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A DOUBLE BLIND PLACEBO CONTROLLED STUDY OF GRANISETRON IN ANTIDEPRESSANT INDUCED SEXUAL DYSFUNCTION

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine in the branch of Psychiatry

Melbourne, 2005

DECLARATION

I, Sean Melville Ording-Jespersen, declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in the branch of Psychiatry at the University of the Witwatersrand, Johannesburg.

It has not been submitted before for any degree or examination at this or any other University.

Signed _____

on this _____ day of _____ 2005.

PUBLICATIONS AND PRESENTATIONS

1. **An original article published in International Clinical Psychopharmacology:**
   Jespersen S, Berk M, Van Wyk C, Dean O, Dodd S, Szabo C, Maud C. A pilot randomised, double-blind, placebo-controlled study of granisetron in the treatment of sexual dysfunction in women associated with antidepressant use. Int Clin Psychopharmacol 2004; 19: 161-164.

2. **A poster presented at the XXIVth Collegium Internationale Neuro-psychopharmacologicum Congress, Paris, France, 20-24 June 2004:**
   Jespersen S, Berk M, Van Wyk C, Dean O, Dodd S, Szabo C, Maud C. A pilot randomised, double-blind, placebo-controlled study of granisetron in the treatment of sexual dysfunction in women associated with antidepressant use [abstract]. Int J Neuropsychopharmacol 2004; 7 (Suppl 1): S342-S343.

3. **A poster presented at the South African Society of Psychiatrists 13th National Conference, Champagne Sports Resort, South Africa, 20-23 September 2004:**
   Szabo CP, Jespersen S, Berk M, Van Wyk C, Dean O, Dodd S, Maud C. A pilot randomised, double-blind, placebo-controlled study of granisetron in the treatment of sexual dysfunction in women associated with antidepressant use.

ABSTRACT

Sexual dysfunction is a common side effect of treatment with antidepressants, particularly those with a serotonergic action. The problem has significant implications for a patient's quality of life and their compliance with medication. Given the often long-term nature of depressive disorders and their treatment this side effect poses a potential management challenge and may have serious prognostic implications.

There are currently few evidence-based treatment strategies for the management of antidepressant induced sexual dysfunction. This study was conducted to evaluate the usefulness of granisetron, a serotonin type-3 receptor antagonist, in the treatment of women experiencing sexual dysfunction due to serotonergic antidepressants.

Twelve women with antidepressant induced sexual dysfunction were assigned to receive either granisetron (N=5) or placebo (N=7) in a 14-day randomised, double blind, placebo controlled drug trial. Two subjects in the granisetron group did not complete the study. Each subject's sexual functioning was assessed at baseline, day 7 and day 14 using both the Arizona Sexual Experience Scale and the Feiger Sexual Function and Satisfaction Questionnaire.

No statistical differences were measured either at baseline or at endpoint between the granisetron and placebo groups. The study did not produce evidence supporting the usefulness of granisetron as an adjunctive medication in women with antidepressant induced sexual dysfunction. Furthermore, this finding does not suggest a primary role for the serotonin type-3 receptor in the pathogenesis of this side effect.

ACKNOWLEDGEMENTS

Firstly, thanks must go to Prof. Christopher P. Szabo and Prof. Michael Berk. Without their supervision and patience this project would in all likelihood never have been completed.

In South Africa, Dr Catherine Maud and Dr Caren Van Wyk, should be thanked for their assistance with the recruitment of subjects. The Department of Psychiatry at the University of the Witwatersrand supported this study from it inception and without that support and the granisetron samples supplied by GlaxoSmithKline an investigator-initiated project such as this would not have been possible.

In Australia, Ms Olivia Dean's assistance with the data analysis and Dr Seetal Dodd's help preparing the poster and the paper for publication are much appreciated. Prof. John Tiller's encouragement and guidance have been invaluable.

Finally, thanks go to the participants who gave generously of their time and effort to take part in the study.

TABLE OF CONTENTS

		Page
DECLARATION		ii
PUBLICATIONS AND PRESENTATIONS		iii
ABSTRACT		iv
ACKNOWLEDGEMENTS		v
TABLE OF CONTENTS		vi
LIST OF FIGURES		ix
LIST OF TABLES		x
NOMENCLATURE		xi
PREFACE		xii
1.0	**INTRODUCTION**	1
1.1	**Normal sexual function**	1
1.1.1	The human sexual response cycle	2
1.1.1.1	The desire phase	3
1.1.1.2	The arousal phase	3
1.1.1.3	The orgasm phase	4
1.1.1.4	The resolution phase	4
1.1.2	The neurobiology of sexual function	5
1.1.2.1	The desire phase	6
1.1.2.2	The arousal phase	7
1.1.2.3	The orgasm phase	9
1.1.2.4	The role of the serotonin type-3 receptor	12
1.1.3	Psychosocial aspects of sexuality	13
1.2	**Sexual dysfunction**	17
1.2.1	Epidemiology	17
1.2.2	Classification and clinical presentation	19
1.2.2.1	Sexual desire disorders	19
1.2.2.2	Sexual arousal disorders	20
1.2.2.3	Orgasmic disorders	21
1.2.2.4	Sexual pain disorders	22
1.2.2.5	Sexual dysfunction due to a general medical condition	22
1.2.2.6	Substance-induced sexual dysfunction	22
1.2.2.7	Sexual dysfunctions not otherwise specified	24
1.2.3	Aetiology	24
1.2.4	Management	25
1.3	**Sexual dysfunction and depression**	26
1.3.1	Epidemiology	26
1.3.2	Classification and clinical presentation	27
1.3.3	Aetiology	27
1.3.4	Management	29

1.4 Sexual dysfunction and antidepressants 30
1.4.1 Epidemiology 30
1.4.2 Clinical presentation and aetiology 31
1.4.2.1 Tricyclic antidepressants 33
1.4.2.2 Monoamine oxidase inhibitors 33
1.4.2.3 Selective serotonin re-uptake inhibitors 34
1.4.2.4 Other antidepressants 36
1.5 Management of antidepressant induced sexual dysfunction 37
1.5.1 Detection, screening and assessment 38
1.5.2 Management strategies 41
1.5.2.1 Conservative, non-pharmacological strategies 41
1.5.2.2 Changing the antidepressant 42
1.5.2.3 Adjunctive strategies 43
1.6 Granisetron 48
1.7 Hypothesis and overall aims 49

2.0 MATERIALS AND METHODS 51
2.1 Overview of the research design 51
2.2 Study group 51
2.2.1 Inclusion criteria 51
2.2.2 Exclusion criteria 52
2.3 Instruments and measurements 52
2.3.1 Mini-International Neuropsychiatric Interview 52
2.3.2 Clinical Global Impression Scale 53
2.3.3 Arizona Sexual Experience Scale 54
2.3.4 Feiger Sexual Function and Satisfaction Questionnaire 54
2.4 The study procedure 55
2.4.1 Screening assessment 55
2.4.2 Visit 1 55
2.4.3 Visits 2 and 3 57
2.5 Statistical analysis 57
2.6 Ethical aspects 58
2.7 Financial aspects 58

3.0 RESULTS 60
3.1 Recruitment and randomisation 60
3.2 Demographic and clinical variables 60
3.3 Mini-International Neuropsychiatric Interview 62
3.4 Clinical Global Impression Scale 62
3.5 Rating scales of sexual dysfunction 63
3.5.1 Arizona Sexual Experience Scale 63
3.5.2 Feiger Sexual Function and Satisfaction Questionnaire 66
3.6 Discontinuations and adverse events 68

4.0 DISCUSSION AND CONCLUSIONS 69
4.1 Introduction and summary 69
4.2 Interpretation and relevance of findings 70
4.2.1 Recruitment and randomisation 70
4.2.2 Demographic and clinical variables 70
4.2.3 Rating scales of sexual dysfunction 74
4.2.4 Discontinuations and adverse events 75
4.3 Strengths and limitations 76
4.4 Conclusions and recommendations 77

APPENDIX A Information and Consent Form 79
APPENDIX B Initial Assessment Form 80
APPENDIX C Clinical Global Impression Scale 82
APPENDIX D Arizona Sexual Experience Scale 83
APPENDIX E Feiger Sexual Function and Satisfaction Questionnaire 84

REFERENCES 85

LIST OF FIGURES

Figure		Page
1.1	Central influences on sexual function	10
1.2	Peripheral influences on sexual function	11
1.3	Potential causes of sexual dysfunction during antidepressant treatment	32
1.4	Treatment of antidepressant induced sexual dysfunction	47
2.1	Schedule of visits as included in each clinical research file	56
3.1	Total scores for the Arizona Sexual Experience Scale	64
3.2	Individual items and total change in score at endpoint for the Arizona Sexual Experience Scale	65
3.3	Total scores for the Feiger Sexual Function and Satisfaction Questionnaire	66
3.4	Individual items and total change in score at endpoint for the Feiger Sexual Function and Satisfaction Questionnaire	68

LIST OF TABLES

Table		Page
1.1	Diagnostic criteria for substance-induced sexual disorders	23
1.2	Assessment of antidepressant induced sexual dysfunction	40
3.1	Descriptive statistics for the Arizona Sexual Experience Scale	65
3.2	Descriptive statistics for the Feiger Sexual Function and Satisfaction Questionnaire	67

NOMENCLATURE

AISD	Antidepressant induced sexual dysfunction
CGI	Clinical Global Impression
DHEA	Dehydroepiandrosterone
DHEAS	Dehydroepiandrosterone sulphate
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4^{th} Edition
GABA	γ-aminobutyric acid
GAF	Global Assessment of Functioning
HPG	Hypothalamic-pituitary-gonadal
ICD-10	International Classification of Diseases and Related Health Problems, 10^{th} Edition
mg	milligrams
MINI	Mini-International Neuropsychiatric Interview
SSRI	Selective serotonin re-uptake inhibitor
$5HT_1$	Serotonin type-1
$5HT_{1A}$	Serotonin type-1A
$5HT_{1B}$	Serotonin type-1B
$5HT_2$	Serotonin type-2
$5HT_{2C}$	Serotonin type-2C
$5HT_3$	Serotonin type-3

PREFACE

The problem of antidepressant induced sexual dysfunction cannot be ignored. It is a commonly encountered problem in clinical practice, particularly amongst patients being treated with serotonergic antidepressants. Practical options for the management of the condition are limited and current evidenced based treatment recommendations are largely unsatisfactory.

At the time that this project was conceived increased stimulation of serotonin type-2 and serotonin type-3 receptors was thought to be a likely mechanism underlying antidepressant induced sexual dysfunction. Furthermore, several anecdotal case reports and an open label study had suggested that granisetron, a serotonin type-3 receptor antagonist, might be useful as a treatment strategy for this condition.

It was therefore natural to further investigate the usefulness of granisetron in more robust experimental conditions. It was hoped that the outcome of this study would both validate a viable management option and clarify the mechanism underlying antidepressant induced sexual dysfunction.

1.0 INTRODUCTION

1.1 Normal sexual function

At first glance human sexuality would appear to be amongst the most simple and natural aspects of human behaviour. However, when the subject is considered a little more carefully it becomes clear that even something as primal as the act of sexual intercourse involves a complex interplay of biological and psychological factors. Furthermore, this interplay takes place against a rich backdrop of environmental influences, cultural meanings and societal norms. In spite of the complexity of human sexual behaviour it has really only been during the last fifty years that many of the taboos previously shrouding this subject in mystery have been cast aside and a more scientific approach applied.

The multiple factors that impact on sexual behaviour are diverse and their interaction is indeed complicated. The nature of a person's interpersonal relationships, current life circumstances and stresses, gender identity and sexual orientation, self-esteem, emotions and personality structure, cognitive processes, developmental experiences across the life-cycle and the process of ageing itself are a few examples (1). Other important influences include physical appearance, genetic factors, physical health, the presence of psychiatric illness and the use of prescribed medications and drugs of abuse (1). It is important to note that normal sexual behaviour may take place in relationships of varying levels of commitment, in heterosexual and homosexual relationships as well as in the context of self-stimulation. These among many factors should be considered when taking a thorough sexual history from a patient. It is, however, beyond the scope of this report to discuss them in detail.

When the subject of normal sexual function is reduced to its most basic principles, the ability of a human being to successfully complete the act of sexual intercourse actually depends on four main factors (2). Firstly, the functional integrity of those parts of the nervous system which control the sexual response cycle must be intact. Secondly, anatomically normal genital organs are necessary. Thirdly, there must be appropriate hormonal stimulation of the genitalia. Fourthly, a psychological environment that is conducive to a sexual response must be present.

The first part of this chapter will therefore outline the normal human sexual response cycle and current understanding of its biological underpinnings. It will also briefly discuss some of the psychosocial factors that are relevant to an understanding of modern sexual behaviour. The basic facts of physiology, psychology and social anthropology as they relate to sexual functioning are an essential foundation of any discussion of sexual dysfunction. It should be noted that he separation of the biological from the psychosocial is in no way intended to imply that human sexuality can be understood as anything but a complex amalgam of both.

Furthermore, sexual dysfunction of any particular cause must always be discussed in the context of what constitutes normal or abnormal sexual function in the general population. For example, male libido reaches its peak at the end of adolescence and then progressively declines (3), whereas women typically reach their peak libido in the fourth decade (4). With advancing age there is a gradual decline in interest in sex and sexual activity. The frequency of intercourse and masturbation tends to decrease and there is an increased incidence of erection and lubrication difficulties. As men grow older premature ejaculation becomes less likely and delayed or absent ejaculation is a more common complaint. Older women are also increasingly likely to experience difficulties with orgasm. However, it is important to stress that sex continues to pay an important part in the lives of men and women at least until their mid-seventies with little if any decline in enjoyment and satisfaction.

1.1.1 The human sexual response cycle

Masters and Johnson (5) divided the sexual response cycle into four phases: excitement, plateau, orgasm and resolution. The Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) (6) also defines a four-phase sexual response cycle based on the motivational psycho-physiological model of Masters and Johnson. As the DSM-IV classification of sexual dysfunction corresponds with the normal phases of the sexual response cycle some discussion of them is warranted.

The first phase is desire, the second is excitement, the third is orgasm and the fourth is resolution. Both men and women pass through the same phases of the sexual response cycle in the same order. Considerable similarity exists between the genders, but there

are also certain differences between them in terms of their patterns of arousal and the physiological responses that occur during the completion of normal sexual intercourse. The male and female sexual response cycles are not discussed separately here although a number of the more important differences are highlighted.

1.1.1.1 The desire phase

This phase refers to the urge people have to engage in sexual activity. It is usually internal thoughts, feelings and fantasies that give rise to the physical signs of arousal, but it is possible that sexual arousal can precede desire. It seems that desire is controlled to some extent by androgens, including testosterone, in both sexes, but environmental and psychological factors are also important. In other words, desire is influenced by a willingness to engage in sex and also by a biological drive. It is true to say that individuals differ widely from one another in the level of their desire, and that it is entirely normal for an individual to experience fluctuations in their interest in sex.

1.1.1.2 The arousal phase

During this phase the physical signs of sexual excitement develop. The level of physical arousal usually escalates quite quickly. Respiratory rate, heart rate, blood pressure and general muscle tension increase in both sexes. The engorgement of blood vessels in the genital area produces swelling of the clitoris and labia and vaginal lubrication in the female. The uterus also becomes engorged and elevated giving the vagina greater length and width. In the male this engorgement is manifest as penile erection, scrotal contraction and testicular swelling. It is normal for the level of excitement to fluctuate during the arousal phase. It may also fluctuate from one occasion to the next and vary from one individual to another.

Physiological arousal continues to build, but it reaches a plateau and does so at a slower pace. In women, further vascular engorgement produces tightening of the vaginal entrance and a deepening in the colour of the genital area. Other physical signs continue to develop and the clitoris withdraws under the clitoral hood. In men, there is a further increase in the size of the penis, which deepens in colour and may secrete a small amount of pre-ejaculate. When foreplay is prolonged it is normal for

arousal to fluctuate in both sexes while it is at the plateau. This fluctuation is more noticeable in men as erections may clearly increase and decrease in intensity. In woman this is experienced as a change in vaginal lubrication.

1.1.1.3 The orgasm phase

Orgasm occurs when sexual arousal reaches a peak of intensity. This results in a series of involuntary rhythmic muscular contractions throughout the pelvic region occurring 0.8 seconds apart. The female may experience anywhere between two and fifteen contractions, which is generally longer than a male orgasm. The female orgasm may last for a few seconds or if stimulation continues then further orgasms may be experienced immediately. The quality and intensity of the female orgasm may vary according to a variety of factors, including the psychological environment and how the orgasm was achieved.

Two separate stages can be identified during the male orgasm. First, emission during which the contraction of the vas deferens, seminal vesicles and ejaculating ducts places semen at the entrance of the urethra. Second, ejaculation, during which the contraction of the penile urethra and surrounding musculature expel seminal fluid under pressure. After the initial three or four contractions they become weak and irregular.

Respiratory rate, heart rate and blood pressure increase sharply in both sexes during this extremely pleasant spasmodic response. The subjective experience of an orgasm appears to be very similar for men and woman, but differences do exist. Women may experience multiple orgasms, but they are also more likely to engage in intercourse without experiencing an orgasm at all.

1.1.1.4 The resolution phase

During the resolution phase the physiological changes produced by sexual arousal subside. If orgasm has not occurred the reduction in sexual tension may be relatively slow or even experienced as unpleasant. The resolution phase is significantly longer for males than females. After an orgasm, males experience a refractory period during

which they are largely unresponsive to further stimulation. The length of the refractory period varies from a few minutes to a few hours and increases with age.

Two important issues emerge from this account of the sexual response cycle. Firstly, although there are obvious anatomical and subtle physiological differences between men and woman, there is also much that is common in their sexual responses. Secondly, and more importantly with regard to the assessment of sexual dysfunction, a certain amount of fluctuation is normal within a single cycle, from cycle to cycle and from individual to individual. A temporary reduction in desire or the intensity of an orgasm is not necessarily pathological.

1.1.2 The neurobiology of sexual function

The mechanisms underlying the physical manifestations of the human sexual response cycle involve a combination of neurological, psychological, vascular and hormonal factors that are co-ordinated by the hypothalamus, the limbic system and various centres in the cerebral cortex (7). It is generally accepted that sexual function is influenced by a variety of neurotransmitters although the exact nature of their interaction still awaits clarification. Both dopamine and serotonin certainly play an important role. There is also evidence that noradrenaline, acetylcholine and γ-aminobutyric acid (GABA) are involved as well. Although the role of a variety of other chemicals remains to be clarified research has also implicated oxytocin, arginine-vasopressin, angiotensin II, growth hormone releasing hormone, substance P, neuropeptide Y and cholecystokinin-8 (8). The interaction of the endocrine system via the steroid sex hormones and the neurological system including both its central and peripheral components underlies the normal human sexual response.

Centrally, it appears that dopamine and serotonin via the hypothalamus and its associated limbic structures modulate testosterone function, at least in part. Significantly, decreased levels of bio-available testosterone may result in symptoms such as a diminished sense of well being or a low mood, persistent unexplained fatigue and changes to sexual function that include decreased libido, reduced sexual receptivity and diminished sexual pleasure (9).

Peripherally, effects on sexual functioning appear to be even more complicated. Oestrogen, testosterone and progestin released by the ovaries or adrenal glands maintain genital structure and function (10). They also influence the availability and function of each other. For example, increasing levels of oestrogen may lead to an increase of sex hormone binding globulin. This binds to testosterone reducing the amount of free testosterone that is available. Furthermore, progestin has anti-oestrogen effects. Oestrogen also influences nerve transmission and sensory thresholds at a peripheral level (11).

The exact relationship between neurological and endocrine processes and neurotransmitter or receptor activity is not properly understood. However, the following overview is an attempt to summarise current knowledge regarding these central and peripheral processes with reference to the phases of the sexual response cycle that are particularly relevant to this report: desire, excitement and orgasm. An attempt will also be made to clarify current thinking on the relative roles of the serotonin type-2 ($5HT_2$) and type-3 ($5HT_3$) receptors.

1.1.2.1 The desire phase

The central nervous system is clearly involved in this phase of the sexual response cycle. Dopamine is thought to have central effects on sexual functioning and to enhance sexual desire. The mesolimbic system is associated with the development of interest in sexual activity and dopamine appears to be required in this area for the maintenance of sexual interest (12). The inhibition of dopamine release may impair libido and erection (13). Experimentally, potent selective antagonism of serotonin re-uptake appears to reduce dopamine activity in the mesolimbic system. This effect is probably mediated by $5HT_2$ receptors (12). In animal models, when serotonin type-1A ($5HT_{1A}$) receptors are stimulated using agonists such as buspirone, sexual activity seems to be facilitated. The $5HT_{1A}$ receptor, coupled to other serotonin receptors, may well play a significant role in alterations in sexual interest (14).

Good evidence exists that the steroid sex hormones play an important role in the development of sexual desire. Oestrogen and the development of desire seem to be linked in women and progesterone may possibly mediate a female's receptivity to the

approaches of her partner (15). Testosterone appears to be the most important sex steroid, but attempts to relate circulating levels of testosterone to sexual desire have been inconsistent (16). The relationship between testosterone, dopamine and serotonin, and the hypothalamus and associated limbic structures is fairly well described in males. However, the interaction is somewhat less conclusive in females. This may be a reflection of the impact of psychosocial factors on sexual desire (17). Oxytocin seems to be related to changes across the menstrual cycle and it possibly has a role in enhancing sexual receptivity (18). There is convincing evidence that increased prolactin causes sexual dysfunction as it depresses sexual activity in the desire, arousal and orgasm phase of the sexual response cycle. Furthermore, elevated plasma prolactin reduces testosterone levels (19).

There has been some speculation that pheromones play a role in the sphere of human desire and attraction. A pheromone is a chemical substance that is secreted by one animal to influence the behaviour of another animal. These chemicals are most commonly detected by the animal's sense of smell and are thought to influence both sexual and other behaviours. The role of pheromones as mediators of human sexual desire is controversial. Some evidence exists to suggest that pheromones may be responsible for the synchronisation of menstrual cycles and ovulation that occurs between women when they live together (20). However, although the role of pheromones has been demonstrated in animal models, there is no convincing evidence that they exert any effect on sexual desire in humans or the higher primates (21).

1.1.2.2 The arousal phase

Both the central and peripheral nervous systems mediate sexual excitement. This phase of the sexual response cycle is mediated in the mesolimbic system at least partially by dopamine. Dopamine appears to enhance a person's subjective sense of excitement (12). Sexual arousal is likely to be related to general reward and pleasure seeking activity, and it certainly seems that dopamine also enhances a person's wish to continue sexual activity once sexual stimulation has been initiated. Inhibition of dopamine release may impair libido and erection (13). These dopaminergic effects can be inhibited by potent selective serotonin re-uptake antagonism (14). Although serotoninergic stimulation appears to generally inhibit sexual function it is thought to

predominantly affect sexual desire, ejaculation and orgasm (7). There is convincing evidence that noradrenaline is involved centrally in the arousal phase (22). Increased serotonergic neurotransmission in the central nervous system can diminish both the effects of dopamine (23) and noradrenaline on sexual functioning (24).

Peripherally, sympathetic and parasympathetic activity mediates the spinal reflexes associated with erection and clitoral engorgement. The parasympathetic nervous system promotes penile and clitoral erection, whereas sympathetic activity mainly moderates arousal (25). This process is mediated in turn by serotonin and several other neurotransmitters that impact on sympathetic and parasympathetic tone (12). Potent selective serotonin re-uptake antagonism may result in inhibition of these important peripheral spinal reflexes (14, 22). It is worth noting the role of acetylcholine as a neurotransmitter in spinal nerves. Cholinergic nerves innervate vascular smooth muscle in the vagina and may be associated with vaginal engorgement during sexual arousal (26). Although its role in sexual intercourse is not clear noradrenergic activity seems to have a close relationship to the onset and maintenance of copulatory behaviour in rats (27). In peripheral tissues serotonin appears to play a role in the initiation of sexual arousal by way of its effects on vascular tone and blood flow. However, serotonin may also interfere with arousal via its effects on sensation, the reduction of adrenergic effects and the inhibition of nitric oxide synthase (28).

Nitric oxide has been implicated in the modulation of sexual arousal at a peripheral level because it mediates the vascular changes required for pelvic engorgement and erection (29). This is demonstrated by sildenafil, a potent phosphodiesterase inhibitor, which augments nitric oxide resulting in smooth muscle relaxation and the flow of blood to the genitalia. Vascular congestion of the clitoris seems to be positively mediated by nitric oxide (30) and vasoactive intestinal polypeptide (31) once sexual stimulation begins. Vasoactive intestinal polypeptide may mediate autonomic effects on pelvic blood flow during arousal (32).

In the central nervous system serotonin acts as a neurotransmitter but in the peripheral system it has vasoconstrictor and vasodilator effects that impact on sexual arousal (28). The presence of adequate levels of oestrogen (33) and testosterone appears to be

required in order for nitric oxide to initiate the vascular congestion that occurs with sexual stimulation (34). Certainly, testosterone seems to be involved in the initiation of sexual activity. In women oestrogen appears to be particularly important in the arousal phase. The declining oestrogen levels associated with menopause may lead to vaginal atrophy and subsequently difficulty with vascular congestion and vaginal lubrication. Prolactin also influences the sexual arousal phase with increasing levels of prolactin having a negative effect on arousal and the subsequent phases of sexual functioning (35).

Given adequate sex steroids, including testosterone in men and oestrogen in females, the potential physiological mechanisms mediating sexual arousal include central dopamine stimulation, the modulation of cholinergic-noradrenergic balance, peripheral α_1-adrenergic receptor agonism and the presence of nitric oxide (35).

1.1.2.3 The orgasm phase

The central nervous system is likely to have some impact on this phase of the sexual response cycle. Dopamine appears to enhance sexual function generally, and this effect is in all likelihood modulated centrally by serotonin. However, orgasm and ejaculation appear to be primarily mediated at the spinal level. The parasympathetic nervous system mediates orgasm and ejaculation, whereas the sympathetic nervous system has a moderating influence on this phase (25).

Sympathetic and parasympathetic tone is important in mediating orgasm and ejaculation. This is at least partly dependent upon the activity of noradrenaline and dopamine that are modulated by serotonin at $5HT_2$ receptors (14, 36). Potent selective serotonin re-uptake inhibition is thought to result in a $5HT_2$ receptor mediated decrease in noradrenaline and dopamine activity required for orgasm and ejaculation. Inhibition of orgasm may occur with serotonergic activation and this is likely to be due to $5HT_2$ receptor stimulation (37) with α-adrenergic receptor antagonism (22). Antagonism of peripheral α-adrenergic and cholinergic receptors in the genitourinary tract impairs sexual function (38). Drugs with potent antagonism of cholinergic and α_1-adrenergic receptors can interfere significantly with the sexual response cycle (39).

Increased serotonergic neurotransmission is associated with a subjective sense of diminished sensation in the genital area (36). Nociceptive sensation is partially modulated by serotonin and this may partially explain the difficulties with orgasm that are associated with diminished sexual sensation. However, it is not clear that the sensations of pain and pleasure involve similar pathways.

In peripheral tissues serotonin may potentially play a role in orgasm by facilitating uterine contractions. It may also, however, interfere with orgasm by stimulation of $5HT_2$ receptors (37). The current understanding of this mechanism is rudimentary, but it may well be related to oxytocin (40). Oxytocin is associated with pelvic contractions and increased systolic blood pressure at the time of orgasm.

The complex neurobiological interactions that influence sexual function are still poorly understood and any attempt to represent them schematically is likely to be an oversimplification. However, the central influences on sexual function are illustrated in Figure 1.1 (35) and the peripheral influences in Figure 1.2 (35).

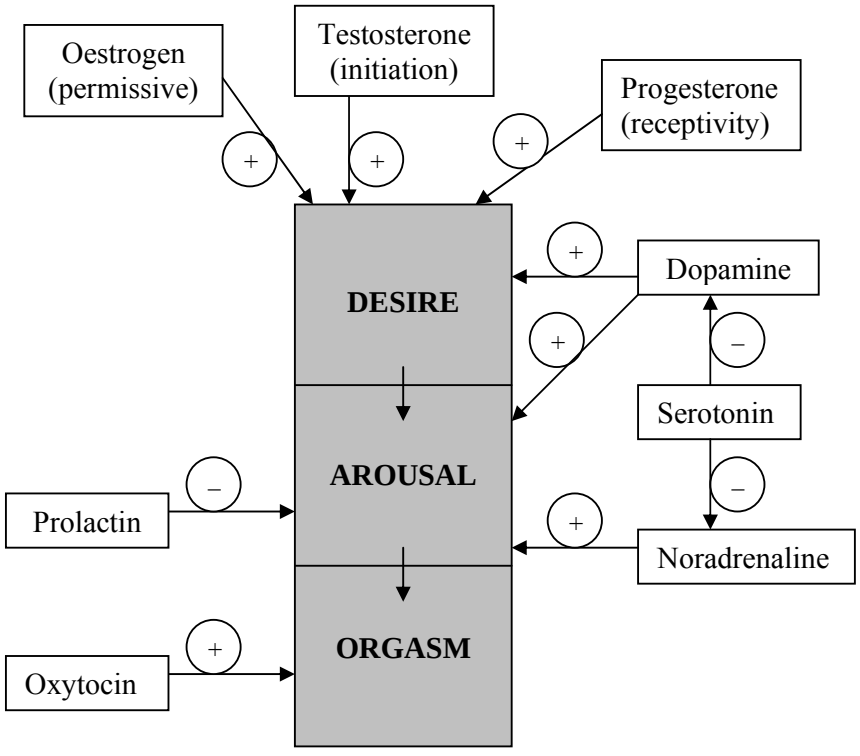


Figure 1.1 Central influences on sexual function (+ indicates a positive effect, – indicates a negative effect)

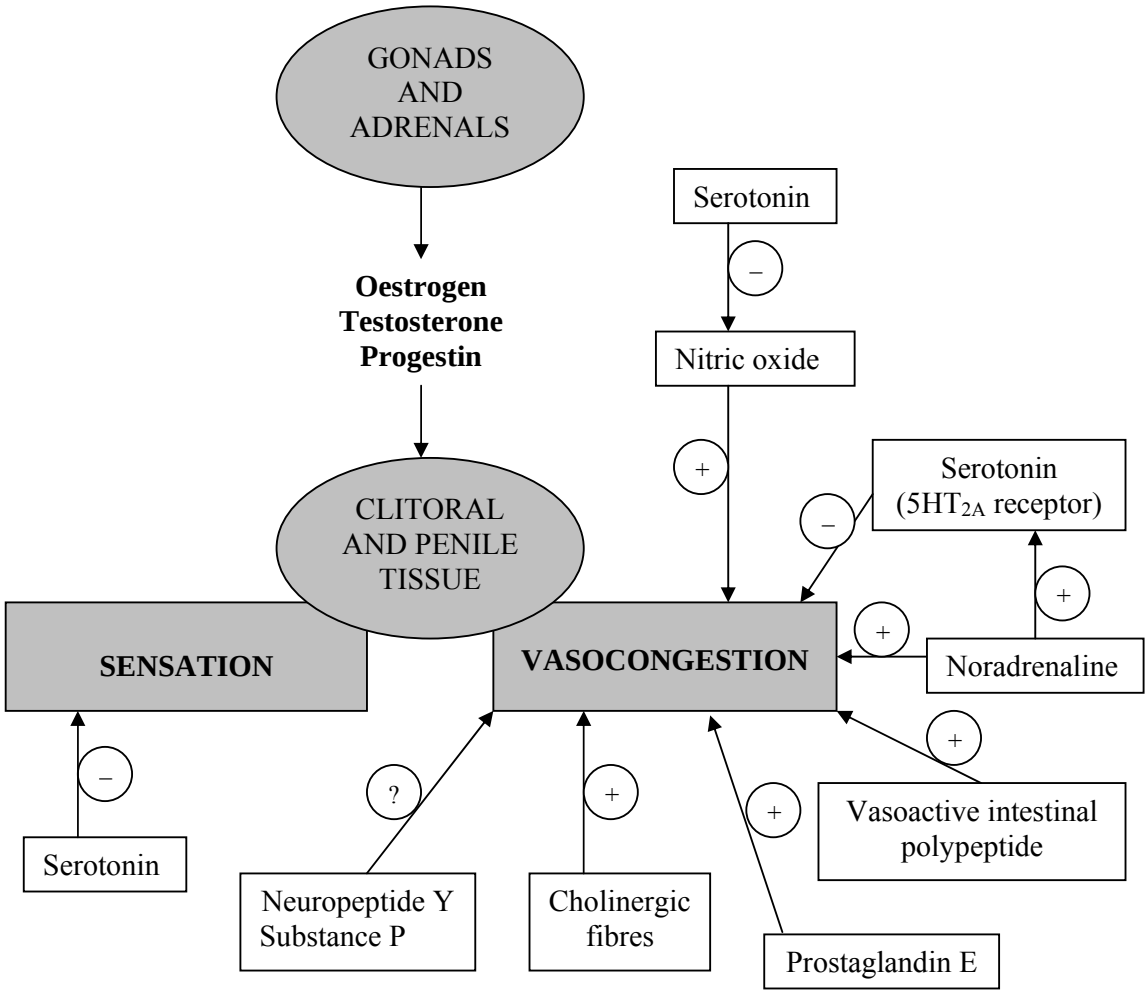


Figure 1.2 Peripheral influences on sexual function ("+" indicates a positive effect, "–" indicates a negative effect, "?" indicates that the effect is unknown)

1.1.2.4 The role of the serotonin type-3 receptor

A reasonable body of data exists concerning the impact of serotonin type-1 ($5HT_1$) and $5HT_2$ receptors on mammalian sexual activity. The sex of the animal and the subtype of serotonin receptor that is activated appear to have a significant influence on sexual activity in experimental settings. In female rats $5HT_{1A}$ receptor activity inhibits lordosis whereas this marker of animal sexual behaviour is facilitated by serotonin type-1B ($5HT_{1B}$) and $5HT_2$ receptor activation. Conversely, activation of the $5HT_{1A}$ receptor enhances male rat copulation and activation of $5HT_{1B}$ and $5HT_2$ receptors inhibits this behaviour (41). In animal models this inhibitory effect of serotonin is mediated by post-synaptic $5HT_2$ receptors, and serotonin type-2C ($5HT_{2C}$) receptor subtype agonists such as *m*-chlorophenylpiperazine provoke sexual excitement in experimental animals (7). There is, however, comparably little known about the role of the $5HT_3$ receptor. The majority of information which exists is derived from the clinical use of pharmacological agents with differing $5HT_3$ receptor activity.

The identification of $5HT_3$ receptors in the brain and the synthesis of relatively selective $5HT_3$ receptor antagonists have stimulated interest in activity at this receptor. The existence of $5HT_3$ binding sites in areas fundamentally involved in mediating sexual behaviour such as the hypothalamus suggest that $5HT_3$ receptor activity may be influential (42). There have been reports of $5HT_3$ receptor antagonists attenuating the effects of increased dopamine activity in mesolimbic structures (43). They may also inhibit certain opiate induced behaviours.

High doses of selective $5HT_3$ receptor antagonists have both enhanced and failed to enhance lordosis in female rats. Granisetron, ondansetron and the experimental $5HT_3$ receptor antagonist MDL 72222 have been shown to facilitate lordosis in sexually disinterested female rats, though in male rats another experimental agent ICS 205-930 failed to affect sexual activity (43).

Endogenous opioids may play a role in the regulation of sexual behaviour (44) and independently of their direct effects it seems that $5HT_3$ receptor antagonists may modulate sexual behaviour via their interactions with the opioids. Morphine appears

to increase hypothalamic $5HT_3$ activity (45) and inhibits copulation in rat models (44). There is preliminary data to suggest that ICS 205-930 may attenuate morphine-induced inhibition of male copulation (41). These findings are consistent with the possibility that agents with $5HT_3$ receptor activity may antagonise the effects of opioids on sexual behaviour.

However, not all data supports a role for the $5HT_3$ receptor (43). The effects of selective $5HT_3$ antagonists MDL 72222, ondansetron and ICS 205-930 on the sexual activity of female rats were examined and male rats were investigated using ondansetron and granisetron. The study found that none of these agents had any affect on female or male copulation. The conclusion was that $5HT_3$ receptors appeared to contribute little to the modulation of sexual activity. Furthermore, although morphine did inhibit copulation in this study, ondansetron and ICS 205-930 failed to reverse this effect. The influence of the $5HT_3$ receptor on opioid induced inhibition of sexual activity is therefore also doubtful.

In summary, the relative role of the $5HT_3$ receptor as a mediator of sexual function remains controversial. It appears that the $5HT_2$ receptor plays a more important role in this regard.

1.1.3 Psychosocial aspects of sexuality

Sexual activity is essential for the survival of a species, but it is not, however, an essential requirement for the survival of the individual (46). Human sexuality has come to be associated with values and meanings that have less to do with our survival as a species than with our ability to function in a complex modern society. A complicated network of psychological and social factors influence sexual behaviour, and by the same token sexual behaviour has important consequences for psychological and social well being.

Masters and Johnson broke new ground in detailing the physical features of the sexual response cycle (5), but their research also demonstrated that many sexual problems are caused by psychological factors. Although modern society is in many ways obsessed with sex, and although sex is an important motivating force that generates

some of people's most powerful emotions, misconceptions about sexuality are common. Generally, animals appear to execute the sex act with a minimum of difficulty, but the values and meanings that humans imbue sexuality with makes their sexual relations considerably more complicated (2).

The term "psychosexuality" is used to describe personality development and functioning as they are affected by an individual's sexuality (1). Sexuality and personality are so entwined that it is impossible to speak of sexuality separately. An individual's sexuality depends on four interrelated factors. Firstly, sexual identity or the person's biological sexual characteristics as defined by chromosomes, external and internal genitalia, hormonal composition, gonads and secondary sex characteristics. Secondly, gender identity or the firm conviction that develops in early childhood of being either male or female. Thirdly, sexual orientation or terms like heterosexual, homosexual and bisexual that are used to describe a person's sexual impulses. Fourthly, sexual behaviour which encompasses a wide range of sexual rituals and practices. These four factors operate throughout the life cycle and have important effects an individual's personality growth, development and functioning.

The sexual response of both males and females is sensitive to the situation in which they find themselves. This situation is comprised of both their current psychological state and their environment. Psychological factors may be far more important in sexual functioning than poorly developed genitalia, hormone deficiency or neurological disturbances (47). Psychological factors include a person's cultural and religious background, their parents' attitudes towards sex and communication on the subject and parental reactions to a child's developing sexuality. Childhood fantasies and experiences, reactions and experiences during adolescence and knowledge of sex organs and their function are also important. Other psychological determinants include previous sexual experiences, self-esteem and the individual's sense of sexuality, masturbation fantasies, expectations of a relationship and attitudes towards contraception, pregnancy and sexually transmitted disease. This sets the stage for the physiological chain of events that make up the sexual response cycle.

There is some value in looking at the factors that are considered to promote rewarding sexual relationships (48, 49, 50, 51). That they relate fairly specifically to

heterosexual couples in a relationship based on sincere commitment and affection is relevant given the focus of this report. Firstly, patients and their partners need accurate information or, in other words, sex education. This relates primarily to knowledge about sex organs and the way in which they function, the human sexual response cycle and the normal fluctuations that occur in sexual desire and performance, reproductive physiology, contraception and the psychosocial determinants of sexual function. Secondly, sexual values and feelings of guilt. Each partner brings to the relationship an at best subtly different social history and set of experiences which impact greatly on the health of their sex life. Thirdly, communication is important. In an area of human relationships that is so emotionally charged the potential for misunderstanding is great and likely to have far reaching implications. Therefore, effective communication regarding differing interpretations of sexual behaviour and expectations of sexual activity is extremely important. Fourthly, perhaps particularly in a long-term relationship the value of sexual fantasy should not be denied or underestimated. Finally, it is vital that both partners have realistic expectations of each other and the sexual relationship they are involved in. It goes without saying that these factors operate against the background of trust that should be a part of any sincere, committed relationship.

Sexual activity does not always take place in the context of a stable long-term relationship. It does, however, always have potential implications of one kind or another and never occurs in complete isolation. Burt & Brower (47) proposed a set of criteria that are can be generalised to most sexual relationships and form the basis for a modern code of sexual ethics that respect human dignity. Firstly, both partners must be certain that they are free of sexually transmitted disease. Secondly, both partners must recognise their responsibility to love and care for the offspring that may result from sexual intercourse. Thirdly, both partners should have some notion of direction and their goals in life and where sexual activity with all its implications fits in to this. Fourthly, one person must not exploit another; the sexual encounter should be an experience of love or at least mutual respect.

The period of rapid social change that took place in the second half of the last century and is often called the sexual revolution has significantly affected the nature of relationships between men and women, the structure of the family and the role of

women in society. In many parts of the world large families are no longer the social or economic asset they once were (2). In first world societies children are expensive, their education is often prolonged and they do not offer the security to their parents that they did previously. In addition, societal pressure on people to form lifelong bonds, marry and have children has lessened. Many men no longer feel that carrying on the family line is of great importance and larger numbers of women are choosing not to marry and to delay having children until later in their reproductive life. As a result, birth rates have fallen throughout the developed world and a woman's status as the child-bearer has declined. It is true that to a certain extent societal pressure still defines a woman's role as a wife and mother, but society is also placing increasing attention on the value of a woman's economic and sexual emancipation.

There is growing emphasis on sex and personal relationships as a basic source of happiness and fulfilment (2). Restrictive attitudes to sex and sexual expression are diminishing and people have had to develop new approaches and new standards. There is an acknowledgement of the individual's right to determine the manner in which they express their sexuality. As society has shifted towards increasingly valuing individual responsibility and respect of a person's right to free choice, sexual activity is no longer a set pattern of behaviour. Instead, it is a form of intimate physical contact for pleasure that can take place in a variety of contexts. Ideally, consenting partners recognise the implications which sexual activity has for the nature of their relationship and the risks of pregnancy and sexually transmitted diseases. The tendency for women to be more financially and emotionally independent has been accompanied by a trend towards more aggressive sexual behaviour of the kind that has traditionally been associated with masculinity. In the context of sexual relationships women are increasing likely to demand equality rather than assume a passive role.

In conclusion, human sexuality is something more than physical sex and something less than every aspect of behaviour directed towards attaining pleasure as espoused by psychoanalytic theory. Sexual behaviour is an immeasurably variable and constantly changing concept. Any investigation into the subject must take cognisance of this reality. It is also important to note that much of our understanding of human sexuality is based on patterns of behaviour observed in relatively homogenous western

countries. This does not adequately address the different beliefs and attitudes that exist towards sexual behaviour in other cultures.

1.2 Sexual dysfunction

Terms such as “sexual complaint”, “sexual dysfunction” and “sexual disorder” are often used interchangeably to describe sexual difficulties of various kinds. For the purposes of this report it is useful to define these terms a little more specifically as they provide a basis for the discussions that follow (35). A sexual complaint is an expression of discontent or pain that refers specifically to problems of a sexual nature. A sexual dysfunction is disturbance in sexual functioning that involves one or more phases of the sexual response cycle or somatic pain associated with sexual activity. A sexual disorder is a sexual dysfunction that meets DSM-IV criteria for a specific sexual disorder. According to DSM-IV diagnostic criteria a sexual disorder must include significant dysfunction and marked distress (6). General terms such as “sexual difficulty” and “sexual problem” refer non-specifically to all of the above.

In keeping with the title of this report an emphasis will be placed on sexual dysfunction in women. A discussion of antidepressant induced sexual dysfunction and its management is impossible without some understanding of sexual dysfunction generally.

1.2.1 Epidemiology

In spite of the fact that reliable epidemiological data is lacking, sexual dysfunction and sexual disorders are undoubtedly common in the general population. The sensitive nature of sexual complaints makes patients reluctant to report them and it is probably also true that clinicians avoid asking about sexual problems or even taking a sexual history for a similar reason (52). There is evidence that the rates at which sexual dysfunction are reported vary significantly depending on the method of data collection selected. The lowest prevalence rates are found with spontaneous self-reporting. Higher prevalence rates are found when confidential questionnaires are used. The highest rates of sexual dysfunction are reported when people are questioned directly about their symptoms (8, 53). This issue should be borne in mind when

selecting an appropriate information-gathering technique for research purposes. It is also not surprising that epidemiological estimates of the prevalence of sexual problems vary widely.

An important 1978 study suggested that approximately half of all couples were troubled by some degree of sexual difficulty (54). In the 1992 National Health and Social Life Survey in the United States 43% of women and 31% of men who had been sexually active in the previous year complained of sexual problems (55). The women's most common complaints were of reduced sexual desire (33%), impaired lubrication (19%) and difficulty attaining orgasm (24%). It also appeared that the women's sexual problems decreased as their age increased, except in the case of the impaired lubrication and arousal difficulties associated with menopause. Younger women reported more problems with sexual desire and difficulty achieving orgasm than older ones. Sexual difficulties in this survey were also associated with poor physical and emotional health, negative experiences of sexual relationships, sexual trauma, declining social status and a negative overall sense of wellbeing. A postal survey conducted recently in England reported similar rates of sexual problems (56) and found an association between psychosocial stresses such as marital conflict and problems with arousal, orgasm and sexual pleasure (57). More than half (52%) of respondents to this survey indicated that they would like to receive professional help for a sexual problem, though only 10% had ever received any such help.

The prevalence of sexual problems obviously varies according to the population that is being surveyed. In a study of patients attending a family practice centre 75% of the sample reported sexual problems of one kind or another (58). Furthermore, prevalence is likely to vary depending on the criteria used to define sexual dysfunction. Many surveys are based on loosely defined terms or criteria other than those defined by the DSM-IV. A 1998 study using DSM-IV criteria reported sexual dysfunction in 26% of normal subjects (59). This is probably one of the most reasonable estimates of the prevalence of sexual dysfunction that exists in current literature.

When it is relevant and available epidemiological data that meets DSM-IV criteria will be provided for the individual sexual disorders discussed below. However, it

appears that overall the most common sexual problems experienced by women are loss of sexual desire, difficulties with orgasm and vaginismus.

1.2.2 Classification and clinical presentation

Sexual disorders are grouped into three broad categories according to DSM-IV: the sexual dysfunctions, the paraphilias and the gender identity disorders (6). The sexual dysfunction classification is in turn subdivided into sexual desire disorders, sexual arousal disorders, orgasmic disorders, sexual pain disorders, sexual disorders due to a medical condition or due to the effects of a substance, and sexual dysfunction not otherwise specified. This subdivision is obviously derived from the various phases of the human sexual response cycle. Resolution is a passive phase and is not associated with any known sexual dysfunction.

Sexual disorders should not be diagnosed if they are caused by another psychiatric condition. For example, the loss of libido associated with major depressive episodes should not be classified as a disorder. This is not to suggest that other psychiatric disorders and their treatment do not produce sexual dysfunction. Furthermore, the onset of a sexual disorder may precede that of a psychiatric condition and therefore occur concurrently with it.

1.2.2.1 Sexual desire disorders

Hypoactive sexual desire disorder

A 1986 review of 22 general population surveys found a higher prevalence of hypoactive sexual desire disorder in females compared to males (females 1% to 35%, males 1% to 15%) (60). Certainly, this appears to be the most common sexual disorder experienced by women. Overall estimates of its prevalence vary from 5% to 46% in the general population and from 10% to 46% in primary care settings (61). In addition, comordity is common. Approximately 40% of women with hypoactive sexual desire disorder appear to also have secondary diagnoses of arousal or orgasm disorders (62). The disorder presents with a lack sexual fantasy and desire for sexual activity (6). This disorder may have a primary cause, but frequently it is related to

temporary stresses or such practical issues as a lack of privacy or the opportunity to have sex. A relationship problem or interpersonal difficulty frequently lies at the root of hypoactive sexual desire disorder.

Sexual aversion disorder

Epidemiological data on this condition are lacking. Sexual aversion disorder differs from hypoactive sexual desire disorder in that there is a distinct aversion to genital sexual contact with a partner (6). Sexual intercourse is actively avoided and can develop into an aversion to other non-genital sexual contact. The onset of sexual activity can precipitate considerable anxiety, and it is thought that a high proportion of people with this disorder have experienced sexual trauma (63).

1.2.2.2 Sexual arousal disorders

Male erectile disorder

This disorder which is also known as erectile dysfunction or impotence has been reported in up to 40% of men at age 40 years and 70% at age 70 years (64). The incidence obviously increases with advancing age. Male erectile disorder presents with the inability to attain an adequate erection or to maintain it until the completion of sexual activity (6). It may be either a lifelong or an acquired condition and its causes may be organic, psychological or a combination of both (1).

Female sexual arousal disorder

Definitive epidemiological data is lacking but the lifetime prevalence of this disorder has been reported as being around 6% in a sample of the general population aged between 55 and 57 years (65) and up to 21% of women attending a premenstrual syndrome clinic (66). Female sexual arousal disorder manifests as an inability to adequately attain and maintain the lubrication and engorgement associated with sexual excitement (1). The condition may for obvious reasons rapidly develop into other sexual disorders including problems with desire and pain during intercourse. Female sexual arousal disorder appears to be more common in women involved in

long-term sexual relationships, though in reality a number of other psychosocial factors have been associated with disordered sexual arousal.

1.2.2.3 Orgasmic disorders

Female orgasmic disorder

Although inhibited orgasm has been reported in between 5% and 30% of females (60), the lifetime prevalence of this disorder in the general population sample aged between 55 and 57 years was only 4% (65). It was found to be about 5% in the survey at a premenstrual syndrome clinic (66). In clinical settings it appears that problems with orgasm are far more common than epidemiological figures suggest. This probably has something to do with the under reporting of the condition. Certainly, difficulty achieving orgasm is a significantly more common problem than female orgasmic disorder as defined by DSM-IV criteria. Female orgasmic disorder presents as a delay in or the absence of orgasm after a normal sexual excitement phase (6). The diagnosis of the disorder should be made in the context of an individual woman's capacity to achieve orgasm. This is likely to be influenced by factors such as her age, degree of sexual experience and the extent of sexual stimulation. A number of biological and psychosocial factors have been associated with the development of this disorder.

Male orgasmic disorder

Male orgasmic disorder occurs when a man achieves ejaculation during intercourse only with great difficulty or not at all. Its prevalence rate in the general population is probably around 5% (60).

Premature ejaculation

Premature ejaculation is a common problem amongst men. It presents with persistent or recurrent ejaculation with minimal stimulation before adequate vaginal penetration or before the person wishes it (6). Again, the diagnosis of this disorder should be made only in the context of factors such as age, the novelty of the sexual partner or

situation, the frequency of recent sexual activity and the duration of the excitement phase. Females are able to have multiple orgasms within a relatively short period of time and therefore there is no disorder in women that is the equivalent of premature ejaculation (63).

1.2.2.4 Sexual pain disorders

Dyspareunia

Dyspareunia refers to the experience of genital pain associated with sexual intercourse in either men or women (6). The anticipation of further pain frequently gives rise to an avoidance of sexual activity and dysfunction in other phases of the sexual response cycle, particularly vaginismus.

Vaginismus

Vaginismus is characterised by the involuntary spasm of the musculature of the outer third of the vagina (6). This interferes with sexual intercourse. Not surprisingly, avoidance of sexual activity and other sexual dysfunctions such as dyspareunia frequently develop.

1.2.2.5 Sexual dysfunctions due to a general medical condition

A variety of medical conditions have been associated with sexual dysfunction. Rates of sexual disorders are higher in medically ill patients (67% versus 25%) and are particularly common in those with endocrine and neurological disorders (35). Increasing problems with sexual function may indicate a progression or inadequate treatment of underlying medical conditions.

1.2.2.6 Substance-induced sexual dysfunction

The DSM-IV diagnostic criteria for substance induced sexual dysfunction are included in Table 1.1 (6). Depending on the nature of the substance the dysfunction may involve impaired desire, arousal orgasm or pain, or a combination of these.

Table 1.1 Diagnostic criteria for substance-induced sexual dysfunction

A.	Clinically significant sexual dysfunction that results in marked distress or interpersonal difficulty predominates in the clinical picture.
B.	There is evidence from the history, physical examination, or laboratory findings that the sexual dysfunction is fully explained by substance use as manifested by either (1) or (2): (1) the symptoms in Criterion A developed during, or within a month of , substance intoxication (2) medication use is aetiologically related to the disturbance
C.	The disturbance is not better accounted for by a sexual dysfunction that is not substance induced. Evidence that the symptoms are better accounted for by a sexual dysfunction that is not substance induced might include the following: • the symptoms precede the onset of the substance (or medication) use or dependence • the symptoms persist for a substantial period of time (eg. about a month) after the cessation of intoxication, or are substantially in excess of what would be expected given the type or amount of the substance used or the duration of use • other evidence that suggests the existence an independent non-substance-induced sexual dysfunction (eg. a history of recurrent non-substance-related episodes)
	Note: This diagnosis should be made instead of a diagnosis of substance intoxication only when the sexual dysfunction is in excess of that usually associated with the intoxication syndrome and when the dysfunction is sufficiently severe to warrant independent clinical attention.
	Code: [Specific substance]-induced sexual dysfunction. (Alcohol; amphetamine or amphetamine-like substance; cocaine; opioid; sedative, hypnotic or anxiolytic; other or unknown substance.)
	Specify if: • **with impaired desire** • **with impaired arousal** • **with impaired orgasm** • **with sexual pain**
	Specify if: • **with onset during intoxication** if the criteria are met for intoxication with the substance and the symptoms develop during the intoxication syndrome

Sexual dysfunction has been linked to a variety of pharmacological agents. Medications used to treat general medical conditions such as digoxin and other cardiovascular agents, antihypertensives, antihistamines, analgesics and steroids, hormonal preparations and the oral contraceptive pill, antineoplastic agents and hypolipidemic drugs have all been implicated (67). Psychotropic medications, including antidepressants, antipsychotics, lithium and sedative or hypnotic agents have also been convincingly implicated. Drugs of abuse including prescription and over the counter medication, alcohol, nicotine and illicit substances may all impact on sexual function. It is important to note that when a substance causes sexual problems this represents a sexual dysfunction rather than a disorder. In order to make this diagnosis a temporal relationship should exist between the onset of sexual side effects and the commencement of a medication known to be associated with sexual dysfunction.

1.2.2.7 Sexual dysfunctions not otherwise specified

This DSM-IV category is for sexual dysfunctions that do not meet the criteria for one of the above specific sexual dysfunctions (6). Of particular relevance to this report are the complaints of diminished genital sensation and loss of intensity of arousal or orgasm (68). These problems are not currently considered sexual disorders although they may well represent sexual dysfunction.

1.2.3 Aetiology

Sexual dysfunction may be due to the organic, pharmacological, psychosocial and situational factors outlined above. When a particular sexual dysfunction is due to predominantly psychological factors it is considered a primary sexual disorder. Prolonged abstinence from sex may in itself suppress sexual desire. Fears of becoming pregnant, rejection by partner or any of the psychosocial factors outlined previously may be significant. Sexual disorders are often caused by a combination of factors. For example, it is unusual for sexual dysfunction due to a physical cause to manifest without the patient being on a medication and experiencing some degree of psychosocial stress at the same time. There is some evidence that chronic stress and anxiety can effect the neurobiological factors outlined previously. Difficulties in the

later phases of the sexual response cycle (arousal and orgasm) can have an indirect effect on libido, in which case the primary phase disturbance should be addressed.

1.2.4 Management

A detailed discussion of the general management of sexual dysfunction is beyond the scope of this report. A detailed account of the management of antidepressant induced sexual dysfunction (AISD) will be given subsequently. In terms of general principles, when there is an underlying medical cause this problem should be addressed. If the cause is a prescribed medication or a drug of abuse then this should be the focus of intervention. For the vast majority of primary sexual dysfunctions the main intervention is likely to be psychotherapeutic. The emphasis of therapy should be on the couple rather than the individual presenting with the problem. Principles include education, communication, and rectifying dysfunctional attitudes towards sex. This may be accompanied by behavioural techniques often set as homework. There are a number of physical interventions that can be used for the problem, and the availability of peripherally acting vasodilator agents has for better or worse revolutionised the treatment of this problem. Hormone replacement therapy may be useful in post-menopausal women complaining of sexual dysfunction (69).

In conclusion, consideration should be given to whether a person has a sexual complaint, a sexual dysfunction or a sexual disorder (35). A psychosocial intervention, sex education, or watchful waiting may best address a sexual complaint. Sexual dysfunction may respond to appropriate treatment of the underlying medical or psychiatric condition. Reducing substances or adding the appropriate antidote, or simply education and psychotherapy to improve sexual responsiveness may be useful. Minimising the number of medications, reducing doses when appropriate, substituting medication while treating underlying condition can lead to improvement. Treatment of primary sexual disorders may include psychotherapy especially if there is a history of trauma. Pharmacotherapy may play a role for some, but at this time there are no registered treatments for women.

1.3 Sexual dysfunction and depression

Although the effect of mood and anxiety on sexual function has long been recognised little research has been undertaken on the subject until fairly recently. Most of the rather limited information that is available has resulted from incidental findings in studies with different aims. Unfortunately the recent surge in interest in AISD has not been accompanied by a corresponding increase in the investigation of the sexual dysfunction caused by depressive illness (70).

1.3.1 Epidemiology

Sexual dysfunction is a common symptom of depression. It has been reported that between 40% and 75% of depressed patients experience the problem in one form or another (70). A 1998 study found that sexual dysfunction was present in 45% of untreated depressed patients (59). A more recent evaluation of 4557 depressed patients in France confirmed that the prevalence sexual dysfunction is high in this group (69%) and concluded that sexual problems amongst these patients were often not optimally treated (71).

Between 40% and 50% of people with depression reported diminished libido and difficulties with sexual arousal in the month before a diagnosis of depression was made in one study (72). In the same study it was found that only 15% to 20% of depressed people experienced difficulties with orgasm before treatment was commenced. Decreased libido has been reported in up to 75% of depressed patients. Its prevalence is similar across cultures and greater in younger patients with depression. An improvement in libido seems to correlate with an improvement in mood along with the other somatic symptoms of depression (70).

It is also worth noting that depression has been reported in about 30% of patients seeking treatment for a variety of sexual disorders (73). A lifetime history of depression has been found in 72% of physically healthy subjects with hypoactive sexual desire disorder compared to 29% of normal controls (74).

1.3.2 Classification and clinical presentation

Major depressive disorder is a severe and frequently chronic illness that places a significant strain on relationships in its own right. Sexual difficulties are often not the priority of the patient and the clinician during the acute stage of a severe depressive episode. Sexual dysfunction is much more likely to be a focus of attention during the recovery or maintenance phase of a depressive illness or when the condition is of mild to moderate severity. Sexual dysfunction may occasionally be the only presenting complaint in a depressive episode (73). Occasionally depressed patients may report an increase in their interest in sex and levels of sexual activity (70). This is likely to be a function of the reversed vegetative features that are associated with atypical depression or alternatively it may represent a search for reassurance and intimacy.

Impaired libido, difficulties initiating sexual activity, a decreased frequency of sexual intercourse, a loss of pleasure in or an aversion to intercourse and a reduction in the quality of sexual relationships have all been described. Difficulties with erection and ejaculation, dyspareunia and delayed or absent orgasm have also been associated with depression (70).
Sexual pain disorders have not been specifically linked to major depression, but problems with desire, arousal and orgasmic function may all be associated (17). The resolution phase occurs passively following orgasm and problems with this phase have not been identified.

1.3.3 Aetiology

A detailed account of the mechanisms underlying the sexual dysfunction associated with depression is beyond the scope of this report. However, it is important that some attempt is made to correlate these factors with the neurobiology of normal sexual function that was discussed previously.

Depression appears to have significant effects on hormonal function and it has been convincingly associated with hypothalamic-pituitary-gonadal (HPG) dysregulation. Psychological stress can affect the HPG axis and it has been shown to interfere with the activity of gonadotropin releasing hormone (75) and reduce testosterone levels in

primate models (76). In humans, psychological stress may either stimulate or suppress plasma testosterone levels (77). Testosterone has been found to be lower in depressed men (78) and to return to normal levels on recovery (79). Oestrogen has been found to be more effective than placebo in the treatment of pre-menopausal women with dysphoric symptoms (80) and severe antidepressant resistant depression (81), and oestradiol levels are lower in post-menopausal depressed women. Studies of luteinising hormone and follicle stimulating hormone secretion indicate a trend towards lower levels of these hormones in depressed pre-menopausal women and depressed men (82). Prolactin levels increase in response to stress in humans (83), possibly by direct inhibition of the gonadotropin releasing hormone stimulated release of luteinising hormone from the pituitary. The regulation of these sex hormones is clearly disordered during episodes of depression via central effects on the HPG axis.

Glucocorticoids are thought to be important stress hormones. Their plasma levels increase in response to psychological stimuli dependent on personality and social factors, and high glucocorticoid levels suppress the HPG axis (84). Glucocorticoids can inhibit testicular testosterone production, an effect that may be caused directly by cortisol or indirectly by corticotropin releasing hormone or adrenocorticotropin (85). Major depression and hypercortisolaemia have consistently been associated with each other (86). This HPG axis hyperactivity is the basis of the cortisol non-suppression seen in dexamethasone suppression tests, the rate of which increases from mild (about 30%) through too severe (about 70%) depression (70). The incidence of decreased libido is 1.5 to 2 times greater in dexamethasone suppression test non-suppressors compared to suppressors in major depression (87). Initial insomnia and decreased libido are the most significant contributors to variance in dexamethasone suppression test results (88).

In the adrenal gland, cholesterol is metabolised to pregnenolone and then to dehydroepiandrosterone (DHEA) and its conjugated sulphate, dehydroepiandrosterone sulphate (DHEAS), or to progesterone and cortisol (70). DHEA and DHEAS are the most abundant products of the adrenal cortex in humans. Cortisol levels usually remain constant as one grows older, but DHEA and DHEAS levels rise during adolescence, peak in early adulthood and thereafter decline gradually. DHEA levels can change rapidly, in contrast to DHEAS levels that are stable and free of circadian

and menstrual changes. DHEA and DHEAS androgenic potency is 3% that of testosterone, but their blood levels in adult men are 100 to 150 times higher. They serve as a precursor to oestrogen, various androgens and androsterone. DHEA levels have been positively related with feelings of wellbeing in women, which in turn predicted measures of sexuality (89). The cortisol versus DHEA ratio is reduced in depression (90) and the ratio returns to normal upon recovery. DHEA is therefore a potential antidepressant. DHEA and DHEAS, pregnenolone and pregnenolone sulphate promote sexual behaviour in rats (91). Their increased concentrations in the amygdala and hypothalamus of male rats exposed to the scent of a receptive female suggests that they have a role in the perception or central nervous system integration of the scent. As sex steroid hormones, DHEA and DHEAS activity appears to involve more subtle interactions rather than the polarised and sexually overt behaviour and reactions characteristic of testosterone and oestrogen (92).

The implication of these findings is that if depression is associated with altered levels of sex hormones, and if these hormonal changes are in turn correlated with negative effects on sexual function, then this is a likely explanation for the sexual dysfunction that is associated with depressive disorders.

1.3.4 Management

A detailed discussion of the management of sexual dysfunction associated with depression is beyond the scope of this report. However, management of the sexual symptoms is obviously aimed at treating the primary depressive condition according to accepted guidelines.

The presence of sexual dysfunction clearly complicates the assessment and possibly management of a problem that is also a potential outcome of the very interventions used to treat depression. Although it makes sense to treat depressive disorders with an antidepressant with a low incidence of sexual dysfunction, particularly if sexual symptoms are a major part of the presenting illness there is little data to support this practice.

1.4 Sexual dysfunction and antidepressants

Not only is sexual dysfunction a common symptom associated with depression, but the use of antidepressant medication can also cause sexual problems. The association of sexual dysfunction with the use of antidepressants has been conclusively demonstrated and antidepressants can clearly both aggravate and provoke sexual side effects (8, 55, 93). The added burden of AISD exacerbates an already difficult situation. As antidepressant treatment is usually a long-term undertaking, the presence of sexual dysfunction is likely to adversely affect the quality of life of patients, their partners and indirectly their families. Although there is not currently any reliable data on the subject, it is estimated that a significant proportion of patients who suffer from severe AISD will discontinue treatment because of that side effect (7). Sexual dysfunction is likely to have a significant impact on a patient's compliance with medication and, therefore, their prognosis and the likelihood of relapse or recurrence.

1.4.1 Epidemiology

The exact prevalence of AISD is not clear. Early estimates that were based on spontaneous self-reporting substantially underestimated the frequency of the condition (94). Later estimates that specifically looked for this side effect reported rates from 20% to 40% (93) and 10% and 50% (95). A prospective Spanish study in 2001 found that the overall incidence of sexual dysfunction in 1022 outpatients was 59.1% when all antidepressants were considered as a whole (7). A 2003 study of 4557 depressed patients in France reported that the frequency with which antidepressant drugs aggravated the sexual dysfunction associated with depression was even higher (71). It found that the frequency of sexual dysfunction was 71% amongst patients treated with antidepressants and 65% in untreated patients. Although estimates of the extent of the problem vary widely for various methodological reasons, the fact remains that AISD is a common problem. It is also true that more recent studies that have looked more aggressively for AISD have tended to report higher prevalence rates. Furthermore, there is some evidence that AISD has a greater prevalence in females (38.7%) compared to males (24.9%) (59).

Sexual dysfunction has been reported as a side effect of all antidepressants, but there is a certain amount of variation from one antidepressant to another in terms of the prevalence, clinical presentation and likely underlying mechanism that produce the AISD associated with their use. These differences are highlighted in the discussion that follows, but an emphasis is placed on those with serotonin re-uptake inhibition as their predominant mechanism of action.

1.4.2 Clinical presentation and aetiology

The specific types of sexual dysfunction associated with antidepressants include decreased libido, erectile dysfunction, delayed ejaculation or orgasm, anorgasmia and decreased genital sensation (96). The commonest complaints are those of decreased libido, impaired erection and difficulties with ejaculation or orgasm (70). Increased libido, improved or spontaneous erections or orgasms, priapism and altered sexual sensations and sensitivity have also been less commonly reported. There is also evidence to suggest that the direct effect of an antidepressant on diminishing libido and orgasm can have indirect adverse effects on sexual arousal over time (71). All sexual side effects, with the possible exception of rare cases of priapism, are thought to be reversible. It is important to note that not every sexual side effect is undesirable (8). For example, serotonergic antidepressants are often effective in the treatment of premature ejaculation and may also be beneficial in the control of paraphilias.

Unfortunately, because both depression and its treatment can disturb the desire, arousal and orgasm phases of the human sexual response cycle, determining which of them is actually causing the sexual problems can be very difficult. Obviously, the temporal relationship between the onset of the sexual dysfunction and the onset of other depressive symptoms or antidepressant treatment may provide a clue. The precise nature of the sexual dysfunction may also suggest whether it is depression or its treatment that is the more likely cause. It has been reported that between 40% and 50% of people with depression complain of diminished libido and problems with arousal in the month before diagnosis, while in comparison only 15% to 20% of patients experience difficulties with orgasm prior to taking an antidepressant (72). Complaints of orgasmic dysfunction with relatively little impairment in desire and arousal are therefore more likely to be caused by the antidepressant. However, it may

in many cases be impossible to discern the underlying cause, and in reality it is likely that multiple factors are involved. Figure 1.3 summarises the potential causes of sexual dysfunction that may be present during antidepressant treatment (12).

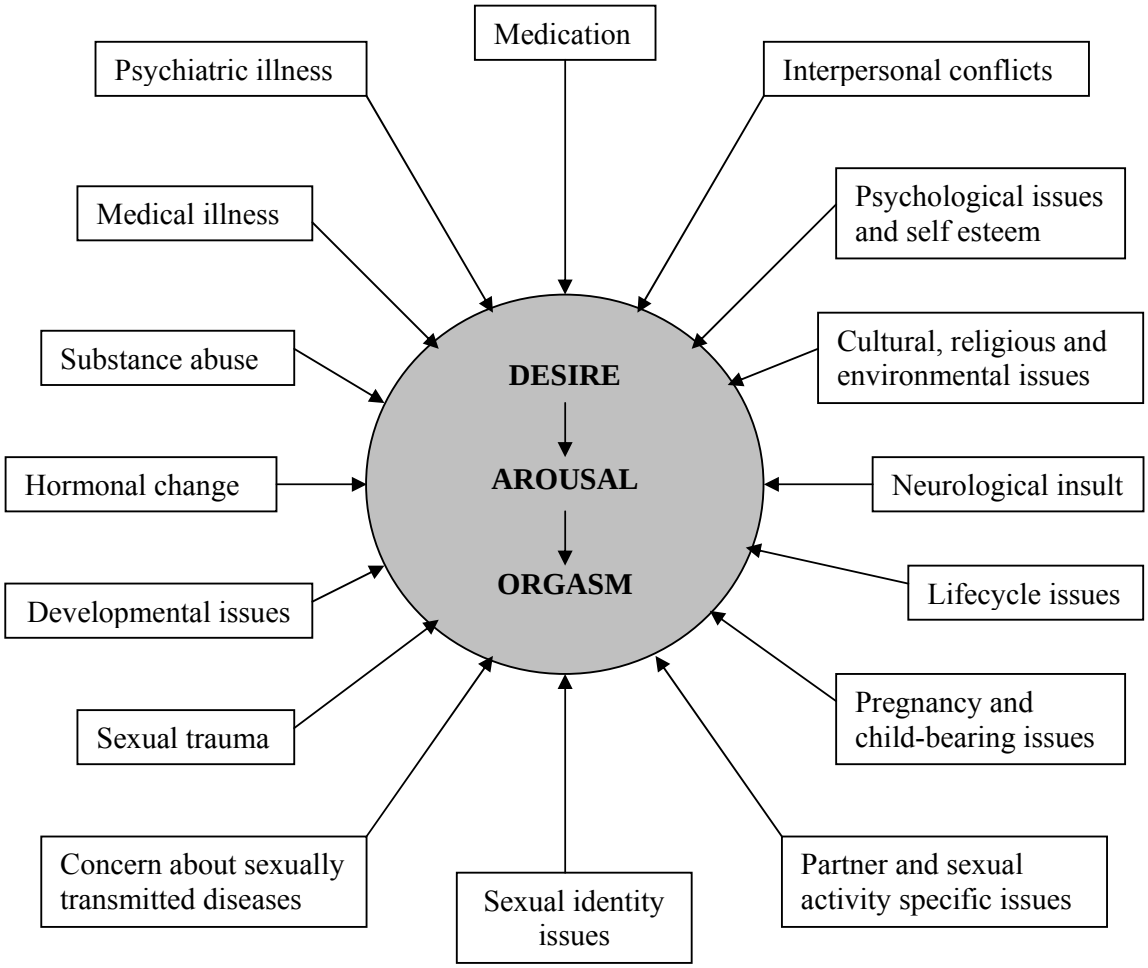


Figure 1.3 Potential causes of sexual dysfunction during antidepressant treatment

As a group, antidepressants can cause sedation, hormonal changes, disturbances of cholinergic-adrenergic balance, peripheral α-adrenergic antagonism, inhibition of nitric oxide and increased serotoninergic activity (17). All of these have been associated with the development of sexual dysfunction. However, the mechanisms that produce AISD are varied and generally poorly understood. A number of newer antidepressants with different mechanisms of action appear to be less likely to cause sexual dysfunction (71). These antidepressants with a lower incidence of sexual dysfunction are invariably either relatively free of serotonergic effects or have highly selective receptor activity at central serotoninergic synapses.

1.4.2.1 Tricyclic antidepressants

The approximate prevalence of sexual dysfunction with tricyclic antidepressants is about 30% (97). Specific problems include decreased libido, erectile dysfunction, delayed orgasm and impaired ejaculation. Painful ejaculation has been reported very rarely. These side effects can probably be best explained by the anticholinergic properties of tricyclic antidepressants, with the possible exception of decreased libido where their dopamine antagonist properties are likely to be involved (98). In addition, to a greater or lesser extent tricyclics also produce serotonin re-uptake inhibition and there appears to be some correlation between that and their propensity to cause sexual dysfunction. The prevalence of delayed orgasm with clomipramine may be double that of other tricyclics (97). Indeed, sexual dysfunction was reported in 95% of subjects involved in a trial of clomipramine for obsessive-compulsive disorder (99). This is possibly as a result of its strong serotonergic mechanism of action. The tricyclic antidepressants are a diverse group of compounds and their lack of receptor selectivity means that a combination of neurotransmitter systems are likely to be involved in the production of their sexual side effects.

1.4.2.2 Monoamine oxidase inhibitors

Overall, about 40% of patients taking irreversible monoamine oxidase inhibitors experience sexual dysfunction (7). Their specific side effects are similar to those of the tricyclic antidepressants (8). The inhibition of monoamine oxidase is neither a

neurotransmitter nor receptor selective mechanism of action, so the cause of sexual side effects with these agents is likely to involve numerous factors and all the monoamine neurotransmitters. The reversible monoamine oxidase inhibitor, moclobemide, appears to be much less likely to cause sexual dysfunction. The prevalence of sexual dysfunction with moclobemide has been reported as only 3.9% (7).

1.4.2.3 Selective serotonin re-uptake inhibitors

AISD is particularly common with serotonergic antidepressants (100). Overall, it appears that the prevalence of sexual difficulties in clients on serotonergic antidepressants is likely to be between 58% and 73% (7). Although this section refers to the SSRI antidepressants it is important to remember that venlafaxine and clomipramine also have a predominantly serotonergic mechanism of action.

The specific sexual problems most strongly associated with SSRIs include decreased libido and delayed orgasm. In a major 2001 study of 1022 subjects citalopram and paroxetine emerged as the worst offenders. (7). Furthermore, significant differences in the prevalence of specific sexual side effects appeared to exist between the individual SSRIs. The overall incidence of sexual dysfunction for citalopram was 72.7%. The specific problems associated with its use included decreased libido (62.1%), delayed orgasm or ejaculation (63.6%), anorgasmia or no ejaculation (51.5%) and erectile dysfunction or decreased vaginal lubrication (34.8%). The overall incidence for paroxetine was 70.7%, while 63.9% experienced decreased libido and delayed orgasm or ejaculation, 52% anorgasmia or no ejaculation and 41.4% difficulties with erection or vaginal lubrication. For sertraline the overall incidence was 62.9%, with 54.7%, 56.6%, 47.1% and 28.9% complaining of decreased libido, delayed orgasm or ejaculation, anorgasmia or no ejaculation and erectile dysfunction or decreased vaginal lubrication respectively. Fluvoxamine (62.3%, 48.1%, 54.5%, 37.6% and 20.8%) and fluoxetine (57.7%, 50.2%, 49.5%, 39.1% and 21.8%) emerged from this study with the lowest incidence of sexual dysfunction. However, the overall incidence of sexual dysfunction with this class of antidepressants was found to be so high that individual differences are of limited clinical usefulness. Head-to-head comparative

studies are required as conclusions drawn from comparisons across trials are relatively meaningless.

These results seem to suggest that paroxetine is associated with higher rates of erectile dysfunction and decreased vaginal lubrication, both of which represent a disturbance in the arousal phase of the sexual response cycle. This may be an exception to the rule or possibly due to selective reporting. Although delayed ejaculation and impaired arousal have been reported previously with fluoxetine (101), it is generally accepted that the SSRIs predominantly affect sexual desire and orgasm. Although they can and do impair arousal, this is a less common finding and it may in many cases be the indirect result of impairments in other phases of the sexual response cycle. Difficulties with orgasm have been particularly strongly associated with SSRIs, and have been present in approximately two-thirds of patients in a number of other studies (102, 103).

Complaints of decreased genital sensation are encountered in clinical settings, but this side effect has received little attention in the current literature. Penile anaesthesia has been reported with fluoxetine in rare cases (104), but this remains an unclear and controversial AISD. The role of serotonin in the peripheral nervous system may represent a plausible explanation of this side effect.

The SSRIs are thought to cause decreased libido and their other sexual side effects by increasing synaptic concentrations of serotonin and stimulating $5HT_2$ and, possibly, $5HT_3$ receptors (70). This results in decreased levels of dopamine activity in mesolimbic structures. SSRIs may cause delayed or absent ejaculation and orgasm by increasing serotonin release from neurones in the descending pathways between the brain and the dorsal horns of the spinal cord. Increased libido and spontaneous ejaculation or orgasm may be due to $5HT_{2A}$ receptor antagonistic effects, although this is a more likely occurrence with the use of trazodone and nefazodone (95). Priapism, although it has been reported with SSRIs, is not considered to be primarily a serotonergic effect; it is likely to be caused by blocking the α-1 adrenoreceptor receptors that inhibit sympathetically mediated penile detumescence (105).

The impact of the SSRI antidepressants on sexual function is perhaps the most significant side effect of this class of drugs. It is certainly an important problem given their widespread and often long-term use. Unfortunately, the use of these agents is seldom accompanied by close monitoring for adverse events, particularly not for AISD.

1.4.2.4 Other antidepressants

The incidence of sexual dysfunction is high with venlafaxine, a serotonin and noradrenaline re-uptake inhibitor. It has been reported in 67.3% of patients using the agent (7). Specific problems associated with venlafaxine include decreased libido (60.0%), delayed orgasm or ejaculation (61.9%), anorgasmia or no ejaculation (41.8%) and erectile dysfunction or decreased vaginal lubrication (40.0%). Decreased libido and delayed orgasm are very common, but disturbances in other phases of the sexual response cycle are only somewhat less so. The mechanism involved is probably similar to that of the SSRIs at lower doses, although at higher doses other neurotransmitters are likely to contribute. This may explain the slightly different side effect profile which venlafaxine has in comparison with the SSRIs.

The extent of sexual dysfunction associated with the use of trazodone has not been clarified (7). Impaired ejaculation and both increases and decreases in libido have been reported and trazodone has been used in some cases to promote erection. Priapism occurs in approximately 0.01% of subjects treated with trazodone (105).

Mirtazapine appears to have relatively low rates of sexual dysfunction with an incidence reported as 24.4% (7). The most common sexual side efffects are decreased libido (20.4%) and delayed orgasm or ejaculation (18.4%). Anorgasmia or no ejaculation (8.2%) and erectile dysfunction or decreased vaginal lubrication (14.2%) are considerably less common. Mirtazapine's selective antagonism of $5HT_2$ and $5HT_3$ receptors is thought to be the main reason why it is associated with relatively little sexual dysfunction (106).

The incidence of sexual dysfunction with nefazodone has been found to be as low as 8.0% (3). Decreased libido (6.0%), delayed orgasm or ejaculation (2.0%), anorgasmia

or no ejaculation (2.0%) and erectile dysfunction or decreased vaginal lubrication (0.0%) are all extremely infrequent side effects. Nefazodone is a potent antagonist of $5HT_2$ receptors and this is like to be the reason for its benign sexual side effect profile (107).

The approximate prevalence of sexual dysfunction with reboxetine is estimated to be between 5% and 10% (108). Various abnormalities of orgasmic function have been described, but other phases of the sexual response cycle are thought to be relatively unaffected by this agent. Reboxetine is a noradrenaline re-uptake inhibitor with no serotonergic activity.

The dopamine enhancing antidepressant, buproprion, appears to have a very low likelihood of causing sexual dysfunction although reliable estimates of the frequency of the problem are lacking (109). Buproprion does not enhance serotonergic activity at central synapses.

In conclusion, major depression is a serious illness that is usually treated with an antidepressant medication. Depression can place a significant strain on relationships in its own right and the further burden of AISD, in addition to impinging on a major area of most peoples lives, is likely to adversely affect compliance and the likelihood of relapse. It negatively impacts on a patient's quality of life, both directly and also through what are often already strained relationships with their partners. This is particularly significant given the often long-term nature of the illness and its treatment. More recent antidepressant drugs with different mechanisms of action appear to have less sexual dysfunction associated with their use. These agents have one of two things in common. Either their pharmacodynamic activity does not significantly involve serotonin, or, if the are serotonergic antidepressants, then they have selective $5HT_2$ (and possibly $5HT_3$) receptor antagonist properties.

1.5 Management of antidepressant induced sexual dysfunction

The management of AISD can be difficult and strategies for tackling the problem have historically been quite unsatisfactory. It is only with the advent of several newer antidepressants with less associated sexual dysfunction that viable treatment options

have become available. Nevertheless, there remain a significant number of patients for whom these agents are either unavailable or inappropriate, and highly serotonergic antidepressants are still commonly prescribed drugs for depressive disorders. AISD is significant problem, yet a paucity of clinical trial data makes it difficult to formulate an evidence-based approach to the management of these side effects. Any discussion of the management of AISD should begin with some guidelines for the assessment of the problem. Subsequently, a number of potential management strategies will be detailed and an attempt made to combine these into a rational approach to the management of the problem.

1.5.1 Detection, screening and assessment

An understanding of the human sexual response cycle and the DSM-IV classification of sexual dysfunction are an important pre-requisite to the assessment of sexual functioning. An assessment of sexual dysfunction should identify which phase or phases of the cycle are involved as well as whether the sexual symptoms meet DSM-IV diagnostic criteria for a sexual disorder. Each disorder should be sub-typed as lifelong or acquired and as generalised or situational. It is obviously important to assess pre-morbid and life-long sexual function compared with the current presentation. However, a person's subjective sense of sexual satisfaction is an important aspect of sexual functioning that is often overlooked and is not accounted for in the DSM-IV (17). Sexual satisfaction may be affected by diminished function in a specific phase of the sexual response cycle or by the global decrease in pleasure that is associated with depression and its treatment. Poor overall sexual satisfaction is a common complaint of people with AISD.

The use of a screening tool or assessment instrument can be very useful. Such a tool should be brief, gender specific and identify which phase of the sexual response cycle is involved. It should also be as non-intrusive as possible, separate illness from the effects of medication and be able to monitor changes over time (17). There are 4 existing scales that meet most of these criteria: the Arizona Sexual Experience Scale, the Changes in Sexual Functioning Questionnaire (Clinical Version), the Derogatis Interview for Sexual Functioning (Short Report) and the Rush Sexual Inventory. The

Feiger Sexual Function and Satisfaction Questionnaire is a useful instrument for describing orgasmic dysfunction and overall sexual satisfaction.

As discussed earlier, patients tend not to spontaneously report sexual problems and often do not respond to casual questioning on the subject. This is no less true of AISD and the presence of sexual difficulties must be specifically inquired after. Interestingly, men appear more likely to report AISD (17). One strategy aimed at overcoming barriers to the discussion of sexual problems is to normalise the issue for the patient. This can be done by initially broaching the subject with a discussion of the frequency of sexual disorders in the general population or associated with specific treatments. Another is to simply provide basic psycho-education on the subject of sexual wellbeing and dysfunction. The discussion should follow a medical model and evaluate each phase of the cycle. Baseline measures of sexual functioning should be obtained whenever a diagnosis of major depressive disorder is made. In addition, it is important to note prior psychosexual adjustment and whether the current level of sexual functioning represents a change from baseline. An idea of fluctuations in sexual functioning associated with changes in the depressive illness and its treatment, or any alteration in psychosocial circumstances should be obtained over time. The use of a screening tool to identify problem areas requiring further discussion may also serve as an introduction to the topic. The discussions should refer generally to sexual activity rather than seeking details of specific behaviours in a way that a patient might view as intrusive.

A thorough assessment of AISD should include the six elements summarised in Table 1.2 (17). This involves a search for other potential causes of the sexual dysfunction as well as an appraisal of each phase of the sexual response cycle and the person's current level of sexual satisfaction. The assessment of sexual dysfunction in depression can be complicated by difficulties in determining the relative contribution of depression itself, of medication, and of underlying pre-existing sexual dysfunction (110). However, a thorough understanding of the problem is essential as it determines what is likely to be the best management strategy. It is also important that ongoing monitoring for improvement occurs over time.

Table 1.2 Assessment of antidepressant induced sexual dysfunction

1.	**Take a thorough sexual history:** • Onset of puberty • Age and nature of the person's first sexual experience • Childhood sexual abuse or adult sexual trauma • Reproductive function and pregnancy • Current phase of menstrual cycle • Peri-menopausal symptoms and menopausal transition • Current relationship status and opportunity for sexual activity
2.	**Take a psychiatric and medical history:** • Look for past and present conditions and document diagnoses • Screen for psychiatric illnesses commonly associated with sexual dysfunction (eg. mood and anxiety disorders) • Screen for common medical causes of sexual dysfunction (eg. neurological, endocrine, auto-immune and urogenital disorders) • Ask specifically about infectious and sexually transmitted diseases
3.	**Identify all substances that might contribute to sexual dysfunction:** • Psychiatric medications • Medications for general medical conditions • Prescription and over the counter preparations • Alcohol, nicotine and illicit drugs
4.	**Evaluate the current level of sexual functioning:** • Pre-morbid and pre-treatment level of sexual functioning • Onset and nature of the sexual dysfunction • Specific and relative effects on each phase of the sexual response cycle (whether desire, arousal or orgasm are primarily effected) • Severity of symptoms, subjective distress and overall sexual satisfaction • Use a screening instrument or rating scale • Impact on partner or others
5.	**Perform a physical examination:** • Brief general examination to screen for physical signs • Targeted examination of particular systems as informed by the history • Full neurological or urogenital examination if appropriate
6.	**Order special investigations as indicated clinically:** • Exclude or evaluate underlying psychiatric and medical conditions • Endocrine investigations (sex hormone binding globulin, free and total testosterone, prolactin levels, oestradiol, follicle stimulating hormone and luteinizing hormone levels, thyroid function tests) • Other common laboratory measures to screen for (blood glucose, haemoglobin A_{1C} and lipid levels)

1.5.2 Management strategies

Once a problem with sexual function has been identified and determined to be secondary to the effects of an antidepressant there are a number of possible strategies for managing the condition. It is convenient to divide these strategies into three broad categories: conservative or non-pharmacological approaches, changing the antidepressant medication and adjunctive strategies. Any decision about which option to choose, and the decision about whether to do anything at all, should be made in close co-operation with the patient.

1.5.2.1 Conservative, non-pharmacological approaches

In cases when the duration of antidepressant therapy is not expected to be long and the patient is agreeable it may be appropriate to do nothing. Furthermore, a small proportion of patients will elect to live with the sexual problems caused by their antidepressant therapy either because their sexual functioning is better overall than when they were depressed or because of a lack of interest or opportunity for sexual activity. Factors like age, relationship status, personality and a variety of psychosocial factors may also effect the patient's decision. In such cases the decision should be respected. The role of the clinician is to identify and monitor the problem and provide psycho-education regarding treatment options. It should however never be assumed that a person does not need nor want to function better sexually.

The most common approach is to wait and see whether tolerance develops to the side effects. It has been reported that in 42% of cases of AISD the approach used is to await spontaneous remission (71). There is evidence to suggest that this will be an acceptable strategy for a small proportion of patients (111). It has been reported that the spontaneous remission of AISD occurs in approximately 10% of cases and that a further 11% will experience a partial remission (7). However, the majority of patients will find this an unsatisfactory option, particularly if antidepressant therapy is likely to be ongoing. Although it is reasonable to wait and see for a period of time and to monitor for any spontaneous improvement, this approach is often incorrectly used as a way to avoid addressing the problem.

A number of other minimally disruptive strategies have been used to manage AISD. It may be useful try and time the patient's ingestion of medication so that it does not correspond with sexual activity. The term delayed dosing has been used to describe this practice and usually the person will only take their daily dose of antidepressant medication after they have engaged in sexual activity (112). Drug holidays or stopping the medication for short periods particularly when sexual activity is anticipated, may also be useful (113). These two strategies are obviously more likely to be useful with the shorter acting antidepressants, but unfortunately they also carry with them a risk of discontinuation symptoms. Drug holidays are seldom used (71). Dosage reduction can some times be helpful (114). Unfortunately, all three of these strategies are associated with the risk of relapse or recurrence and patients should be warned that depressive or anxiety symptoms could re-emerge. The patient, family and clinician should monitor the mental state carefully when employing these strategies.

Psychotherapeutic interventions may be a further option. Although the main cause of the sexual problem is the antidepressant, it is worth remembering that sexual activity does not take place in a vacuum and that psychosocial factors are almost certainly at play. It may well be useful to employ behavioural and cognitive behavioural techniques, relationship counselling and perhaps a range of other psychotherapies that are the cornerstone of sex therapy. Unfortunately, little is known about the efficacy of these approaches in AISD and further investigation is needed in this area (115). Nevertheless, basic psychosocial interventions should be a part of any management plan and not be left as a last resort, particularly when the risks of changes to medication are high.

1.5.2.2 Changing the antidepressant

Because less invasive strategies may in fact end up being more disruptive than invasive strategies, it is therefore often more logical to switch to a different antidepressant. Generally one would choose an alternative antidepressant that is less associated with the specific sexual difficulty being experienced. Switching to a non-serotonergic antidepressant or to another serotonergic antidepressant that is less associated with sexual problems may be an appropriate strategy for some patients (116). Examples of suggested antidepressants are bupropion, nefazodone, mirtazapine

(112) and reboxetine (117). The sexual side effect profiles of these agents have been described previously. The potential side effects of these drugs should be matched to the patient's clinical condition, physical condition, sensitivity to side effects and experience of sexual dysfunction.

Guidelines produced by the American Psychiatric Association recommend the substitution of antidepressants causing sexual dysfunction with one of these newer drugs in cases where patients complain of sex problems (118). In about 39% of cases physicians manage AISD by changing antidepressant treatment (71).

The drawback of this strategy is that any change of medication is accompanied by risk of relapse or recurrence. The fact that a patient recovered from their depressive or anxiety disorder on one agent is no guarantee that another agent will be as efficacious. There is also no guarantee that the patient will be free of sexual difficulties on the new medication, or that they will not experience some other equally or more distressing side effect. Furthermore, a change to a different antidepressant will simply not be an option for a significant proportion of patients. This may be due to the severity of their past episodes and the risks associated with relapse, a previous history of poor response or intolerable side effects on those agents, or such mundane factors as cost and availability.

1.5.2.3 Adjunctive strategies

Because the above options are of limited usefulness and at best are only viable for a modest percentage of patients suffering from AISD, adjunctive strategies have been enthusiastically pursued. The term adjunctive refers to the use of a second or add-on agent to augment the pharmacological action of the antidepressant. In the case of AISD it is hoped that use of an augmenting agent will modify the side effect profile of the first drug. Unfortunately, adjunctive therapies are rarely proposed to patients (71) and there is a limited amount of clinical trial evidence on their use for this problem (112). Controlled data is lacking and is mostly in the form of case reports and small open label studies. As a result these adjunctive strategies are based mainly on a combination of current understanding of the mechanism of antidepressant action and the neurobiology of the sexual response phenomenon. The decision is often based

more on the anecdotal experience of the treating clinician than any solid evidence base. The use of a number of agents for the pharmacological treatment of AISD has been suggested. They have usually been used anecdotally as augmenting agents to target sexual side effects in cases where patients continue to take their antidepressant therapy.

Dopamine clearly plays an important role in the neurochemistry of the sexual response cycle and several open studies and case reports have suggested the usefulness of agents augmenting dopaminergic neurotransmission as adjunctive therapies. Bupropion, taken either daily (119, 120) or on an as needed basis (121) may be beneficial, particularly for disturbances of orgasm. Doses of between 75 and 150 milligrams (mg) per day in divided doses are recommended for patients on SSRIs or venlafaxine (12). The usual precautions for bupropion should be taken and possible drug interactions considered. Amantadine, a dopaminergic agonist, has been reported to be useful, again for orgasmic dysfunction (122, 123). A dose of 100 mg twice daily has been recommended, but caution is advised in those patients predisposed to psychosis (12). The usefulness of ropinirole has also been suggested (124).

A variety of stimulants including pemoline (18.75 to 75 mg per day), dextroamphetamine (5 to 40 mg per day) and methyphenidate (5 to 40 mg per day) have been reported to be of value (125, 126). However, their use as augmentation strategies is not without its own risks, most notably agitation, insomnia and misuse. Positive effects have been demonstrated on desire, arousal and orgasm in those patients taking SSRIs and venlafaxine.

The cholinergic enhancers bethanechol (10 to 50 mg per day) and neostigmine (50 mg taken one hour before sex or up to 200mg per day in divided doses) have been used with some success for arousal difficulties on antidepressants with anti-cholinergic side effects (12).

Noradrenaline is involved in the sexual response cycle and noradrenergic agents have also been investigated. Yohimbine, a α-2 adrenergic receptor antagonist, was reported to be of use for all phases of the sexual response cycle (127, 104, 128). A dose of

5.4 mg has been suggested, but caution is advised as the agent can exacerbate anxiety and precipitate panic attacks (12).

An open trial of sildenafil reported efficacy in AISD (129). The efficacy of sildenafil for the treatment of AISD has been confirmed in a 6-week, randomised, placebo-controlled trial of 90 men (138) and also for the treatment of ejaculatory delay caused by selective serotonin re-uptake inhibitors or SSRIs (139). A dose of 50 to 100 mg per day is suggested for difficulties with desire, arousal and orgasm (12). The agent is contra-indicated for use with nitrates and the usual precautions should be followed when prescribing sildenafil.

However, it is agents that modify serotoninergic neurotransmission that have the greatest face validity in the treatment of SSRI induced sexual dysfunction. This is not surprising considering the modulatory influence of serotonin in the sexual response cycle and the proposed mechanisms by which serotonergic antidepressants are thought to cause AISD. Cyproheptadine, a $5HT_2$ and histamine antagonist, is perhaps the most widely used agent for this indication, though evidence for its benefits on orgasm are those best documented (130, 131, 132, 133, 134, 135, 136). The recommended dosage range is 4 to 12 mg as required (12). Cyproheptadine useful for the AISD associated with both SSRIs and venlafaxine, but it can be sedating and has been associated with the re-emergence of depressive symptoms. Agents which antagonise $5HT_2$ receptors, such as nefazodone (50 to 150 mg per day), have been shown to be useful as augmentation agents (137). This is in addition to the fact that they appear to be associated with lower levels of sexual dysfunction than SSRI's, when used alone in the treatment of depression. Mirtazapine (15 to 45 mg per day), an antagonist of $5HT_2$, $5HT_3$ and α_1 and α_2 adrenergic receptors, similarly, is associated with lower levels of antidepressant induced sexual dysfunction and may be useful as an augmentation strategy. Both nefazodone and mirtazapine appear to be most useful for orgasmic disturbance (12). The potential risks of using multiple antidepressants in combination should not be overlooked when choosing this option.

Ginkgo biloba has been reported as useful for difficulties with libido, arousal and orgasm at doses between 180 and 240 mg per per day in divided doses (12). However,

negative studies do exist for the treatment of AISD with both Ginkgo biloba (140) and sumatriptan (141).

In a single case report granisetron, an anti-emetic with $5HT_3$ antagonism as its mechanism of action, has been reported as useful in this indication (142). A previous positive open label study (141) has suggested that granisetron may be a promising agent meriting study under double blind conditions. The recommended dose is 1 mg per day as required. Two small negative studies have, however, failed to establish the usefulness of granisetron (143, 144).

In conclusion, and notwithstanding the lack of good evidence-based data, Figure 1.4 outlines a rational approach to the treatment of AISD. The flow diagram represents the author's opinion and clinical experience. It reflects a balance between the existing level of evidence for particular interventions and that intervention's relative tolerability. It is impossible in such a broad guideline to take into account the myriad of individual factors that might impact on the decision as to which intervention is most appropriate for a particular patient. In all instances the use of these strategies should be preceded by a thorough assessment and be individually tailored to the patient's specific needs. A patient's response or failure to respond to an intervention should be actively followed-up by ongoing monitoring.

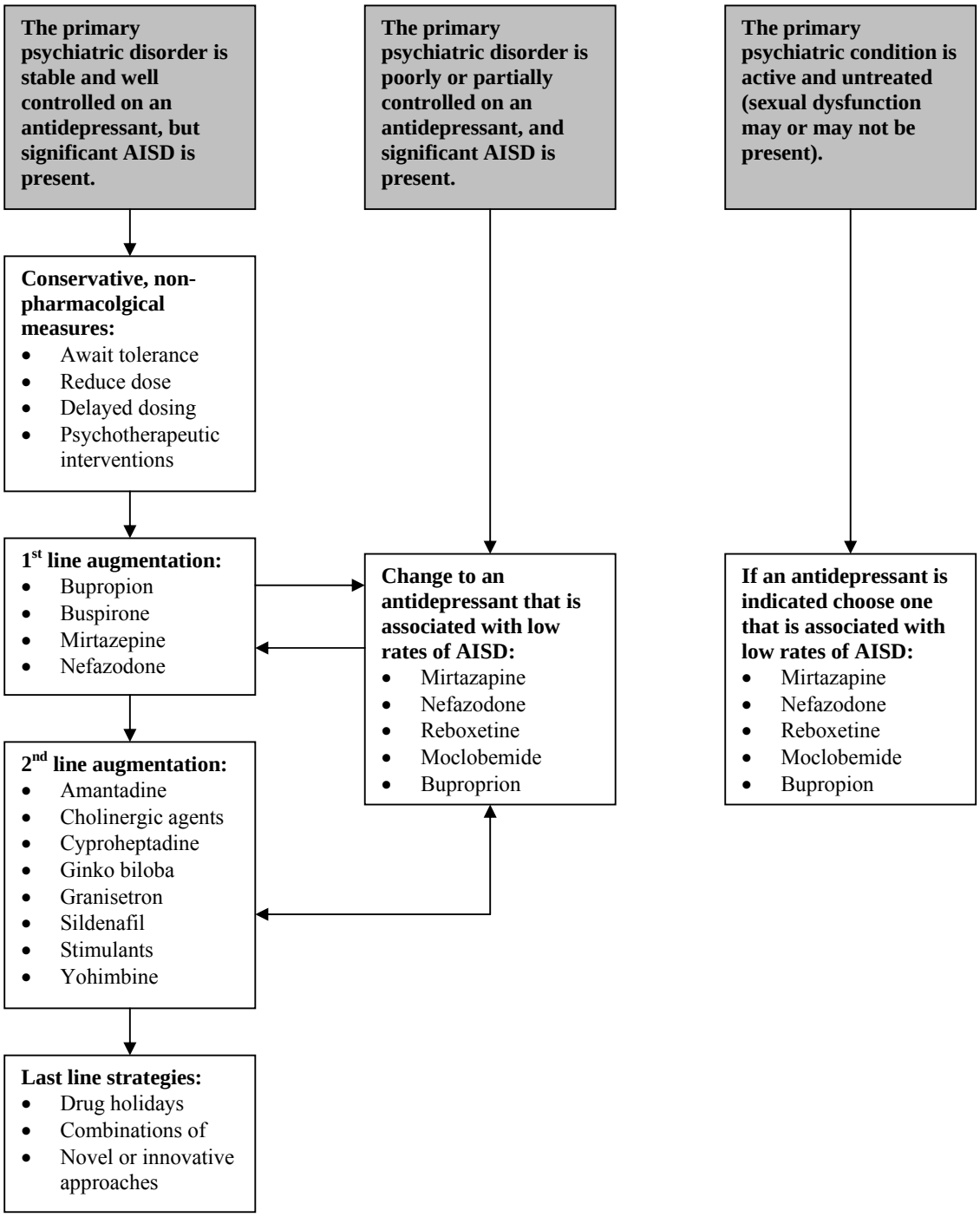


Figure 1.4 Treatment of antidepressant induced sexual dysfunction

1.6 Granisetron

Granisetron is classified as an anti-emetic and anti-vertigo medication (145). It is available in a 3 mg ampoule for intravenous injection, and in an oral 1 mg tablet. The latter will be the preparation used for this trial. The recommended anti-emetic dose is 1 mg twice daily orally. Granisetron is a selective antagonist of $5HT_3$ receptors and has minimal affinity for other serotonin binding sites. It is thought to produce its anti-emetic effect by antagonising $5HT_3$ receptors on abdominal vagal afferents that are stimulated by serotonin released from the gastro-intestinal mucosa when cytostatic agents are administered (146). It also acts on $5HT_3$ receptors in the central nervous system, but this does not appear to contribute significantly to the anti-emetic effect.

Granisetron is considered to be a safe agent. It has been thoroughly evaluated in large volunteer studies (147). Both single and repeated intravenous doses greatly in excess of that which is recommended were well tolerated by healthy volunteers. No serious adverse events were reported. There were no consistent or clinically important cardiovascular effects. Granisetron did not influence the volunteers' mental state, psychomotor performance or electroencephalogram. With repeated administration of doses far in excess of that which would be used clinically, two volunteers developed a transient and self-limiting elevation of alanine transaminase and aspartate transaminase, which may have been produced by granisetron. There was no other evidence of a drug-related effect on clinical chemistry or haematology. The only adverse event that was reported consistently more frequently with granisetron than placebo was constipation. Generally this subsided spontaneously after 24 to 72 hours, and in no case did it necessitate withdrawal from the study or the use of a laxative. Headaches and somnolence have been reported. Minor skin reactions are infrequent. In overdose the predominant symptom is headache. There is no antidote, and management is supportive.

Granisetron exhibits linear kinetics, and is rapidly eliminated (148). It is metabolised in the liver and excreted in the urine and faeces. Present experience indicates that no dosage adjustment is necessary, but usual care should be taken when prescribing it to the elderly or those with hepatic or renal impairment. There is no drug interaction

with benzodiazepines, antipsychotics and anti-ulcer drugs. It does interact with phenobarbitone.

Granisetron's highly selective antagonism of $5HT_3$ receptors in the central nervous system makes it a useful agent with which to block increased serotonergic activity at this receptor.

1.7 Hypothesis and overall aims

The possibility that agents which antagonise $5HT_3$ receptors might counteract the enhanced neurotransmission at that receptor caused by serotonergic antidepressants and thus reduce the sexual side effects of those agents prompted this trial of granisetron. The aim of the study was to assess the efficacy of granisetron as an augmentation strategy for the treatment of AISD in women taking a range of serotonergic antidepressants. Its purpose was to test the hypothesis that granisetron would be more efficacious than placebo for this indication in a randomised controlled trial.

A number of factors contributed toward the development and undertaking of this study.

Firstly, scientific value and benefit. There was considerable interest at that time in the $5HT_3$ receptor as a possible mechanism by which serotonergic antidepressants produced their sexual side effects. Furthermore, the relative roles of the $5HT_3$ and $5HT_2$ receptor in AISD were not as clear as they are now. Whether the outcome of this study demonstrated a significant improvement in sexual dysfunction for granisetron over placebo or not, it was hoped that the mechanism by which serotonergic antidepressants caused sexual dysfunction might be better understood.

Secondly, as discussed previously, current management options for AISD are inadequate and those adjunctive treatment strategies that do exist are not supported by randomised controlled trials. It was thought that a viable and validated augmentation strategy for the treatment of AISD would greatly improve the tools at the clinician's disposal and the quality of life of patients with this problem. Switching strategies

carry an appreciable risk of relapse. The newer antidepressants like nefazodone and mirtazapine are associated with lower, but not altogether insignificant, levels of sexual side effects, and it is often not possible to treat all individuals with these agents. Adjunctive therapies were therefore considered to be of benefit to patients.

Thirdly, it is widely accepted that sexual problems in general and AISD in particular are largely under-reported. It was hoped that the study would highlight the extent of the problem and the necessity for careful screening and treatment.

Furthermore, it appears that there is a significant psychological component to even AISD. This is evidenced by the extent to which a placebo response is observed in trials of this nature. It was therefore anticipated that participants in the trial would not only be safe from harm, but that they would also experience an improvement in their sexual functioning whether they received the active drug or not. There is certainly evidence to suggest that patients often benefit from the close scrutiny their symptoms receive during the course of a clinical trial.

2.0 MATERIALS AND METHODS

2.1 Overview of the research design

The design of this prospective study was that of a randomised double blind, placebo controlled drug trial. Following an initial screening assessment to determine whether they were suitable for the study participants were randomly and consecutively assigned to one or other of the two trial groups. Both the investigator and the participants were blinded as to which group they had been assigned and which medication was being administered. The blind was maintained for the duration of the study and was only broken at its conclusion for the purpose of statistical analysis.

The treatment group received the active drug and the placebo group an inactive placebo preparation. The participants were followed up for a 2-week study period during which time their clinical condition was monitored and changes in their symptoms were objectively measured using three rating scales. An assessment was to be attempted on the day of study termination if the patient withdrew prior to the end of the trial.

2.2 Study group

A total of 12 females aged between 18 and 65 participated in the study. They were recruited from the outpatient psychiatry department at Tara, The H. Moross Centre as well as from three private psychiatric practices in South Africa. In an attempt to keep the sample as homogenous as possible and to avoid the use of different rating scales for male sexual dysfunction, entry to the study was restricted to only females. A clinical diagnosis was made according DSM-IV criteria and a structured clinical interview, the Mini-International Neuropsychiatric Interview (MINI), was done at baseline to confirm the diagnosis.

2.2.1 Inclusion criteria

In order to be included in the study participants had to be experiencing AISD. No specific diagnosis was required for inclusion in the trial, but it was anticipated that the

majority of subjects would be diagnosed with major depressive disorder or one of the anxiety disorders. The presenting symptoms of their psychiatric illness had to be in remission as defined by a Clinical Global Impression (CGI) Severity of Illness sub-scale score of 1 or 2. All participants had to be taking antidepressant maintenance treatment for their psychiatric illness. The range of acceptable antidepressants included any which had serotonergic activity as their predominant mechanism of action. Every woman participating in the trial was required to be using contraception (an oral contraceptive, an implant, an intra-uterine device or the double barrier method) unless she was post-menopausal.

2.2.2 Exclusion criteria

Any participants who had undergone a change in their psychotropic treatment in the last two months were excluded from the study, as were all those with an active, clinically significant Axis I disorder as defined as a CGI Severity of Illness sub-scale score greater than 2. If a comorbid Axis 1 disorder was present it also had to be judged to be in remission. Also excluded were participants who displayed an acute systemic medical disorder or a medical disorder that required frequent changes in medication. Patients with pre-existing cardiac disease were also excluded. Any participants that were unable to comply with either the requirements of informed consent or the treatment protocol were excluded. Patients with a history of sexual dysfunction prior to either the primary illness or treatment were excluded.

2.3 Instruments and measurements

2.3.1 Mini-International Neuropsychiatric Interview

The MINI is a widely used research tool. It was designed as a brief structured interview for the major Axis I disorders in DSM-IV and the International Classification of Diseases and Related Health Problems, 10th edition (ICD-10). Evaluation of the MINI has shown that the tool has acceptably high validation and reliability scores (149). The Clinician Rated (Version 4.4) edition was used for the purposes of this study. The MINI comprises seventeen broad categories of questions that cover a range of psychiatric disorders. It not only makes psychiatric diagnoses

according to DSM-IV criteria, but also provides information on whether these episodes are current or past.

2.3.2 Clinical Global Impression Scale

The CGI is a crude but well-validated tool for assessing the overall severity of psychiatric illness (150). It has been extensively used in numerous clinical and research settings. There are 2 sub-scales to the CGI, both of which were used in this study.

The Severity of Illness sub-scale of the CGI rates the investigator's assessment of the overall severity of the participant's clinical condition at the time of that interview. It provides no longitudinal information. It is also important to note that this assessment referred to the overall severity of the psychiatric condition and not to the severity of sexual dysfunction. The investigator simply scores the participant as the most appropriate of the scale's seven items ranging from "1. Normal, not at all mentally ill" to "7. Among the most severely mentally ill". In this study the severity sub-scale was administered at baseline and all subsequent visits. It was used to exclude participants from the study who had an active clinically significant Axis 1 psychiatric disorder. This was quantified as a CGI severity score of greater than 2. Furthermore, should this score have risen to greater than 2 on any of the subsequent visits then the participant would have been excluded from the study.

The Global Improvement sub-scale of the CGI rates the investigator's assessment of any change in the participants clinical condition compared to the last CGI assessment. It was therefore completed at Visit 2 and Visit 3, but not at baseline (when no previous rating existed). It provides information about change over time. It is again important to note that the CGI global improvement score referred to any change in the participants overall clinical condition and not to their sexual dysfunction, although in reality it could be anticipated that a reduction in sexual dysfunction was likely to result in a global improvement. The investigator scores the participant's global improvement on a 7 item scale ranging from "1. Very much improved" to "7. Very much worse". Should a participant have had a CGI global improvement score of 6 or

more (much worse or very much worse) then they would have been withdrawn from the study.

A copy of the CGI Scale as it was used in this study is provided in Appendix C.

2.3.3 Arizona Sexual Experience Scale

The Arizona Sexual Experience Scale has been validated and widely used in clinical drug trials (151). It includes 6 items, although only 5 of them are relevant to females. The item related to erectile dysfunction was not used in this study which included only female participants. The scale rates a number of aspects of sexual functioning including interest in sex, arousal, orgasm and sexual satisfaction, as well as improvement since the last medication change. It may be used for heterosexual and homosexual populations regardless of the availability of a sexual partner. A global score greater than or equal to 19 or any individual question responses of 5 or more indicate significant sexual dysfunction. The scale may be used to monitor changes in function over time. The investigator administers the scale and the participant's responses are recorded on a 6 point Likeart type scale.

The scale was administered at baseline, day 7 and day 14 of the trial period. It was one of the two primary measures of sexual dysfunction used in the study. It was used in addition to the Feiger Sexual Function and Satisfaction Questionnaire because it covers a range of parameters of sexual function, whereas the Feiger scale focuses mainly on orgasm. A copy of the Arizona Sexual Experience Scale has been included in Appendix D.

2.3.4 Feiger Sexual Function and Satisfaction Questionnaire

The Feiger Sexual Function and Satisfaction Questionnaire has also been validated and wide used (152). It also comprises 6 items that include enjoyment and overall satisfaction, but focus predominantly on the participant's experience of and ability to achieve orgasm. The investigator administers the scale and the participant's responses are recorded on a 4 or 5 point Likeart type scale.

The scale was administered at baseline, day 7 and day 14 of the trial period. It was one of the 2 primary measures of sexual dysfunction used in the study. A copy of the Feiger Sexual Function and Satisfaction Questionnaire is included in Appendix E.

2.4 The study procedure

The study procedure is outlined in the schedule of visits included in Figure 2.1; it is slightly modified from the one that was included in each participant's clinical research file.

2.4.1 Screening assessment

Each potential participant referred to the investigator underwent an initial screening visit to determine whether they were suitable to participate in the trial. If they did appear suitable they received extensive education regarding the study and their right not to be involved. If they were willing to participate they then signed the Information and Consent Form to give their written informed consent. They were provided with a copy of the Information and Consent Form, which is also included in Appendix C. Once they had signed the consent form some patients progressed immediately to the baseline assessment while others did the baseline assessment on a separate occasion.

2.4.2 Visit 1

The baseline assessment included a semi-structured interview designed by the investigator to gather relevant demographic and clinical data. A copy of this semi-structured interview, the Initial Assessment Form, is included in Appendix D. The MINI, CGI Severity of Illness sub-scale, the Arizona Sexual Experience Scale and the Feiger Sexual Function and Satisfaction Questionnaire were all completed at this vist. The participants were then randomised to receive either granisetron one tablet (1 mg) or placebo at night.

ITEMS TO BE COMPLETED	**VISIT 1** BASELINE DAY 0	**VISIT 2** WEEK 1 DAY 7	**VISIT 3** WEEK 2 DAY 14
Information and Consent Form			
Initial Assessment Form			
Mini-International Neuro-psychiatric Interview (MINI)			
Clinical Global Impression Scale (Severity of Illness)			
Clinical Global Impression Scale (Global Improvement)			
Arizona Sexual Experience Scale			
Feiger Sexual Function and Satisfaction Questionnaire			
Notes: • **Clinical condition** • **Adverse events** • **Medication changes**			

Figure 2.1 Schedule of visits as included in each clinical research file (grey areas indicate that the item is to be completed at that visit)

2.4.3 Visits 2 and 3

All participants underwent a brief unstructured interview to ascertain whether there had been any changes in their clinical condition. They were asked about their compliance with trial medication and if they had taken any additional treatments or changed their psychiatric medication in any way. Information that the patient volunteered regarding their sexual dysfunction was recorded. Subjects were also asked about any side effects or adverse events that they had experienced. This information was recorded in their research file and a brief note of any relevant information was also made in their clinical file.The participants were then rated on both the CGI severity and global improvement sub-scales. The Arizona Sexual Experience Scale and the Feiger Sexual Function and Satisfaction Questionnaire were also completed.

2.5 Statistical analysis

The analysis was performed on data collected from 12 participants, 5 of them in the granisetron group and 7 in the placebo group. In addition to the CGI scores and the two rating scales used to assess sexual dysfunction, the analysis also included descriptive statistics of demographic and clinical data reported as means and standard deviations.

Statistical analysis was performed as placebo versus granisetron. The Kruskal-Wallis Test for non-parametric analysis of variance was used to assess differences in proportion of the means between the two groups. Both total and individual item scores from the rating scales were compared. Absolute changes on the rating scales were calculated by comparing the score at baseline with that at termination. All tests were two-tailed and p values of less than 0.05 were considered to be statistically significant. The power of the analysis was weakened as a result of the low number of participants.

Subjects that had been randomised into the study and subsequently withdrew consent or discontinued participating were included in the statistical analysis. Provided they had undergone the first assessment and had baseline data recorded that last observation was carried forward.

2.6 Ethical aspects

Whenever trial medication is administered to human subjects a question arises as to whether any possible risks to the patient are sufficiently counterbalanced by the anticipated benefits to the patient, the broader community or scientific knowledge. Particularly in clinical drug trials, the safety of the patient is paramount. In the case of this study risk were low. Granisetron is considered a safe and well-tolerated agent with no known serious side effects (147). It is not a new or experimental drug. The anticipated benefits for the participants and the scientific reasons for doing the study have already been discussed at some length.

All participants received extensive education and gave full written informed consent before they were entered into the study. Those who were unwilling or unable to give their written informed consent were excluded from participation. The Committee for Research on Human Subjects of the University of the Witwatersrand approved the study protocol. In addition, permission was obtained from Tara, The H. Moross Centre to conduct the study in its outpatient department.

To protect confidentiality all study material was marked only with the participant's initials and study number. All data was completely de-identified before being entered into an electronic database and only the investigator held a record that could identify the responses of individual participants based on their initials. Their clinical file was marked with a sticker to ensure that any clinician seeing the patient was aware that they were participating in a clinical trial.

Participants were immediately withdrawn from the study if they withdrew their consent, deteriorated or experience distressing adverse effects to the trial medication. The study was conducted in accordance with the Medical Research Council guidelines for medical research.

2.7 Financial aspects

This study was an investigator-initiated research project. The investigator and the Department of Psychiatry at the University of the Witwatersrand were responsible for

the minimal expenses related to conducting the study. GlaxoSmithKline supplied granisetron samples to the investigator at no cost. They did not, however, sponsor any other aspect of the trial.

3.0 RESULTS

3.1 Recruitment and randomisation

During the recruitment phase of the study approximately 40 women were screened for their suitability and approached for their informed consent to participate. Ultimately, only 12 of them were randomised into the trial. Of those 12 women, 5 were randomised to the granisetron group and 7 to the placebo group. There were 2 premature discontinuations, both of which were from the granisetron group. Both the subjects discontinued after they had been randomised but before they had commenced taking any trial medication. The reason given for discontinuation was related to a change in their personal circumstances rather than to the study itself.

3.2 Demographic and clinical variables

All participants were female in accordance with the study protocol that excluded males from the sample. The mean age ± SD of the granisetron group was 43.25 ± 16.82 and that of the placebo group was 33.00 ± 5.29 years. All participants were either married or involved in a long-term relationship at the time that they participated in the trial. Three participants were married in the granisetron group and 5 were married in the placebo group. In the granisetron group 4 participants and in the placebo group 5 participants described themselves as being formally employed. The two groups did not differ significantly at baseline on any of the demographic parameters.

All 12 participants had an Axis I diagnosis of major depressive disorder in remission. In the granisetron group there were no other past or present Axis I disorders diagnosed. In the granisetron group, 3 of the participants had a single comorbid DSM-IV disorder which was in remission on Axis I (generalised anxiety disorder, panic disorder or bulimia nervosa). One participant in the granisetron group and 1 participant in the placebo group were diagnosed with Cluster C personality traits. In all the other participants Axis II disorders were deferred. In terms of comorbid medical conditions, 1 participant in the granisetron group had multiple stable medical conditions (hypercholesterolaemia, hypertension and backache) and 1 participant had

a single stable medical condition (menopause) reflected on Axis III. In the placebo group 2 participants had a single Axis III diagnosis (hypotension and possible temporal lobe epilepsy). No significant abnormalities were found on the physical examinations of any of the women who participated in the trial. Three women in the granisetron group and 2 in the placebo group reported mild to moderate stress levels. The others had nothing recorded on Axis IV. None of the women in either group had a Global Assessment of Functioning (GAF) score rated by the investigator as being less than 80 on Axis V. The mean ± SD GAF score was 92.50 ± 2.89 for the granisetron group and 87.00 ± 6.71 for the placebo group.

The mean period in remission ± SD of Axis I disorders in months was 7.00 ± 3.46 in the granisetron group and 4.8 ± 2.77 in the placebo group. For the granisetron group the mean number of previous episodes was 4.00 ± 4.08 and for the placebo group 4.40 ± 5.18. The mean duration of psychiatric illness in years was 8.75 ± 5.06 for granisetron and 9.40 ± 5.37 for placebo.

All the participants receiving granisetron were on antidepressant treatment with citalopram, although one of those subjects was receiving nefazodone in combination with citalopram. In the placebo group there were 3 participants on citalopram, 3 on fluoxetine and 1 on sertraline. One of those patients on citalopram was also being treated with topiramate. The mean dose in citalopram equivalents was 45.00 ± 12.91 mg for granisetron and 30.00 ± 10.95 mg for placebo. The average duration on current treatment in months was 5.25 ± 1.71 for granisetron and 11.57 ± 12.46 for placebo.

In the granisetron group, 2 patients were on medication other the oral contraceptive pill, 1 on two agents (amiloretic and quertran powder) and the other on just diotroxil. In the placebo group there were 4 subjects on other medication, 1 on spirolina, 1 on acuretic, 1 on clonazepam and 1 on eltroxin, caltrate plus and gluroplex. In terms of contraception, 3 participants were using an oral contraceptive pill, 1 had undergone a tubal ligation and 1 participant in the granisetron group was post-menopausal and was not using any method of contraception or hormone replacement therapy. In the placebo group, 3 participants were on oral contraceptives, 2 were using condoms, 1 had an intra-uterine device and 1 participant was not using any contaception before the trial as her partner had had a vasectomy.

The mean duration of sexual dysfunction in months was 12.25 ± 8.73 for granisetron and 7.71 ± 6.40 for placebo. When asked to describe the specific symptoms of their sexual dysfunction as part of the semi-structured interview one woman in both the granisetron and 2 in the placebo group complained of impairments in all phases of the sexual response cycle. Eleven women complained of a loss of desire and interest in sex (the single exception being in the placebo group). Ten women reported difficulties with orgasm (1 in each group did not). The most common presentation of sexual dysfunction in these women was a combination of lack of desire and difficulties with orgasm (6 in total). Only 4 woman complained of a lack of arousal (2 in the granisetron group and 2 in the placebo group), and this was always in combination with a disturbance of at least one other phase of the sexual response cycle.

There were no statistically significant differences in any of these clinical variables between the 2 groups.

3.3 Mini-International Neuropsychiatric Interview

The MINI confirmed the clinical diagnosis made according to DSM-IV criteria in all cases. In all cases the primary diagnosis was major depressive disorder in remission. Other secondary diagnoses made on the MINI corresponded with those made clinically according to DSM-IV criteria.

3.4 Clinical Global Impression Scale

None of the participants that participated in the study experienced any significant change in their clinical condition as evidenced by their CGI severity and global improvement scores over the 2-week trial period. The mean total change in CGI severity score ± SD was 0.00 ± 0.00 for the granisetron group and 0.00 ± 0.00 for the placebo group. The mean total change in CGI global improvement score ± SD was 0.30 ± 0.50 for the granisetron group and 0.00 ± 0.00 for the placebo group.

There was no significant difference between the CGI severity scores of the granisetron and placebo group at baseline. The mean ± SD CGI severity score at baseline was 1.00 ± 0.00 for the granisetron group and 1.2 ± 0.4 for the placebo

group. There was no significant difference between the CGI severity scores of the granisetron and placebo group at endpoint either. The mean ± SD CGI severity score at baseline was 1.00 ± 0.00 for the granisetron group and 1.20 ± 0.40 for the placebo group. The CGI global improvement scores at endpoint were also not significantly different between the granisetron and placebo groups. The mean ± SD CGI global improvement scores at endpoint were 3.80 ± 0.50 in the granisetron group and 3.70 ± 0.80 in the placebo group.

3.5 Rating scales of sexual dysfunction

3.5.1 Arizona Sexual Experience Scale

On individual items of the Arizona Sexual Experience Scale the following proportion of the 12 participants rated their symptoms of sexual dysfunction as being of moderate or greater severity. Nine (75%), interest in sex, ability to get aroused or excited and ability to achieve orgasm, and 10 (83%), overall sexual satisfaction.

There was no statistically significant difference between the two groups on the mean ± SD baseline total scores of the Arizona Sexual Experience Scale (granisetron group 25.0 ± 3.8; placebo 19.6 ± 9.5). At baseline the total scores ranged from 20 to 28 for the granisetron group and 18 to 30 for the placebo group. All 5 participants in the granisetron group and 6 of the 7 subjects in the placebo group had a score of 5 or greater on at least one item of the Arizona Sexual Experience Scale at baseline. At the endpoint the mean scores between the two groups were also not statistically different on this scale (granisetron 20.3 ± 9.7; placebo 12.4 ± 6.5; p=0.497). The total scores for both groups at the Baseline, Week 1 and Week 2 assessments are illustrated graphically in Figure 3.1.

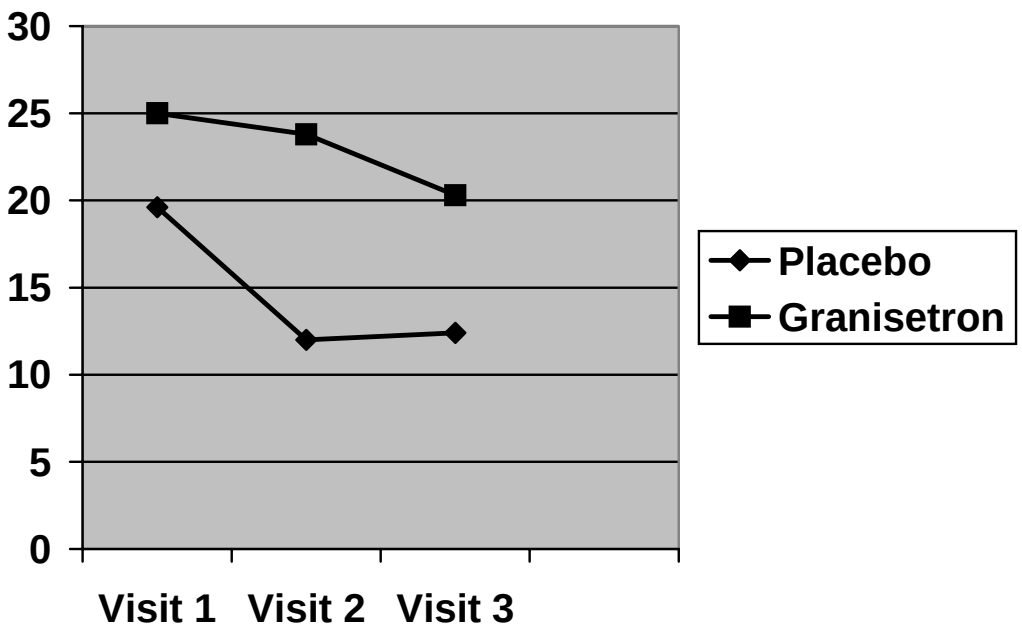


Figure 3.1 Total scores for the Arizona Sexual Experience Scale (at Baseline, Week 1 and Week 2 assessments)

The change in total scores from baseline to endpoint represents an 18.8% reduction (25.0 to 20.3) for the granisetron group and a 36.7% reduction (19.6 to 12.4) for the placebo group. There was also no statistically significant difference between the granisetron group (4.8 ± 7.6) and placebo group (7.1 ± 7.4) in terms of the overall change in total scores over the 2 weeks of the trial. When sub-analyses were performed on the individual items of the Arizona Sexual Experience Scale no significant differences were present on any of these sub-scales.

Descriptive statistics for the change from baseline to endpoint for both the individual items and the total scores are detailed in Table 3.1. This data is presented graphically in Figure 3.2.

Table 3.1 Descriptive statistics for the Arizona Sexual Experience Scale (M indicates Mean, SD indicates Standard Deviation)

	Placebo								Granisetron							
Item	Baseline		Week 1		Week 2		Total change		Baseline		Week 1		Week 2		Total change	
	M	SD	M	SD	M	SD	M	SD	M	SD	M	SD	M	SD	M	SD
1	4.4	1.5	2.9	1.9	2.9	1.7	1.6	1.5	5.5	1.0	5.3	1.0	4.3	2.4	1.3	2.5
2	4.6	1.4	3.0	2.0	2.9	1.7	1.7	1.5	4.8	1.5	4.3	2.1	4.3	2.4	0.5	1.0
3	4.9	1.5	3.3	2.1	3.4	1.9	1.4	1.8	4.8	1.9	4.8	1.5	3.8	2.6	1.0	2.0
4	4.6	1.0	3.1	1.6	3.6	1.3	1.1	1.5	5.8	0.5	5.5	0.6	4.3	2.1	1.5	1.9
5	4.5	1.2	2.8	0.8	2.8	0.8	1.4	1.6	4.3	0.5	4.0	0.0	3.8	0.5	0.5	0.6
Total	19.6	9.5	12.0	6.8	12.4	6.5	7.1	7.4	25.0	3.8	23.8	4.9	20.3	9.7	4.8	7.6

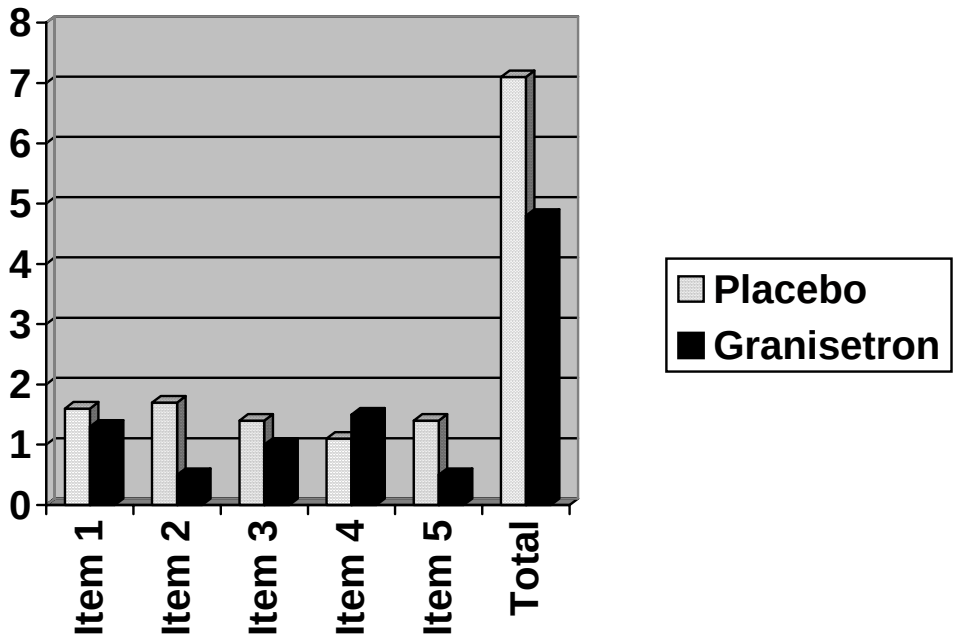


Figure 3.2 Individual items and total change in score at endpoint for the Arizona Sexual Experience Scale

3.5.2 Feiger Sexual Function and Satisfaction Questionnaire

On individual items of the Feiger Sexual Function and Satisfaction Questionnaire the following proportion of patients rated their sexual dysfunction as being of moderate or greater than moderate severity. Six (50%), enjoyment of sex; 11 (91%), overall satisfaction with sex; 8 (66%), difficulty achieving orgasm; 6 (50%), inability to achieve orgasm; 9 (75%), satisfaction with ability to achieve orgasm and satisfaction with intensity of orgasm.

There was no statistically significant difference between the two groups on the mean baseline scores of the Feiger Sexual Function and Satisfaction Questionnaire (granisetron 23.0 ± 4.6; placebo 20.1 ± 4.9). At the endpoint the mean scores between the two groups were also not statistically different on this scale (granisetron 18.0 ± 6.8; placebo 16.4, ± 5.1; p=0.703). The total scores for both groups at the Baseline, Week 1 and Week 2 assessments are illustrated graphically in Figure 3.3.

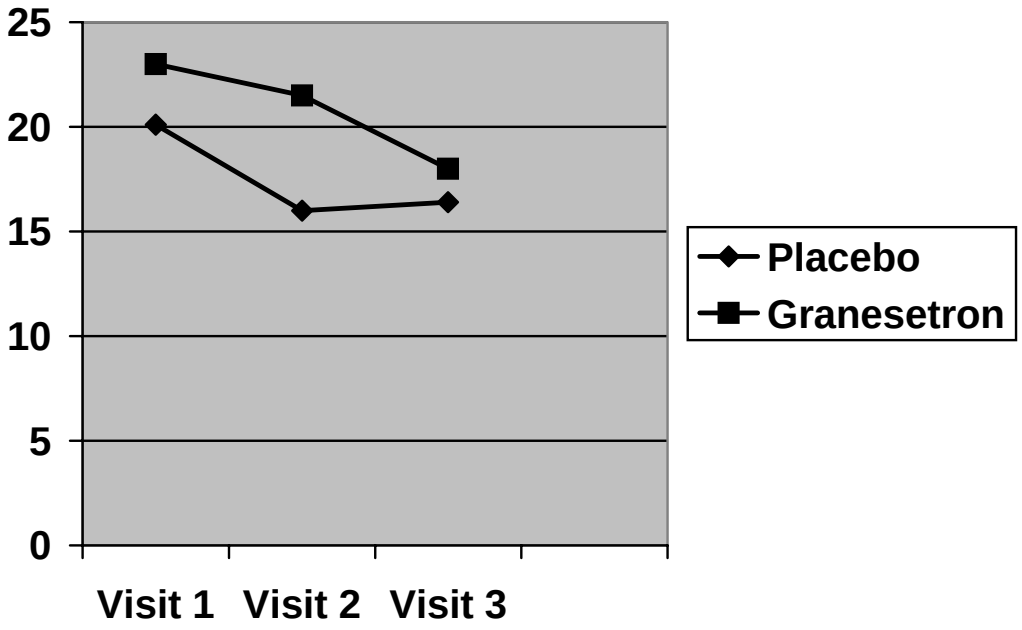


Figure 3.3 Total scores for the Feiger Sexual Function and Satisfaction Questionnaire (at Baseline, Week 1 and Week 2 assessments)

The change in total scores from baseline to endpoint represents a 21.7 reduction (23.0 to 18.0) for the granisetron group and a 18.4% reduction (20.1 to 16.4) for the placebo group. There was also no statistically significant difference between the granisetron group (5.0 ± 7.6) and placebo group (5.1 ± 7.2) in terms of the overall change in total scores over the 2-weeks of the trial. When sub-analyses were performed on the individual items of the Feiger Sexual Function and Satisfaction Questionnaire no significant differences were present on any of these sub-scales.

Descriptive statistics for the change from baseline to endpoint for both the individual items and the total scores are detailed in Table 3.2 and this data is presented graphically in Figure 3.4.

Table 3.2 Descriptive statistics for the Feiger Sexual Function and Satisfaction Questionnaire (M indicates mean, SD indicates standard deviation)

	Placebo								Granisetron							
Item	Baseline		Week 1		Week 2		Total change		Baseline		Week 1		Week 2		Total change	
	M	SD	M	SD	M	SD	M	SD	M	SD	M	SD	M	SD	M	SD
1	2.4	0.8	2.1	0.7	1.9	0.7	0.6	0.8	3.8	0.5	3.3	1.0	3.3	1.0	0.5	1.0
2	4.1	0.9	3.1	1.1	3.1	1.1	1.0	1.0	5.0	0.0	5.0	0.0	4.3	1.0	0.8	1.0
3	4.0	1.4	3.0	1.9	3.4	1.7	0.6	1.4	3.3	2.1	3.0	1.8	2.3	1.9	1.0	2.0
4	3.0	1.9	2.3	1.9	2.6	1.7	0.4	1.5	3.3	2.1	3.0	1.8	2.3	1.9	1.0	2.0
5	3.3	1.3	2.7	1.3	2.7	1.3	0.6	1.0	3.8	0.5	3.5	1.0	3.0	1.2	0.8	1.0
6	3.3	1.3	2.7	1.3	2.7	1.3	0.6	1.0	4.0	0.0	3.8	1.5	3.0	1.2	1.0	1.2
Total	20.1	4.9	16.0	5.1	16.4	5.1	5.1	7.2	23.0	4.4	21.5	4.6	18.0	6.8	5.0	7.6

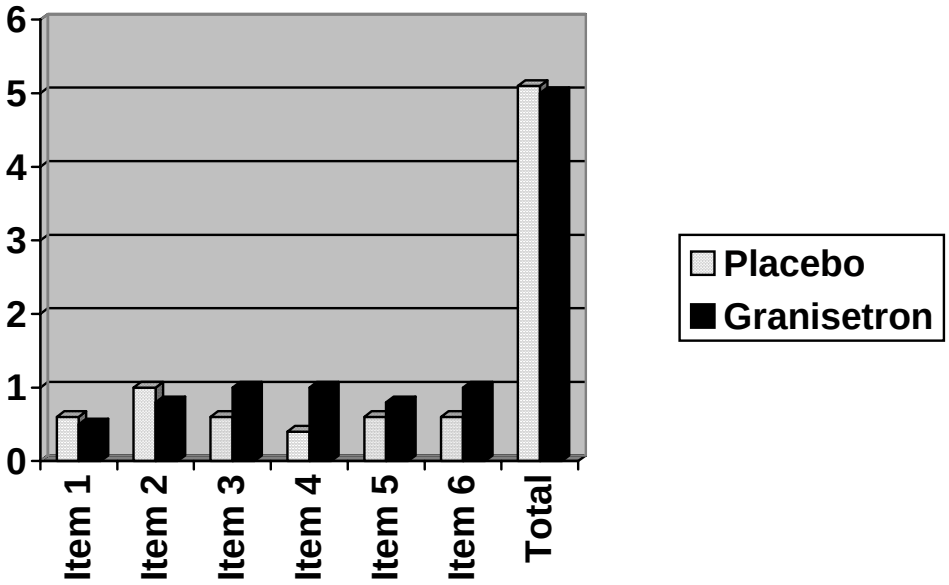


Figure 3.4 Individual items and total change in score at endpoint for the Feiger Sexual Function and Satisfaction Questionnaire

3.6 Discontinuations and adverse events

Other than the two discontinuations which took place after randomisation but before trial medication was commenced there were no further discontinuations during the course of the trial. With regard to treatment emergent adverse events, 3 participants in the granisetron group reported headaches, 2 reported constipation and 1 reported experiencing fatigue. In the placebo group 2 participants reported headaches and 1 developed a breast blister during the two-week period of the trial. They were all described as being of mild severity and in no instance required treatment or discontinuation from the trial. No serious adverse events were reported. There was no statistically significant difference in terms of adverse events between the 2 groups.

4.0 DISCUSSION AND CONCLUSIONS

4.1 Introduction and summary

Sexual dysfunction is a common side effect of treatment of serotonergic antidepressants. The problem has a significant impact on a patient's quality of life and compliance with medication. Given the often long-term nature of depressive and anxiety disorders this obviously has important implications for the prognosis and successful management of these conditions.

This report began by describing the human sexual response cycle and summarising the neurobiological and psychosocial factors that underlie normal sexual function. It then gave an overview of sexual dysfunction generally, sexual dysfunction associated with depression and sexual dysfunction dysfunction associated with antidepressant treatment. The management of AISD was discussed with an emphasis on the biological interventions that are more relevant in the context if this report. It was necessary to describe the trial drug, granisetron, in some detail because its mechanism of action (selective $5HT_3$ antagonism) is central to the rationale for this study.

The hypothesis of the study was that granisetron would prove to be an efficacious augmentation strategy for AISD when investigated under randomised double blind placebo controlled conditions. This hypothesis was based on current thinking at the time that AISD was caused by increased serotonergic activity at $5HT_2$ and $5HT_3$ receptors.

The methods and materials of the study were described and the results of primary and secondary measures reported on. The results of this study were negative in that they did not find granisetron to have efficacy for this indication.

Although the study sample was small and may well have failed to detect a significant difference when in reality a difference was present (a type-2 error), its findings are in keeping with other recent literature. Current thinking favours the role of the $5HT_2$ receptor over the $5HT_3$ receptor in the pathogenesis of AISD.

4.2 Interpretation and relevance of findings

4.2.1 Recruitment and randomisation

Recruitment to the study proved much more difficult than had been anticipated. Forty women were screened and approached for their informed consent to participate. Ultimately, only twelve were randomised into the trial. The most common reason given for not participating was related to the inconvenience of attending the assessments. In addition, a large number of woman who at first appeared suitable for the study were prevented from participating because of one or other of the exclusion criteria. The most troublesome exclusion criteria were those requiring the onset of the sexual dysfunction to be temporally related to commencing the antidepressant and the requirement that there had been no change in their medication over the preceding two months. The vast majority of women screened were determined to be unsuitable before they were approached to sign written informed consent, but a small number who were otherwise both suitable and willing refused to participate when asked to sign the informed consent form. The reason given for this was that although they were willing to try an experimental medication, they felt intimidated by signing a legal document.

Of the 12 women who were randomised into the trial 5 were randomised to the granisetron group and 7 to the placebo group. This difference in numbers arose because of the small sample size and the random allocation of subjects to either the granisetron or placebo groups. The 2 premature discontinuations were due to a change in their personal circumstances or problems unrelated to the study itself.

4.2.2 Demographic and clinical variables

The granisetron and placebo groups were well matched in that there were no significant differences between their demographic variables at baseline. The sample was homogenous in that all participants were female. The variation in mean age (43.25 ± 16.82 versus 33.00 ± 5.29 years), although not significant, may have introduced some bias given that age is a significant factor determining what is considered normal sexual function. It was important to control for the fact that all

participants were either married or involved in a long-term relationship. In order for the instruments to detect changes in sexual function during the 2-week period of the trial the subjects needed to have the opportunity to engage in sexual activity. Employment status was reported in that it was a further indicator of the wellbeing or functional intactness of the sample group.

Clinical variables were also well matched with no significant differences between the granisetron and placebo groups at baseline.

Although participants were always likely to be in remission because of the inclusion criteria, the finding that all 12 of them had a diagnosis of major depressive disorder was somewhat surprising. The relative lack of comorbid anxiety disorders was also unexpected. The use of the MINI in this study validated the clinical diagnosis made by the investigator. Beyond the clinical interview and MINI no formal assessment of personality was completed. If, based on that, the finding that only 1 subject in the granisetron group and 1 subject in the placebo group had significant personality disorder traits, then the undetected presence of personality factors may have introduced a sample bias. Personality is clearly intimately involved in the individual's expression of sexuality and sexual behaviour.

Although there was not any statistical difference in terms of medical comorbidity it is possible in a sample of this size that the presence of even stable medical conditions could have introduced a bias. The participant in the granisetron group with multiple cardiovascular risk factors is of particular concern because of the impact of these factors on sexual functioning. Similarly, the woman in the placebo group with possible temporal lobe epilepsy may have had a medical reason that accounted for her sexual dysfunction. Epilepsy is known to impact on sexual function. The fact that no significant abnormalities were found on the physical examinations of any of the women who participated in the trial supports the contention that they were a generally healthy sample.

The relatively low prevalence of stress reported (5 participants in total reported mild to moderate stress levels) was somewhat surprising. This was most likely associated with the fact that as a group they were, by all indications other than sexual

functioning, stable and well. This was reflected by their GAF scores which were all 80 or above and had a mean ± SD of 92.50 ± 2.89 for the granisetron group and 87.00 ± 6.71 for the placebo group.

The mean period in remission and the mean duration of psychiatric illness in years was similar for both groups. However, the mean number of previous episodes varied more widely in the placebo group, partially as a result of the higher number of participants and small sample (n=7 versus n=5).

The fact that all the participants receiving granisetron were on antidepressant treatment with citalopram whereas in the placebo group the antidepressant agent varied more widely may have introduced a bias in spite of the statistical difference not being significant. Different SSRI's are associated with different reported rates of sexual problems, but these differences are probably not clinically significant. Of more concern was the patient on a combination of citalopram with topiramate for possible temporal lobe epilepsy and the participant who was receiving nefazodone in combination with citalopram. The nefazodone had been used (successfully) to augment a partial response of the patient's depressive symptoms to citalopram; it was not being used as an augmentation strategy for AISD though it is possible that it may have had a beneficial effect on these side effects before entry into the study. The fact that sexual dysfunction was experienced whilst taking nefazodone would tend to suggest this was not significant. The mean dose in citalopram equivalents (45.00 ± 12.91 mg for granisetron and 30.00 ± 10.95 mg for placebo) and the average duration on current treatment (5.25 ± 1.71 months for granisetron and 11.57 ± 12.46 months for placebo) varied between the 2 groups. Although this was not significantly different it is thought that the incidence of AISD rises with the antidepressant dose.

The concurrent use of non-psychiatric medications by women participating in the trial is noted, although the impact of those agents on sexual function is not clear. The use of these medications was evenly distributed between the two groups (2 participants on 3 agents in the granisetron group and 4 participants on 7 agents in the placebo group). However, although quantitatively there was not a statistical difference, qualitatively it was difficult to control for the differential effects of these drugs. Both the oral contraceptive pill and menopause have been associated with hormonal changes that

can effect sexual functioning. It is therefore possible that this was a confounding factor in the 3 participants on oral contraception and the 1 participant who was post-menopausal in the granisetron group, and the 3 participants on oral contraception in the placebo group. This was, however, a difficult variable to control for given the requirements of ethical research and the problems with recruitment. Each woman's position in the menstrual cycle was unfortunately not asked or recorded. There is significant evidence to suggest that the different phases of the sexual response cycle vary according to stage in the menstrual cycle.

The mean duration of sexual dysfunction (12.25 ± 8.73 months for granisetron and 7.71 ± 6.40 months for placebo) was longer than the mean duration on current treatment (5.25 ± 1.71 months for granisetron and 11.57 ± 12.46 months for placebo). This would appear to contradict the exclusion criterion that taking the serotonergic antidepressant should predate the onset of sexual dysfunction; in other words it suggests that there was not a causal link between the two. In reality this statistic is an artefact caused by the way the question about duration on current treatment was phrased in the semi-structured interview done at baseline. This variable refers specifically to the duration on current dose and drug. In fact, every individual in the sample had been on a lower or higher dose of the same antidepressant well before the onset of sexual side effects.

The specific symptoms of sexual dysfunction that the participants reported as part of the semi-structured interview were in keeping with that reflected in the literature. Three women had impairments in all phases of the sexual response cycle, eleven complained of a loss of desire and interest in sex and 10 woman reported difficulties with orgasm. The most common presentation of sexual dysfunction in these women was a combination of lack of desire and difficulties with orgasm while only 4 women complained of a lack of arousal that was always in combination with a disturbance of at least one other phase. This is again in keeping with current literature.

In accordance with the study protocol and inclusion and exclusion criteria, all participants had a CGI severity score of 2 or less. The granisetron and placebo group were also well matched at baseline in terms of the degree of severity or remission of their Axis 1 disorder. The finding that there was no change in CGI severity scores

between baseline and endpoint confirmed that there was no change in the subjects' clinical condition during the trial period. This was confirmed by the CGI global improvement scores that were not significantly different between either baseline and endpoint or granisetron and placebo groups. Participation in the study did not therefore impact on the stability of the participants' psychiatric disorder.

4.2.3 Rating scales of sexual dysfunction

The finding that on the Arizona Sexual Experience Scale 75% of participants rated their interest in sex, ability to get aroused and ability to achieve orgasm as being at least moderately impaired is in keeping with the information obtained in the semi-structured interview and other literature on the subject. That 83% of them reported moderate or greater dissatisfaction with their overall sexual functioning is also significant.

It is interesting that on the individual items of the Feiger Sexual Function and Satisfaction Questionnaire only half rated the impairment in their ability to enjoy sex as being moderate or worse. Moderate or greater difficulty achieving orgasm and complete anorgasmia were reported (66% and 50%), but significantly satisfaction with the ability to achieve orgasm and satisfaction with the intensity of orgasm (75%) were more common. As with the Arizona scale moderate or greater impairment in overall satisfaction with sex was a common complaint (91%).

The lack of any statistically significant differences between the granisetron and placebo groups on the baseline total scores and baseline individual item scores of both rating scales indicates that the 2 groups were evenly matched in terms of the severity and range of their sexual dysfunction. The severity of sexual dysfunction reported in the sample met the requirements for the rating scales to be valid.

The fact that overall change in total scores and the mean scores between the two groups at endpoint is not statistically different on either scale is the pivotal finding of this study. That sub-analyses performed on the individual items of both scales also failed to reveal significant differences is also important for two reasons. First, it

confirms the negative findings and secondly it excludes the possibility that granisetron was superior to placebo for a particular subtype of sexual dysfunction.

On the Feiger scale the reduction from 21.7% (23.0 to 18.0) for granisetron compared with the 18.40% (20.1 to 16.4) reduction for placebo hints at a weak trend towards the superiority of granisetron. However, the 18.8% (25.0 to 20.3) reduction in total scores of the granisetron group compared to the 36.7% (19.6 to 12.4) reduction for the placebo group from baseline to endpoint represents a vivid illustration of the failure of granisetron to show efficacy on the Arizona scale. These results are likely to be a function of the small sample size and a considerable placebo effect. This would be in keeping with research on depressed patients and sexual dysfunction; marked placebo responses are a frequent finding in these studies.

4.2.4 Discontinuations and adverse events

As discussed earlier there were two discontinuations after the participants had been randomised. There is, however, no question of these discontinuations being due to granisetron as neither of them had commenced trial medication at the time that personal circumstances caused them to withdraw their consent. There were no further withdrawals once medication had been started.

The adverse events and new side effects reported in both the granisetron and placebo groups were considered by the participants to be of mild severity. Headaches and constipation are recognised as potential side effects of treatment with granisetron. In this study the 3 participants who reported headaches, the 2 that reported constipation and the 1 who reported fatigue in the treatment group may well have experienced side effects that were causally related to granisetron. However, the incidence of these complaints was not statistically different to that in the placebo group, possibly because of the small sample size. The breast blister experienced by 1 patient in the placebo group did not appear to be related to participation in the trial. No serious adverse events were reported

It therefore seems that both granisetron and placebo were safe and well tolerated within the context of this study. This finding is in keeping with existing data on

granisetron and its benign side effect profile probably lowers the threshold of clinicians for using an adjunctive strategy of doubtful efficacy.

4.3 Strengths and limitations

The strengths of this study lie in its design. Randomised, double blind, placebo controlled trials are considered to deliver the highest level of evidence. The scientific reasoning behind the study and its experimental methodology were sound. At the time this project was conceived the problem of AISD was extremely topical and the deficiency of evidence-based data in the area widely acknowledged. The study was both relevant and conducted according to high ethical standards. This study highlights an unfortunate lack of knowledge regarding the pathogenesis of AISD, as well as the urgent need for better treatment options.

The most serious shortcoming of the study relates to its small sample size and consequently the weakened power of the statistical analysis. A sample of 12 subjects is inadequate to base any definitive conclusions on and the likelihood of a type-2 error is high. However, whilst the study would certainly have been stronger if there had been more participants, its negative outcome is in keeping with other similar negative studies and with current thinking around the relative roles of the $5HT_2$ and $5HT_3$ receptors.

In retrospect it may have been unwise to restrict participation to only female subjects. Although this restriction simplified the assessment of gender specific sexual dysfunction and averted the use of different rating scales for men and woman, the cost of a homogenous sample was that it unfortunately halved the number of potential subjects available for recruitment. The net result of this was that the difficulties with recruitment and the small sample size offset the gains made in terms of being able to generalise the result to all females with AISD. Attempts to extend recruitment to a number of private practice settings also met with limited success. Interestingly, during the course of recruiting to this study it appeared that men were far more likely to complain about their sexual difficulties and express an interest in participating than were woman.

It is possible that the 2-week duration of the trial was too short a period for statistically significant differences to emerge between the treatment and placebo groups. Unfortunately, the length of the trial was restricted to a certain extent by financial constraints and the cost of the trial medication involved. Furthermore, a previous open label study which suggested that granisetron was of benefit in AISD did so when the agent was used not only for less than 2 weeks but also when it was used on an as required basis.

Another potential problem common to many studies of this nature is that it may not have adequately controlled for certain unavoidable confounding variables. For example, although participants with pre-existing sexual dysfunction were excluded from the study, this piece of information relied solely on the subject's recollection and subjective report. It would have been very difficult to quantify and hence control for any number of other potentially confounding psychosocial variables. However, given that psychological and social factors are inevitably also determinants of sexual functioning, the study should have perhaps taken greater cognisance of each individual subject's personality structure and current life and relationship circumstances. It is quite possible in a sample this small that these factors could have affected the measured improvements in sexual function.

4.4 Conclusions and recommendations

The results of this study do not support the use of granisetron as an adjunctive strategy for the treatment of AISD in women taking serotonergic antidepressants. Furthermore, the results of this trial do not support a primary role for the $5HT_3$ receptor in the aetiology of AISD.

It has not been conclusively proven that granisetron has no usefulness in the treatment of AISD. Anecdotal reports of positive responses to adjunctive treatment of AISD with granisetron continue to arise from time to time. However, anecdotal reports are often conflicting, and that is after all the reason why such matters are tested in randomised placebo controlled trials. The outcomes of several admittedly limited studies of this nature have not supported the efficacy of granisetron for this indication.

Furthermore, although a role for the $5HT_3$ receptor has not been conclusively excluded, the focus of research subsequent to the initiation of this study has shifted away from the $5HT_3$ receptor. It appears that the $5HT_2$ receptor is a much more plausible mediator of the sexual dysfunction caused by antidepressants with serotonergic activity. Perhaps the strongest indication of the role of the $5HT_2$ receptor is provided the newer antidepressants mirtazepine and nefazodone which have a much lower incidence of sexual dysfunction associated with their use. Both of these agents have strong antagonistic activity at the $5HT_2$ receptor.

Although a definitive randomised study that addresses the limitations of this and other similar work would be desirable to conclusively discount the usefulness of granisetron and the role of the $5HT_3$ receptor, the weight of evidence does not suggest this should be a priority. It is likely that solutions to the problem of AISD and theories as to their cause lie elsewhere. Further research should aim to further clarify the role of the $5HT_2$ receptor and its subtypes, possibly using selective $5HT_2$ receptor antagonists in randomised double blind placebo controlled conditions. The emphasis of further research in this area will probably look more closely at the development of new generation antidepressants with highly selective receptor activity and a lower association with sexual problems. As is the case with the sexual dysfunction associated with depression, sexual dysfunction generally and even normal sexual functioning, AISD is probably related to not only multiple pharmacological and physiological factors, but to a myriad of psychosocial factors too.

It should be stressed that clinicians are still not screening adequately for and assessing AISD. Furthermore, they are a long way from having a comprehensive range of effective evidence-based management options for the problem. The area is most definitely still worthy of further research as the problem represents a major obstacle to the effective treatment of anxiety disorders and depressive illnesses. The impact of sexual dysfunction on the quality of life of patients taking antidepressants and their families cannot easily be quantified and should not be underestimated.

INFORMATION AND CONSENT FORM

A double blind placebo controlled study of granisetron in antidepressant induced sexual dysfunction.

My name is Dr Sean Jespersen. I am a psychiatrist from the Department of Psychiatry at the University of the Witwatersrand. This study is a research project on people who develop sexual side effects while they are being treated with antidepressants. Currently, there are no widely accepted treatments for this problem. The sexual side effects of antidepressants include diminished sex-drive and difficulty attaining orgasm. I would be most grateful for your participation in this study.

Taking part in the study involves you taking one tablet a day for two weeks. The tablet that you receive may be either granisetron (Kytril) or a dummy medication (a placebo). Neither you nor I will know which you are taking. You will be asked to visit me three times during the course of the two-week period you are involved in the study.

Kytril is a medication registered for the treatment of nausea and vomiting. It is considered safe and has few side effects of its own. The most common side effects are headache and constipation. There is reason to believe that Kytril may relieve the problems with sexual functioning that are associated with taking antidepressants. It blocks a particular type of receptor in the brain that is thought to be a part of the reason why antidepressants cause sexual side effects.

The aim of the study is to better understand antidepressant induced sexual dysfunction and to develop better treatments for the problem. Your participation in the study is voluntary and you are free to refuse to participate or withdraw your consent at any time. If you refuse to participate you will not be disadvantaged in any way. The results of the study will be strictly confidential and only your initials and study number will be used. There will be no costs to you to participate.

Your help with the project is much appreciated.

Please sign below to acknowledge that you consent to participate in the study having read the INFORMATION AND CONSENT FORM and having understood the implications of your participation.

Signature of participant:

Name: Date:

Signature of witness:

Name: Date:

APPENDIX B Initial Assessment Form

INITIAL ASSESSMENT FORM Date:

1. Demographic data

Initials: Kit / study number:

Age: Gender:

Marital status: Employment:

2. Multi-axial diagnosis

Axis I:

Axis II:

Axis III:

Axis IV:

Axis V:

3. Psychiatric history

Period in remission:

Number of previous episodes:

Duration of psychiatric illness

4. Medication

Current psychiatric medication:

Duration on current psychiatric medication:

Other current medication:

Allergies:

5. Sexual history

Symptoms of sexual dysfunction:

Duration of sexual dysfunction:

Contraception:

6. Physical examination

7. Exclusion criteria (exclude participant if any of the following are "NO")

Written informed consent has been signed: YES / NO

The subject is able to give informed consent and comply with the protocol: YES / NO

The woman is on contraception: YES / NO

There has been no change of psychotropic medication in the last 2 months: YES / NO

CGI score is 1 or 2: YES / NO

Any comorbid Axis I disorder is in remission: YES / NO

Any medical illness is stable: YES / NO

There is no history of cardiac disease: YES / NO

The sexual dysfunction is temporally related to the antidepressant: YES / NO

Signed: Date:

APPENDIX C Clinical Global Impression Scale

CLINICAL GLOBAL IMPRESSION SCALE			
Severity of Illness To be completed at Visits 1, 2 and 3. Record the participant's response in the appropriate column.	**Visit 1** **Baseline** **Day 0**	**Visit 2** **Week 1** **Day 7**	**Visit 3** **Week 2** **Day 14**
1. Normal, not at all mentally ill 2. Borderline mentally ill 3. Mildly mentally ill 4. Moderately mentally ill 5. Markedly mentally ill 6. Severely mentally ill 7. Among the most severely mentally ill			
Global Improvement To be completed at Visits 2 and 3. Record the participant's response in the appropriate column.	**Visit 1** **Baseline** **Day 0**	**Visit 2** **Week 1** **Day 7**	**Visit 3** **Week 2** **Day 14**
1. Very much improved 2. Much improved 3. Minimally improved 4. No change 5. Minimally worse 6. Much worse 7. Very much worse			

APPENDIX D Arizona Sexual Experience Scale

ARIZONA SEXUAL EXPERIENCE SCALE (FEMALES)			
To be completed at Visit 1, 2 and 3. Record the participant's response in the appropriate column.	**Visit 1 Baseline Day 0**	**Visit 2 Week 1 Day 7**	**Visit 3 Week 2 Day 14**
How has your interest in sex been over the past week? 1 = Greater than normal 2 = Normal 3 = Minimally diminished 4 = Moderately diminished 5 = Markedly diminished 6 = Totally absent			
How has your ability to get sexually aroused or excited been over the past week? 1 = Greater than normal 2 = Normal 3 = Minimally diminished 4 = Moderately diminished 5 = Markedly diminished 6 = Totally absent			
How has your ability to achieve orgasm been over the past week? 1 = Greater than normal 2 = Normal 3 = Minimally diminished 4 = Moderately diminished 5 = Markedly diminished 6 = Totally absent			
How would you rate your overall sexual satisfaction? 1 = Greater than normal 2 = Normal 3 = Minimally diminished 4 = Moderately diminished 5 = Markedly diminished 6 = Totally absent			
How would you rate your overall improvement since your last medication change? 1 = Very much improved 2 = Much improved 3 = Minimally improved 4 = Unchanged 5 = Minimally worse 6 = Much worse			

APPENDIX E Feiger Sexual Function and Satisfaction Questionnaire

FEIGER SEXUAL FUNCTION AND SATISFACTION QUESTIONNAIRE (FEMALES)			
To be completed at Visit 1, 2 and 3. Record the participant's response in the appropriate column.	**Visit 1 Baseline Day 0**	**Visit 1 Week 1 Day 7**	**Visit 1 Week 2 Day14**
How would you describe your ability to enjoy sex during the past week? 1 = Fully enjoyed 2 = Sometimes enjoyed 3 = Rarely enjoyed 4 = Never enjoyed			
Overall, how satisfied were you with your sexual function during the past week? 1 = Completely 2 = Highly 3 = Moderately 4 = Slightly 5 = Not at all			
How often did you have difficulty achieving orgasm during the past week? 1 = Rarely or never 2 = Occasionally 3 = Frequently 4 = Usually 5 = Always			
How often were you unable to reach orgasm during the past week? 1 = Rarely or never 2 = Occasionally 3 = Frequently 4 = Usually 5 = Always			
How satisfied were you with your ability to achieve orgasm during the past week? 1 = Highly 2 = Moderately 3 = Slightly 4 = Not at all			
How satisfied were you with the intensity of your orgasm during the past week? 1 = Highly 2 = Moderately 3 = Slightly 4 = Not at all			

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