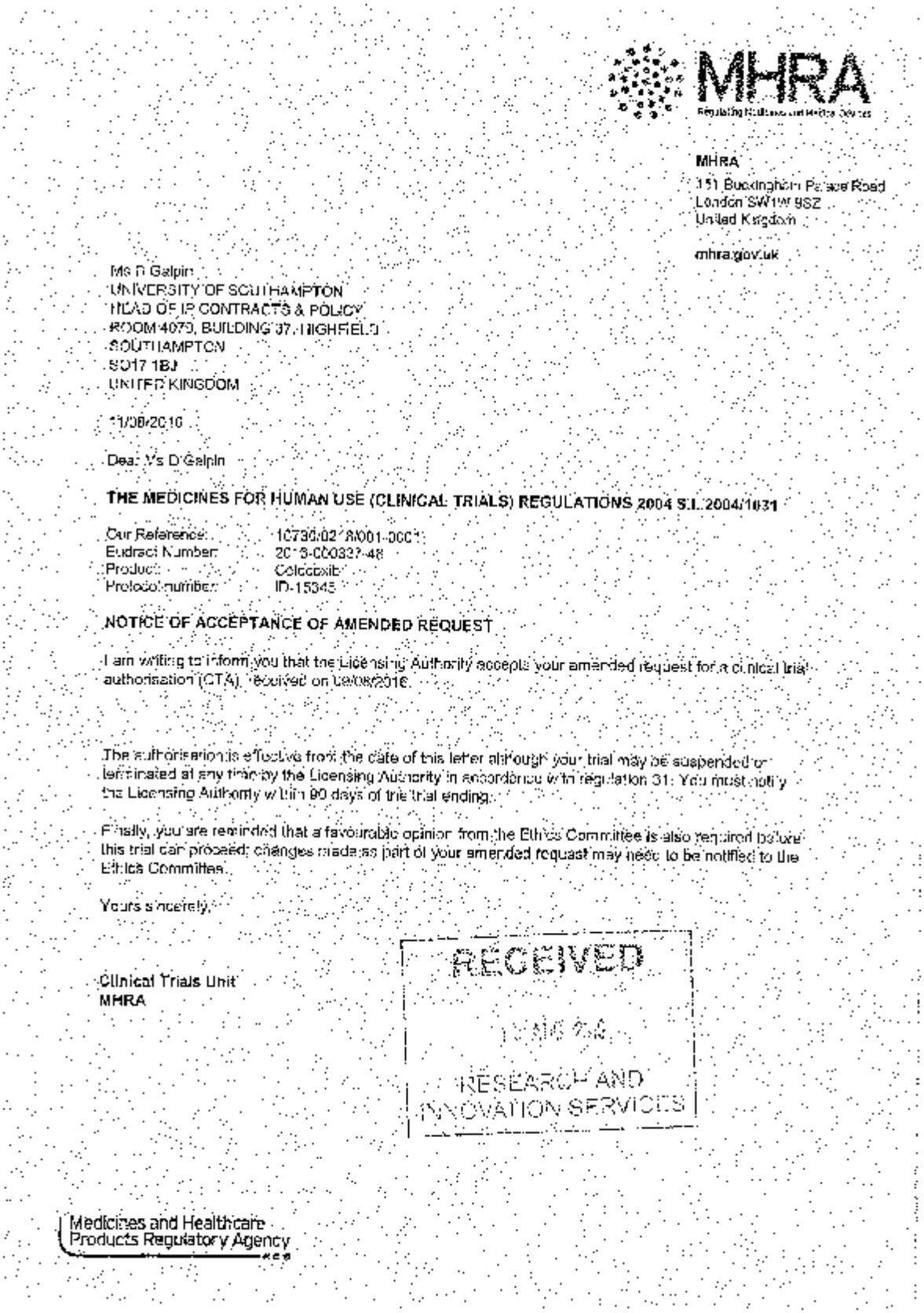
HRA Training
We are pleased to welcome researchers and research management staff at our training days – see details at http://www.hra.nhs.uk/hra-training/.

If you have any queries about the issue of this letter please, in the first instance, see the further information provided in the question and answer document on the HRA website.

Your IRAS project ID is 170365. Please quote this on all correspondence. Yours sincerely
Isobel Lyle Senior Assessor
Tel 0207 9722496
Email: hra.approval@nhs.net or Isobel.lyle@nhs.net

Copy to: Ms Diana Galpin, Sponsor contact, Southampton University rgoinfo@soton.ac.uk
Ms Penny Bartlett, R&D, Southern Healthcare Foundation NHS Trust,
Penny.bartlett@southernhealth.nhs.uk

E.3 Medicines and healthcare products regulatory agency approval



MHRA

Regulating Medicines and Medical Devices

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Ms D Galpin
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11/08/2016

Dear Ms D Galpin

THE MEDICINES FOR HUMAN USE (CLINICAL TRIALS) REGULATIONS 2004 S.I. 2004/1031

Our Reference: 10736/02/A001-0001
Eudract Number: 2016-000327-48
Product: Celecoxib
Protocol number: ID-15345

NOTICE OF ACCEPTANCE OF AMENDED REQUEST

I am writing to inform you that the Licensing Authority accepts your amended request for a clinical trial authorisation (CTA), received on 08/08/2016.

The authorisation is effective from the date of this letter although your trial may be suspended or terminated at any time by the Licensing Authority in accordance with regulation 31. You must notify the Licensing Authority within 90 days of the trial ending.

Finally, you are reminded that a favourable opinion from the Ethics Committee is also required before this trial can proceed; changes made as part of your amended request may need to be notified to the Ethics Committee.

Yours sincerely,

Clinical Trials Unit
MHRA

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Medicines and Healthcare Products Regulatory Agency

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