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THE UNIVERSITY OF SOUTHAMPTON

Antidepressant drugs and sexual dysfunction

Two volumes

Volume 1

David Stewart Baldwin
MB BS FRCPsych

Thesis submitted for the degree of Doctor of Medicine

University Department of Mental Health
School of Medicine
Faculty of Medicine, Health and Life Sciences

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ABSTRACT

FACULTY OF MEDICINE, HEATH AND LIFE SCIENCES
MENTAL HEALTH

Doctor of Medicine

ANTIDEPRESSANT DRUGS AND SEXUAL DYSFUNCTION

by David Stewart Baldwin

Epidemiological studies indicate that depression is associated with impairments in sexual function and satisfaction, and the results of placebo-controlled randomised trials indicate that antidepressant drugs can be associated with the development of sexual dysfunction. Certain classes of antidepressants may associated with greater risks of developing treatment-emergent sexual dysfunction, but many previous investigations have methodological flaws that reduce the confidence which can be placed in the study findings.

This thesis describes a series of investigations that examined the relationships between depressive illness, antidepressant treatment, and sexual dysfunction, conducted between 1997 and 2003, involving over 1100 patients. A point prevalence study in 83 secondary care patients taking antidepressant drugs found that sexual dysfunction was reported by 75% of the sample.

A double-blind randomised controlled trial comparing the selective serotonin re-uptake inhibitor (SSRI) paroxetine with the 5-HT_2 antagonist nefazodone, in the acute and continuation treatment of patients with DSM-III-R major depression (n=108) showed the two antidepressants had similar overall efficacy, but nefazodone was associated with significantly greater improvements in genital symptoms.

A second double-blind randomised controlled trial comparing paroxetine with a serotonin-noradrenaline re-uptake inhibitor in the acute treatment of patients with DSM-IV major depression (n=303) showed the two antidepressants had similar overall efficacy, but had significantly different effects on genital symptoms and on particular items on the sexual function questionnaire, developed for use in the point prevalence study.

A third double-blind randomised controlled trial comparing paroxetine with the selective noradrenaline re-uptake inhibitor reboxetine in the acute treatment of patients with DSM-IV major depression (n=70) again found that the two antidepressants had similar efficacy, but with significantly different effects on sexual function, as assessed by the visual analogue items of the Rush Sexual Inventory.

A fourth double-blind randomised controlled trial comparing paroxetine with the more selective SSRI escitalopram in the acute and continuation treatment of patients with DSM-IV major depression (n=323) found no difference in overall efficacy, or effects on sexual function, assessed by the Arizona Sexual Experiences Scale (ASEX).

There is at present no consensus on the best approach to management of patients with sexual dysfunction associated with antidepressant treatment. A randomised placebo-controlled augmentation study with the 5-HT_{1A} and 5-HT_{1D} agonist CEB-1555 in 289 remitted depressed patients with sexual dysfunction associated with treatment with two SSRIs (fluoxetine or paroxetine) found no significant advantage for the investigational compound in relieving sexual dysfunction, assessed by the ASEX.

A five-year follow-up study in patients who participated in the point prevalence study (n=48) found that sexual dysfunction persisted in most patients, emphasizing the need for further research into the development of treatment approaches to sexual dysfunction in this patient group.

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PREFACE

As with many research projects, the idea of investigating the relationships between depression, antidepressant treatment and sexual dysfunction arose during the management of a single patient, when I treated a young depressed woman with the selective serotonin reuptake inhibitor (SSRI) paroxetine in the early part of 1992. She made a good response to treatment, but complained that the drug had made it impossible for her to achieve orgasm.

The clinical trial databases for paroxetine and the other available SSRIs (fluoxetine, fluvoxamine and sertraline) indicated that sexual dysfunction could occur during treatment, but this was an uncommon event. Whenever appropriate, I had previously asked my patients about possible loss of sexual interest, as a symptom that might support the diagnosis of depression; I then started to ask my patients whether they experienced worsened sexual problems during antidepressant treatment, and found that this occurred in a substantial minority. My developing interest led to my first publications on this subject (Baldwin, 1995; Baldwin and Thomas, 1996).

At that time, it was clear that the incidence of sexual dysfunction reported as a treatment-emergent adverse effect during randomised controlled trials bore little relationship to the incidence of sexual dysfunction seen during antidepressant treatment in routine clinical practice. It was also clear that doctors and patients found it hard to discuss sexual problems in depression and during antidepressant treatment. As President of the national self-help organisation Depression Alliance, I thought it would be interesting to write a public education leaflet on this subject, and '*Depression and Your Sex Life*' (which included a checklist that could be completed by patients prior to seeing their doctors, to facilitate discussion of a sensitive subject) was published in 1996. Chapter 1 of this thesis reviews the epidemiology of sexual dysfunction in the general population and in samples of depressed patients, and summarises studies that have examined the effects of antidepressant drugs on sexual function.

In the same year, the results of the acute treatment phase of a double-blind randomised controlled trial comparing paroxetine with the novel antidepressant drug nefazodone became available (Baldwin *et al*, 1996). The clinical trial database for nefazodone (a drug with both SSRI and 5-HT_2 receptor antagonist properties) had indicated that nefazodone was associated with a relatively low incidence of treatment-emergent sexual dysfunction, compared to other antidepressants (Baldwin, 1996), supporting the observation of pre-clinical studies that indicated that drugs with 5-HT_2 receptor antagonist properties had facilitatory effects on sexual behaviour, in some animal models. However, there was no difference between paroxetine and nefazodone in the reported incidence of sexual problems during double-blind treatment in this study. Having published the results of the continuation phase of the study (Baldwin *et al*, 2001), I then reviewed the data relating to scores on the genital symptoms item (item 14) of the

Hamilton Rating Scale for Depression (HAM-D) in those patients who entered both the acute and continuation phases of double-blind treatment, to examine how genital symptoms changed over time, with the two drugs, the results being described in chapter 2.

Having embarked upon an examination of the point prevalence of sexual problems among patients taking antidepressant drugs and attending my outpatient clinic, using a modified version of the checklist in the Depression Alliance leaflet, I was struck by the many possible factors that could affect sexual function adversely, these being considered in chapter 3. It was clear that more research was needed into the effects of antidepressants on sexual function, with the use of detailed questionnaires and scale both before and during antidepressant treatment.

My deepening interest in this subject happily coincided with the development of further antidepressant drugs which were expected to have fewer adverse effects on sexual function than the SSRIs. I was interested to know whether drugs with noradrenaline or combined noradrenaline-serotonin re-uptake inhibitory properties might produce less adverse effects on sexual function than the SSRI paroxetine, and was also interested to examine whether greater selectivity for serotonin re-uptake was beneficial or detrimental.

Through discussions with a number of pharmaceutical companies, I was able to influence the incorporation of measures of sexual function and satisfaction in a series of industry-supported double-blind randomised controlled trials of the treatment of patients with major depression. In most patients genital symptoms (as assessed by item 14 of the HAM-D) improved as depression lifted. There were significant differences in the effects on sexual function (as assessed by specific rating scales) between compounds with varying pharmacological properties, despite similar overall antidepressant efficacy, but the clinical significance of these differences is uncertain. The design and results of these three separate studies are reported in chapters 4, 5, and 6.

Many treatment strategies have been proposed for the management of patients with sexual dysfunction associated with antidepressant treatment, but no approach is ideal. Based on the results of a placebo-controlled augmentation study of the 5-HT_{1A} agonist buspirone, and the encouraging results of pre-clinical studies, I then helped with the design and execution of a placebo-controlled augmentation study of an investigational compound with this property (CEB-1555) in remitted depressed patients with sexual dysfunction associated with treatment with paroxetine or another SSRI, fluoxetine. The results of this study are reported in chapter 7.

A follow-up study of the patients who had participated in the original prevalence study found that most patients remained troubled by sexual difficulties, despite changes in psychiatric diagnosis and

psychotropic drug treatment. The results of the follow-up study are presented in chapter 8, and support the need for further research into the course and treatment of sexual function associated with depression and antidepressant treatment.

ACKNOWLEDGEMENTS

I wish to acknowledge the considerable support and interest of my two supervisors, Professor Chris Thompson (School of Medicine, University of Southampton) and Professor Dinesh Bhugra (Institute of Psychiatry, London); both provided many insightful and helpful comments on the development of this thesis. I am also grateful to Professor Stuart Montgomery (Imperial College, London) and Professor Malcolm Lader (Institute of Psychiatry, London) for their encouragement and gentle cajoling, over the course of six years. The treatment studies reported within this thesis include a total of almost 1200 patients, recruited by doctors at many study sites, and I wish to acknowledge the joint contribution they have all made in furthering knowledge in this area.

The studies described in most of the chapters in this thesis necessarily involved collaboration with colleagues both within and outside the University of Southampton. Dr Karen Mellors of the pharmaceutical company Bristol-Myers Squibb was helpful in providing me with raw data from the randomised controlled trial described within chapter 2. Mr Jon Birtwistle was much involved in data collection and entry during the point prevalence study reported in chapter 3. Dr Emmanuelle Weiller was instrumental in providing me with raw data from the randomised controlled trial described within chapter 4. Dr Simon Dando and Dr Kevin Bridgman of the pharmaceutical company Pharmacia Ltd kindly arranged for me to receive raw data from the acute treatment study described within chapter 5. Dr James Cooper of the pharmaceutical company Lundbeck Ltd was a valued colleague in helping design the study and providing data from the randomised controlled trial reported in chapter 6. The placebo-controlled augmentation study described in chapter 7 was made possible through active collaboration with Dr John Hutchison, Mr Jason Mann and Dr Andy Smithers. Mrs Anna Lambert was responsible for much of the data collection during the follow-up study described within Chapter 8.

The University of Southampton received funding from Bristol-Myers Squibb, Pharmacia Ltd, and Lundbeck Ltd in recognition of the time involved in my participation in the design, execution and analysis of the randomised controlled trials described in chapters 2, 5, and 6. Similar grants were made to the University from other companies, in recognition of the time involved in study design and data analysis in the randomised controlled trials described in chapters 4 and 7.

My mother and father have been constant and reassuring figures through troubled times in the last six years. My children Susannah and Oliver had to put up with much paternal grumpiness whilst not really understanding why. Throughout the period of research and writing, Dr Julia Sinclair has provided boundless loving inspiration, for which I am and always will be grateful.

AUTHOR'S DECLARATION

The work that forms the basis of this thesis was carried out in the University of Southampton, Faculty of Medicine, Health and Life Sciences, School of Medicine, University Department of Mental Health (Professor Robert Peveler). This work was done mainly whilst in registered postgraduate candidature. Although some of the work was done jointly with others, the vast majority is my original work. None of the material within the thesis has been submitted for another degree.

The text, tables, figures and references amount to a total of 66,600 words.

David Stewart Baldwin
MB BS FRCPsych

CHAPTER 1: REVIEW OF ANTIDEPRESSANT DRUGS AND SEXUAL DYSFUNCTION

The overall aim of this chapter is to provide an introduction to the literature on sexual function in patients with depressive disorders. It starts with an overview of the two main classifications of sexual problems, and continues with a review of the literature on the epidemiology of sexual dysfunction. It then reviews the literature on the epidemiology of sexual dysfunction in depressed patients, and highlights methodological problems inherent in conducting research in the area. After this, it provides an introduction to the physiology of male and female sexual behaviour. This is followed by an account of the adverse effects of antidepressant drugs on sexual function and satisfaction (including comments on their use in premature ejaculation), and a review of the strategies employed in the management of patients with sexual dysfunction associated with antidepressant treatment. This is followed by an introduction to the methods employed to investigate patients with sexual difficulties. The chapter concludes with an overview of the pharmacological properties of the antidepressant and investigational drugs examined in treatment studies described in subsequent chapters. Previous publications have provided an account of some of these areas (e.g. Baldwin *et al*, 1997; Baldwin, 2001; Baldwin and Mayers, 2003): where necessary, these accounts have been developed and updated within this chapter.

CLASSIFICATION OF SEXUAL DYSFUNCTION

The normal human sexual response cycle is divided conventionally into four phases, described briefly below. Disorders of the sexual response can occur at one or more phase.

1. *Desire.* Typically this consists of fantasies about, and the desire to have, sexual activity.
2. *Excitement.* The subjective sense of sexual pleasure and accompanying physiological changes, namely penile tumescence and erection in men; and pelvic congestion, swelling of the external genitalia, and vaginal lubrication and expansion in women.
3. *Orgasm.* Sexual pleasure peaks, with release of sexual tension and rhythmic contraction of the perineal muscles and reproductive organs. In men, the sensation of ejaculatory inevitability is followed by ejaculation of semen. In women, contractions of the outer third of the vaginal wall occur.
4. *Resolution.* The sense of muscular relaxation and general well-being. Men are physiologically refractory to erection and orgasm for a variable period, whereas women may be able to respond to further stimulation.

The two main classifications of sexual dysfunction are those provided by the World Health Organisation and the American Psychiatric Association. Both distinguish sexual dysfunction from gender identity disorders and paraphilias. The tenth edition of the *International Classification of Mental and Behavioural Disorders* (ICD-10) (World Health Organisation, 1992) uses the term 'sexual dysfunction' to cover the

ways in which an individual is unable to participate in a sexual relationship as he or she would wish. The disturbance must occur frequently, and persist for at least six months. The ICD-10 classification of sexual dysfunction, not caused by organic disorder or disease is listed below. Examples of the diagnostic criteria for ICD-10 defined sexual dysfunctions are provided in Appendix 1.1.

F52.0 lack or loss of sexual desire
F52.1 sexual aversion and lack of sexual enjoyment
F52.2 failure of genital response
F52.3 orgasmic dysfunction
F52.4 premature ejaculation
F52.5 non-organic vaginismus
F52.6 non-organic dyspareunia
F52.7 excessive sexual drive
F52.8 other sexual dysfunction, not caused by organic disorder or disease
F52.9 unspecified sexual dysfunction, not caused by organic disorder or disease

The fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) (American Psychiatric Association, 1994) describes sexual dysfunction as a disturbance in sexual desire and in the psychophysiological changes that characterise the normal sexual response cycle, that causes marked personal distress and interpersonal difficulty. The DSM-IV classificatory scheme is shown below.

Sexual desire disorders
302.71 Hypoactive sexual desire disorder
302.79 Sexual aversion disorder
Sexual arousal disorders
302.73 Female sexual arousal disorder
302.73 Male erectile disorder
Orgasmic disorders
302.73 Female orgasmic disorder
302.74 Male orgasmic disorder
302.75 Premature ejaculation
Sexual pain disorders
302.76 Dyspareunia
306.51 Vaginismus
Other disorders
Sexual dysfunction due to a general medical condition
(coded 625.8, 608.89, 607.84, 625.0, 608.89, 625.8, 608.89)

Substance-induced sexual dysfunction
(coded 291.8 [alcohol] or 292.89 [amphetamine, cocaine, opioids, sedatives, etc.])
302.70 Sexual dysfunction not otherwise specified

According to the DSM-IV, sexual dysfunction can be categorised further into various sub-types. These are whether the dysfunction is lifelong or acquired; whether it is generalised or situational; whether it is due psychological factors; and whether it is due to combined (i.e. psychological and biological) factors. Simplified examples of the diagnostic criteria for some forms of DSM-IV defined sexual dysfunction are provided in Appendix 1.2.

Although the DSM-IV approach appears rigidly operationalised, there is some scope for exercising clinical judgement. For example, when considering the diagnosis of hypoactive sexual desire disorder, the judgement of deficiency or absence of desire need to take account of factors that affect sexual functioning such as age and the personal context. Similarly, the diagnosis of female orgasmic disorder should be based on judgement that the woman's orgasmic capacity is less than would be reasonable for her age, sexual experience and the adequacy of the sexual stimulation she receives.

Chapter seven of this thesis describes a randomised placebo-controlled treatment study in patients with sexual dysfunction associated with antidepressant treatment. For this reason, DSM-IV substance-induced sexual dysfunction is described in rather more detail than other sexual dysfunctions. The DSM-IV states that substance-induced sexual dysfunction (whether due to a drug of abuse, a medication, or a toxin exposure) should be specified according to the aspect of the sexual response cycle that is affected (i.e. desire, arousal, orgasm, pain). It also notes that that the clinical presentation resembles other forms of sexual dysfunction, but the full criteria for these disorders need not be met. Finally, it provides some guidance on determining whether the dysfunction is indeed substance-induced, by asking clinicians to consider whether the symptoms had their onset whilst the patient received the substance or medication; whether the symptoms resolved promptly after stopping the substance or medication; and whether there was a prior history of sexual dysfunction, not related to substances or medication.

It has been argued that the categorical approach to sexual dysfunction adopted by the ICD-10 and DSM-IV simply serves 'to obscure the varied and often unique ways in which individuals and couples present with sexual problems'. Certainly, it is usual to find that when one aspect of the sexual response is affected, other aspects are also impaired, and doctors are encouraged to 'look beyond' presenting complaints to find the most appropriate diagnosis (Bancroft, 1989).

Recent criticisms of the burgeoning number and the categorical approach to descriptions of variations in sexual activity have warned about the medicalisation of sexual behaviour and the 'creation' of disorders

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PLEASE NOTE: The following pages (pages 27-63) are missing from the original bound thesis and therefore unavailable to view.

of antidepressants in increasing ejaculatory latency time is dose-dependent: a double-blind randomised study found no differences in efficacy between 20 mg or 40 mg daily doses of paroxetine (Waldinger *et al*, 1997). Open-label studies suggest that the efficacy of SSRI antidepressants in increasing ejaculatory latency time can be enhanced through combination with local lidocaine ointment (Atan *et al*, 2000), or sildenafil (Salonia *et al*, 2002; Chen *et al*, 2003).

There have been few investigations of the mechanism of action of serotonergic antidepressants in premature ejaculation, but it may involve central as well as peripheral components. Fluoxetine has been found to increase the penile sensory threshold, without affecting the sacral evoked response or cortical somatosensory evoked potential tests (Yilmaz *et al*, 1999). Successful treatment with clomipramine has been found to increase the emotional response to erotic stimulation (Rowland *et al*, 2003).

MANAGEMENT OF SEXUAL DYSFUNCTION ASSOCIATED WITH ANTIDEPRESSANTS

Many approaches have been adopted for the management of patients with sexual dysfunction associated with antidepressant treatment (reviewed in Baldwin, 2001; Zajecka, 2001; Baldwin and Mayers, 2003). These include expectant management (i.e. waiting for the problem to resolve); behavioural strategies to modify sexual technique; individual and couple psychotherapy; delaying the intake of antidepressants until after sexual activity; reduction in daily dosage; 'drug holidays', adjuvant treatments, and switching to a different antidepressant. The psychological and behavioural approaches are outside the scope of this review. The following section is based upon a computerised literature search of relevant case reports and series, and randomised placebo-controlled trials, performed in June 2003.

Expectant management

There is little data on the persistence of sexual dysfunction with continuing antidepressant treatment. Adaptation appears more likely when the initial disturbance is mild, and related to changes in orgasm, rather than in sexual desire or arousal (Montejo-Gonzalez *et al*, 1997). In a case series of 143 patients treated with antidepressants for six months, 14 patients (9.7%) reported partial improvement, and 16 (11.2%) reported complete remission of sexual dysfunction: no improvement occurred in 113 patients (79.0%) (Montejo *et al*, 2001).

Reduction in dose

There is some data to suggest that the sexual side effects of antidepressants are dose-related (Herman, et al 1990; Benazzi and Mazzoli, 1994; Zajecka *et al*, 1997). Gradual reduction of the daily dosage may

be useful in some patients, providing they are in symptomatic remission and the reduced dose does not potentially compromise efficacy.

Drug holidays

Brief interruptions (2-3 days) to antidepressant treatment have been advocated as an approach to SSRI-induced sexual dysfunction, and found helpful in 50% of breaks in small numbers (n=10) of patients taking either paroxetine or sertraline (Rothschild, 1995). However, this approach puts the patient at risk of discontinuation symptoms and relapse of depression. Furthermore, a drug holiday is only possible with SSRIs with a short half-life and not with fluoxetine, where sexual side effects may not resolve until a few weeks after stopping treatment (Lane, 1997).

Adjuvant treatments

Many adjuvant compounds have been advocated for relieving sexual dysfunction associated with psychotropic drug treatment, including amantadine, bupropion, buspirone, cyproheptadine, dexamphetamine, *Ginko biloba*, granisetron, mianserin, mirtazapine, neostigmine, olanzapine, prostaglandin E (by intracavernosal injection) sildenafil and yohimbine (reviewed by Zajecka, 2001). However, the results of placebo-controlled studies in this area have generally failed to distinguish between 'active' treatments and placebo.

Amantadine

Used in the treatment of extra-pyramidal movement disorders, amantadine both enhances the release and inhibits the re-uptake of dopamine. It has been reported to reverse sexual dysfunction associated with SSRI treatment, when used at either daily doses of 100 mg two or three times per day, or at doses of 100-400 mg two hours before anticipated sexual activity (Balogh *et al*, 1992; Shrivastava *et al*, 1995; Balon, 1996). However, a placebo-controlled study found no advantage for amantadine in improving sexual function in female patients treated with antidepressant drugs (Michelson *et al*, 2000).

Bupropion

Although the precise mechanism of action is unknown, bupropion appears to enhance noradrenergic and dopaminergic neurotransmission. Two placebo-controlled augmentation studies have produced conflicting results on whether bupropion can ameliorate SSRI-induced sexual dysfunction (Clayton *et al*, 2000; Masand *et al*, 2001). Furthermore, a retrospective review in 27 patients found that sexual dysfunction occurred in 11 patients (41%) when they were receiving combination bupropion-SSRI treatment, not significantly different to the rate (52%) when they were taking either agent alone (Bodkin *et al*, 1997). There is a theoretical risk of combining bupropion with antidepressants that inhibit the cytochrome P450 2D6 and 3A4 hepatic iso-enzymes (e.g. fluoxetine, paroxetine), as this could lead to a dangerous increase in bupropion levels, but a recent open-label augmentation study with bupropion

(150 mg/day) indicates that it can be usefully and safely combined with fluoxetine, paroxetine or venlafaxine (Kennedy *et al*, 2002).

Buspirone

This anxiolytic drug with 5-HT_{1A} agonist properties has been advocated for treating patients with sexual dysfunction associated with SSRI treatment. A retrospective review of 16 patients who complained of sexual dysfunction with SSRIs found that 11 (69%) rated their sexual function as much or very much improved when buspirone was added (Norden, 1994). However, two placebo-controlled trials have produced conflicting results: in the first (Landen *et al*, 1999) there was a non-significant trend favouring buspirone over placebo; in the second there were no differences between treatment groups (Michelson *et al*, 2000). The potential efficacy of buspirone in relieving sexual dysfunction may arise from direct 5-HT_{1A} effects in facilitating orgasm, or through its dopaminergic agonist effects and the α_2-antagonist properties of a major metabolite 1-pyrimidinylpiperazine, which together can suppress the effects of serotonin on dopamine and noradrenergic neurotransmission (Zajecka, 2001).

Cyproheptadine

As mentioned above, the 5-HT_2 antagonist properties of mirtazapine and nefazodone may be responsible for their reported relatively lower propensity to cause sexual dysfunction, than SSRIs. The antihistamine and 5-HT_2 antagonist cyproheptadine may be helpful in relieving sexual dysfunction associated with TCAs, MAOIs and SSRIs, when used at daily doses of 4-16 mg. However it is associated with drowsiness and weight gain, and possibly with a return of depressive or obsessive-compulsive symptoms (McCormick S *et al*, 1990; Feder, 1991; Goldbloom and Kennedy, 1991; Aizenberg *et al*, 1995).

Dexamphetamine and other stimulants

A few case reports have described the use of dexamphetamine or other psychostimulants (methylphenidate and pemoline) to reverse sexual dysfunction associated with SSRI treatment, either through daily dosage or through ingestion 1-2 hours before anticipated sexual activity (e.g. Bartlik *et al*, 1995). Many precautions need to be observed before use.

Ginkgo biloba

Numerous case reports and an uncontrolled study (Cohen and Bartlik, 1998) have described the use of this herbal extract, at daily doses between 60-240 mg, to relieve sexual dysfunction associated with SSRI treatment. The mechanism of this effect is uncertain but may result from increased peripheral blood flow. However, a recent small (n=19) placebo-controlled augmentation study with *Ginkgo biloba* found no difference between treatments in reversing sexual dysfunction associated with antidepressant treatment (Kang *et al*, 2002).

Granisetron

A case report describing the use of this 5-HT_3 antagonist to reverse anorgasmia associated with SSRI treatment (Nelson *et al*, 1997) suggested it might be beneficial, but a subsequent double-blind placebo-controlled augmentation study (n=31) found no evidence of efficacy for granisetron (Nelson *et al*, 2001).

Mianserin

Three reports describe the addition of mianserin (which possesses 5-HT_2, 5-HT_3, α_1 and α_2 antagonist properties) to patients troubled by sexual dysfunction associated with SSRI treatment. In the first, mianserin was found helpful in relieving sexual dysfunction in 9 of out of 15 male patients (Aizenberg *et al*, 1997); in the second, it helped improve sexual function in 11 of 16 female patients (Aizenberg *et al*, 1999). In the third, mianserin augmentation improved function in 15 out of 17 patients (88%) receiving SSRIs for psychiatric sequelae of traumatic brain injury (Dolberg *et al*, 2002).

Mirtazapine

Switching studies indicate that mirtazapine may be useful in patients who developed sexual dysfunction with SSRI treatment. However, a placebo-controlled study found no significant advantage for mirtazapine (or olanzapine or yohimbine) in relieving sexual dysfunction in patients taking SSRIs (Michelson *et al*, 2002).

Olanzapine

In a placebo-controlled augmentation study in female patients troubled by sexual dysfunction with SSRI treatment, this 'atypical' antipsychotic drug (with 5-HT_2 receptor antagonist properties) was associated with a greater improvement in sexual satisfaction, but there was no significant difference from placebo on diary ratings of overall sexual functioning (Michelson *et al*, 2002).

Sildenafil

The PDE5 inhibitor sildenafil has been used to relieve sexual dysfunction associated with psychotropic drugs. In a sub-group of 136 depressed patients included within the placebo-controlled clinical trial database, 76% described improvements with sildenafil, compared to 18% of the group who received placebo (Price 1999). In an open study, sildenafil was effective in 10 of 14 patients with antidepressant drug-induced sexual dysfunction (Fava *et al*, 1998). A double-blind placebo-controlled study in 160 men with erectile dysfunction and co-morbid minor depression found that response of erectile problems to sildenafil treatment was associated with a significant reduction in depressive symptoms (Seidman *et al*, 2001). Two placebo-controlled augmentation studies with sildenafil have found it efficacious in relieving men with sexual dysfunction associated with antidepressant treatment, benefits occurring in all areas of sexual function (Nurnberg *et al*, 2001; Nurnberg *et al*, 2003).

Yohimbine

Case reports and a retrospective case series (Ashton *et al*, 1997) have described the beneficial use of this α_2-antagonist in relieving sexual dysfunction associated with TCA or SSRI treatment, at either 5.4 mg 1-2 hours before anticipated sexual activity or daily doses of 5.4 mg t.d.s. However, the controlled study that also included olanzapine and mirtazapine found no advantage for yohimbine over placebo (Michelson *et al*, 2002).

Switching to a different antidepressant

Switch to bupropion

In a study of 28 men troubled by sexual dysfunction during treatment with TCAs or MAOIs, 24 (86%) described improved sexual function (Gardner and Johnston, 1985). Similar effects were seen in 31 patients (men and women) who developed anorgasmia or inhibited orgasm during fluoxetine treatment: switching to bupropion was associated with improved orgasm in 29 patients (94%) and improved libido in 25 (81%) (Walker *et al*, 1993).

Switch to mirtazapine

In 20 patients with sexual dysfunction associated with SSRIs, sexual function improved in 9 of 12 patients (75%) who completed 6 weeks mirtazapine treatment, although 6 patients developed irritability and 9 reported sedation (Gelenberg *et al*, 1998). A second study in 11 patients who stopped SSRIs because of sexual problems found that mirtazapine treatment did not result in the re-emergence of sexual dysfunction (Koutouvidis *et al*, 1999). These observations are supported by findings in a group of 25 depressed outpatients, indicating that mirtazapine treatment had beneficial effects on sexual function (Boyarsky *et al*, 1999).

Switch to moclobemide

Randomised controlled trials and observational studies indicate that treatment with this reversible inhibitor of monoamine oxidase type A is associated with a low incidence of sexual dysfunction. Two uncontrolled studies suggest that switching to moclobemide can be helpful in patients with sexual dysfunction associated with other antidepressants (Ramasubbu, 1999; Montejo *et al*, 2001).

Switch to nefazodone

As described above, the 5-HT_2 antagonist effects of nefazodone may be beneficial in preserving sexual function in depressed patients. An uncontrolled study in 41 patients troubled by sexual dysfunction during previous treatment with other antidepressants found that switching to nefazodone was

associated with improvement in five dimensions of sexual function, improvement being noted in 31 (75.6%) patients (Montejo *et al*, 2001). A randomised controlled trial in patients with sexual dysfunction associated with sertraline treatment compared the effects of re-exposure to sertraline with switching to nefazodone, and found that sexual dysfunction re-emerged significantly less frequently with nefazodone, the advantage being seen after two weeks of double-blind treatment (Ferguson *et al*, 2001).

Switch to tianeptine

The novel antidepressant tianeptine, licensed in France and China, appears associated with a low incidence of sexual dysfunction (Bonierbale *et al*, 2003). A small (n=23) open-label study in patients with sexual dysfunction associated with other antidepressants found that switching to tianeptine was associated with improvement in 16 (72.7%) patients (Atmaca *et al*, 2003).

It can be seen that many differing treatment approaches have been found helpful in the management of patients with sexual dysfunction associated with antidepressant treatment, but there have been few randomised double-blind placebo-controlled trials. The best evidence appears to be for switching to nefazodone in patients with sexual dysfunction associated with sertraline treatment, and for the addition of sildenafil in men with antidepressant-associated erectile dysfunction. However nefazodone is no longer available for clinical use in European countries and sildenafil treatment is often not feasible, because of comorbid physical illness and concomitant medication. As such there is a need for further randomised placebo-controlled studies in patients with sexual dysfunction associated with antidepressants. Chapter 7 of this thesis describes the design and results of a placebo-controlled study with the investigational compound CEB-1555, a 5-HT_{1A} and 5-HT_{1D} agonist.

ANTIDEPRESSANT AND OTHER DRUGS EXAMINED IN THE STUDIES IN THIS THESIS

Chapters two, four, five and six of this thesis describe the results of double-blind randomised controlled trials, each comparing two antidepressant drugs with different pharmacological properties. The selective serotonin re-uptake inhibitor paroxetine is examined in each study. Chapter two describes a study in which paroxetine is compared with nefazodone; chapter four reports a comparison of paroxetine with a serotonin-noradrenaline re-uptake inhibitor; chapter five describes a comparison of paroxetine and reboxetine; and chapter six includes the findings from a comparison of paroxetine with escitalopram. The pharmacological properties of these antidepressants are summarised below: more detailed accounts are available elsewhere (e.g. Leonard, 1996; Taylor *et al*, 1995; Baldwin and Carabal, 1999; Baldwin, 2002). Finally, chapter seven reports a placebo-controlled study of an investigational

compound (CEB-1555) in the treatment of sexual dysfunction associated with fluoxetine or paroxetine: there is little published data concerning the compound, but its most important properties are described.

Paroxetine

Paroxetine is a selective serotonin re-uptake inhibitor (SSRI) approved for use in the United Kingdom in the treatment of patients with depressive illness and in a broad range of anxiety disorders (panic disorder, social phobia, obsessive-compulsive disorder, generalised anxiety disorder and post-traumatic stress disorder). It has proven efficacy in both the short-term and long-term treatment of each of these conditions.

Paroxetine potently inhibits the re-uptake of 5-HT into rat cortical synaptosomes *in vitro*; it also weakly inhibits the re-uptake of noradrenaline, but the relevance of this to its antidepressant and anxiolytic efficacy is contested (Hyttel, 1994). The principal metabolites of paroxetine do not possess clinically significant pharmacological activity, at least at therapeutic doses. Paroxetine is over 90% bound to plasma proteins; the elimination half-life is variable but is generally around one day. Metabolism is via oxidation, then subsequent sulphonation and glucuronidation. It inhibits the hepatic cytochrome P450 2D6 isoenzyme *in vitro*, and this may enhance plasma levels of co-administered drugs including certain TCAs, phenothiazines, type Ic anti-arrhythmics and metropolol (Brosen and Buur Rasmussen, 1996).

The results of double-blind randomised controlled trials comparing paroxetine to TCAs indicate that they have similar overall efficacy, although TCAs are marginally but significantly more efficacious in the sub-group of hospitalised patients (Anderson, 2001). Paroxetine enjoys the principal advantages seen with all SSRIs over TCAs, namely fewer drop-outs due to side effects, greater safety when take in overdose, and ease of prescription, there being no need for dose titration (Beaumont *et al*, 1996). The most common side effects with paroxetine in the clinical trial database are nausea and headache; however, few patients stop treatment due to nausea and the incidence of headache is only slightly greater than that with placebo (Boyer and Feighner, 1996). Like other SSRIs paroxetine can be associated with treatment-emergent sexual dysfunction, the subject of this thesis. The most recent estimates of the incidence of sexual dysfunction with paroxetine treatment vary between 36-43% (Clayton *et al*, 2002) and 70.7% (Montejo *et al*, 2001). Recent media attention has attempted to link paroxetine with suicide and dependence. There is no convincing evidence that paroxetine can provoke suicidal or aggressive behaviour (Baldwin, 2000), but rapid discontinuation of paroxetine treatment can result in distressing but short-lived withdrawal symptoms (Rosenbaum *et al*, 1998; Hindmarch *et al*, 2000; Michelson *et al*, 2000).

Nefazodone

Nefazodone is a phenoxyethyl triazolinone phenypiperazine compound, identified as a potential antidepressant from both its ability to reverse reserpine-induced ptosis (a classical screen for antidepressant compounds) and its high affinity for the 5-HT_{2A} receptor. It also shows activity in the social interaction model of anxiety in rats. Nefazodone inhibits 5-HT_{2A} binding *in vitro* in studies using animal models and membranes from human cortex. It has negligible affinity for muscarinic cholinergic and histaminergic H_1 receptors, with a lower affinity than trazodone (the 'parent' compound) for α_1-adrenergic receptors. The two major metabolites of nefazodone also possess some ability to block 5-HT_{2A} receptors; a third metabolite, m-chlorophenylpiperazine, which can be anxiogenic, is found in low concentrations (less than 5% at peak steady-state concentrations of nefazodone). It has no monoamine oxidase inhibitory activity and no affinity at other major binding sites, but produces a dose-dependent inhibition of 5-HT re-uptake and a modest inhibition of noradrenaline re-uptake. The 5-HT re-uptake inhibitory properties of nefazodone have been demonstrated in *in vitro*, *ex vivo* and human pharmacology studies, at clinically relevant doses (Taylor *et al*, 1995).

The results of randomised double-blind placebo-controlled trials with nefazodone demonstrate that it has antidepressant efficacy in both the acute and continuation phases of the treatment of patients with major depressive episodes (Mendels *et al*, 1995; Feiger *et al*, 1999). The findings of double-blind comparator-controlled studies indicate that it has similar efficacy to the antidepressant drugs imipramine (Rickels *et al*, 1995), sertraline (Feiger *et al*, 1996) and paroxetine (Baldwin *et al*, 1996; 2001). Treatment studies comparing it with SSRIs suggest that nefazodone caused less treatment-emergent sleep disturbance and anxiety (Zajecka *et al*, 1996). An analysis of the clinical trial database suggests that it was associated with a low incidence of reported treatment-emergent sexual dysfunction (Baldwin, 1996).

The same database indicates that the most common adverse events during nefazodone treatment were dry mouth, somnolence, dizziness, nausea, constipation, blurred vision and postural hypotension (Preskorn *et al*, 1995). Nefazodone became available for clinical use in the United Kingdom in 1996. Perhaps because of the need for dose-titration, twice-daily dosage, and doubts relating to its efficacy at doses less than 400 mg per day, it made little impact on antidepressant prescribing. Nefazodone was withdrawn in March 2003, for largely economic reasons, although it had been associated with reports of liver function test abnormalities (Baldwin, 2000).

Serotonin-noradrenaline re-uptake inhibitor studied in chapter four

For contractual reasons, I am presently unable to disclose the name of the serotonin-noradrenaline re-uptake inhibitor compared to paroxetine in chapter four. It has a double substituted cyclopropane ring structure, and was identified as a potential antidepressant on the basis of its equal potency for inhibiting

the re-uptake of serotonin and noradrenaline. It increases extracellular levels of both 5-HT and noradrenaline after acute administration as measured by intracerebral microdialysis, but has no effect on dopamine re-uptake. It possesses no monoamine oxidase inhibitory activity, and is devoid of interactions at any known neurotransmitter receptor or ion channel. It has no active metabolites, the main metabolic route being by glucuronide conjugation, with 90% eliminated in the urine. It does not induce or inhibit enzymes in the cytochrome P450 system and shows low protein binding, and therefore has a low risk of drug interactions.

The antidepressant efficacy of this SNRI was established through the results of double-blind randomised controlled trials comparing it to placebo, tricyclic antidepressants (TCAs) or SSRIs in inpatients and outpatients fulfilling DSM-III criteria for major depressive disorder. A meta-analysis of studies versus TCAs in the treatment of patients with major depression shows it to be of similar efficacy but with improved tolerability. By contrast, it shows superior efficacy and similar tolerability to SSRIs. Like paroxetine and nefazodone, it too is effective in preventing new episodes of illness over one year in patients with recurrent depression.

The SNRI has a relatively benign side effect profile: in the clinical trial database only vertigo, increased sweating, anxiety, hot flushes and dysuria occurred more frequently than with placebo. Dysuria is more common than during TCA treatment and for this the compound should be avoided in men with prostatomegaly.

Reboxetine

Reboxetine became available for use in the United Kingdom in 1997. It is a specific noradrenaline re-uptake inhibitor with activity in rodent models predictive of antidepressant efficacy in humans (e.g. antagonism of reserpine-induced ptosis, and increase in REM sleep latency). Reboxetine is a racemic mixture of two enantiomers, the S,S enantiomer being the more potent inhibitor. Reboxetine has little effect on 5-HT or dopamine re-uptake, does not inhibit monoamine oxidase activity, and has low affinity for alpha-adrenergic and muscarinic receptors. *In vitro* evaluations of the neuronal uptake of radio-labelled noradrenaline in rat cortex have found similar degrees of inhibition with reboxetine and the TCA desipramine after 21 days of administration. Reboxetine also induces a down-regulation of β-adrenergic receptors after five days of treatment, accompanied by a desensitisation of the activity of noradrenaline-dependent adenylate cyclase (Riva *et al*, 1989; Baldwin and Carabal, 1999).

Absorption is rapid, the terminal elimination half-life of around 13 hours allowing twice-daily administration. It shows linear pharmacokinetics, unaffected by multiple dosing, gender or hepatic insufficiency, although doses should be reduced in elderly patients and in severe renal impairment. Reboxetine does not interact with the principal isotypes of the cytochrome P450 system, and has a low

potential for drug-drug interactions. However, reboxetine is metabolised by CYP 3A4, and it should be used cautiously when prescribed with drugs that are either metabolised by CYP 3A4 (e.g. antiarrhythmic drugs) or drugs that potently inhibit CYP3A4 (e.g. ketoconazole) (Baldwin *et al*, 2000).

The results of double-blind placebo-controlled trials indicate that reboxetine has antidepressant efficacy in both the acute and continuation phases of the treatment of depression. It has similar efficacy to desipramine and fluoxetine, and may have advantages over fluoxetine in improving social function, in remitted patients (Dubini *et al*, 1997; Massana *et al*, 1999). In an analysis of the clinical trial database involving over 2600 patients reboxetine appeared generally well tolerated, the rate of discontinuation from treatment because of adverse events being similar to that with placebo. Dry mouth (27%), constipation (17%) and increased sweating (14%) were all significantly more frequent with reboxetine than with placebo, but less common than with imipramine or desipramine. Adverse events were similarly frequent with reboxetine (67%) and fluoxetine (65%). Between 4-12 % of patients, mainly men, develop urinary hesitancy, and reboxetine should not be prescribed to men with prostatic enlargement.

Escitalopram

Like reboxetine, the SSRI citalopram is a racemic mixture, consisting of an S-(+)-enantiomer, escitalopram and an R-(-)-enantiomer, R-citalopram. *In vitro* and *in vivo* studies demonstrate that escitalopram is more potent than citalopram, whereas R-citalopram is practically devoid of 5-HT re-uptake inhibitory effects. For example, in rat brain synaptosomes, escitalopram, citalopram and R-citalopram show IC_{50} (where smaller numbers indicate greater potency) values of 2.1, 3.9 and 280 nM respectively (Sanchez and Brennum, 2000). Escitalopram is the most selective SSRI available for clinical use. The level of selectivity, expressed as the ratio between affinities for 5-HT and noradrenaline (NA) transporter proteins is 7100 for escitalopram, compared to 3900 for citalopram, 2700 for sertraline, 540 for fluoxetine and 450 for paroxetine. In addition, escitalopram has either no or minimal activity in more than 140 receptor binding, uptake and enzyme activity assays. As such the pharmacological effects of escitalopram are likely to arise exclusively from its 5-HT reuptake inhibitory effects (Owens *et al*, 2001).

Animal models indicate that escitalopram possesses effects shared with other antidepressants. For example, the rat chronic mild stress (CMS) model indicates that escitalopram and citalopram reverse the CMS-induced decrease in sucrose intake to a similar extent as TCAs. With escitalopram this effect is seen after only one week, compared to four weeks with the TCA imipramine, and two weeks with citalopram, suggesting that escitalopram may have an earlier onset of antidepressant-like action (Montgomery *et al*, 2001).

When it became available for clinical use in the United Kingdom (July 2002) the clinical trial programme for escitalopram in the treatment of major depressive disorder included four placebo-controlled trials, three of which also included citalopram as an active comparator, to demonstrate the assay sensitivity of the trial. The results of the two studies already published indicate that 10-20 mg daily doses of escitalopram are significantly more efficacious than placebo in the short-term treatment of patients with major depression (Burke *et al*, 2002; Wade *et al*, 2002). The results of a pooled analysis indicate that escitalopram has an earlier onset of antidepressant effect than citalopram, and greater overall efficacy, as measured by change in mean score on the Montgomery-Asberg Depression Rating Scale (MADRS, Montgomery and Asberg, 1979). Like citalopram, escitalopram has a benign side effect profile: analysis of the clinical trial database indicates that nausea, delayed ejaculation, insomnia, diarrhoea, somnolence, dizziness and sinusitis were all more common with escitalopram than with placebo, but only nausea occurred in more than 10% of patients.

CEB-1555

The neurotransmitter functions of serotonin are mediated by at least fourteen distinct sub-receptor sub-types. Of these, the 5-HT_{1A} receptor sub-type has probably been studied the most extensively. Several 5-HT_{1A} receptor agonists (e.g. buspirone, ipsapirone, gepirone, and flesinoxan) have been developed, and together with recently discovered 5-HT_{1A} receptor antagonists these provide a means to characterise the roles of 5-HT_{1A} receptors in animal models of various human problems such as emesis, sexual dysfunction, anxiety and depression. These studies provide strong evidence that selective 5-HT_{1A} receptor agonists may represent a novel approach to the treatment of various types of sexual disorder.

The compound studied in chapter seven, CEB-1555, is an investigational drug for the reversal of SSRI treatment-induced sexual dysfunction. It is a serotonin receptor agonist with a high degree of selectivity for the 5-HT_{1A} receptor sub-type and weak affinity for 5-HT_{1D} receptors. The efficacy of the compound in animal models has been established in a variety of experimental paradigms including sexual arousal, emesis, anxiety and depression. In male rats single doses affect sexual behaviour by reducing the latency and stimulus threshold for ejaculation. It also induces increases in the efficiency and rate of copulation at relatively low doses (1.0 to 100 µg/kg, subcutaneously). This increased 'copulatory efficiency' (i.e. the number of intromissions divided by the total number of mounts) suggests that the compound improves the capacity of male rats to achieve erections sufficient for intromission. In addition, the increased copulatory rate indicates that it elevates sexual drive. These effects are in agreement with previous observations of increases in sexual function in patients treated with the 5-HT_{1A} receptor agonist buspirone, and with the finding that buspirone ameliorated sexual dysfunction associated with SSRI treatment (Landen *et al*, 1999). The findings suggest that the drug could be useful for treating human disorders related to erectile response, sexual drive, and orgasmic reflexes.

The dosage in the study described in chapter seven was 300 μg (or placebo) orally once daily for 4 weeks. This dose was chosen following the single, ascending dose safety and tolerability study where doses of 100 μg to 500 μg were administered. Dosing commenced with four volunteers receiving a single 500 μg dose. Three volunteers reported 13 adverse events, including 2 graded as 'moderate' and 2 as 'severe'. Based on these findings, the planned dosing of these and additional volunteers at dose levels ≥500 μg was terminated. The safety and tolerability of lower single doses (100 to 400 μg) was evaluated in eight new volunteers and found acceptable, with the 300 μg dosage considered the highest dose to be generally tolerated well.

The safety and tolerability of this dose given as a single dose was evaluated in 31 healthy volunteers. These volunteers reported 46 adverse events, compared with 17 adverse events reported by 35 volunteers treated with placebo in the same studies. The most frequent adverse events associated with administration were dizziness, somnolence, asthenia and nausea, with or without vomiting. Headache was reported slightly more frequently following treatment with the drug than with placebo. Information on the severity of adverse events reported was available for one study: two were graded moderate but short lasting (one episode of vomiting, 1 minute duration, and dizziness, 50 minutes duration), all other events were graded mild. The frequency and severity of events appeared dose-related. It was therefore thought appropriate to use the highest generally well-tolerated dose of 300 μg in further studies.

SUMMARY

Human sexual behaviour is affected by biological, psychological, interpersonal and cultural factors. In both men and women, sexual behaviour involves a complex interplay between circulating hormones, central and peripheral neurotransmission, and local mechanisms. Alterations to this balance can result in 'sexual dysfunction', a disturbance in sexual desire and in the psychophysiological changes that characterise the normal sexual response cycle, which causes marked personal distress and interpersonal difficulty.

In the two major classificatory schemes, the broad group of sexual dysfunctions is categorised into disturbances in sexual desire, arousal and orgasm, but there is much symptomatic overlap between diagnoses. Assessment of sexual dysfunction can involve intrusive objective measures, but most investigations utilise patient-completed questionnaires and rating scales, such as the RSI (used in the treatment study described in chapter 5) and the ASEX (employed in the treatment studies described in chapter 6 and 7). A novel sexual function questionnaire is described in chapter 3, and compared to the ASEX in chapter 8.

The results of the literature reviews allow a number of conclusions to be drawn. First, sexual problems are common in community and primary care settings, the most prevalent being erectile dysfunction in men (approximately 2-30% in men aged 40 years and older) and vaginal dryness in women (approximately 25% of women aged 60 years and older). However, low consensus on definitions of sexual dysfunction across investigations hampers attempts to compare study findings.

Second, sexual dysfunction is more common in samples of depressed individuals than in the general population. Problems in terminology and case ascertainment limit some study findings, but the findings of large case-control community epidemiological investigations and smaller case-control studies in clinical samples show that loss of sexual interest is significantly more common in depressed patients, being at least twice as prevalent as in matched non-depressed subjects.

Third, most antidepressant drugs have adverse effects on sexual function, but accurate identification of the incidence of treatment-emergent dysfunction has proved troublesome, and most investigations of sexual dysfunction associated with antidepressants have methodological flaws. Treatment-emergent sexual dysfunction may be less frequent with bupropion, moclobemide, nefazodone and reboxetine than with other antidepressants. There is a need for further randomised double-blind comparator-controlled studies, with regular assessments of sexual function and satisfaction from baseline and throughout treatment. Chapters 2, 4, 5 and 6 of this thesis report the findings of randomised controlled treatment studies, all with paroxetine as an active comparator.

Fourth, many approaches have been adopted for management of patients with sexual dysfunction associated with antidepressant treatment, but there have been few randomised placebo-controlled studies, and these have generated disappointed results, other than revealing efficacy for augmentation with sildenafil in patients undergoing treatment with SSRIs, or switching to nefazodone in sertraline-treated patients. Chapter 7 of this thesis describes the rationale, method and findings of a double-blind augmentation study with a novel psychotropic compound in patients with sexual dysfunction associated with fluoxetine or paroxetine treatment in remitted depressed patients.

CHAPTER 2: CHANGES IN LIBIDO DURING ANTIDEPRESSANT TREATMENT

AIM OF THE INVESTIGATION

The preceding literature search has demonstrated that changes in sexual function and satisfaction are common in antidepressant-treated depressed patients. The aim of this study was to examine in detail one aspect of the sexual response - sexual desire (or libido) - in psychiatric outpatients experiencing major depressive episodes. The presence of reduced libido was ascertained by the scores on one item (item 14, 'genital symptoms') of the Hamilton Rating Scale for Depression (HAM-D) (Hamilton, 1960) which is perhaps the most well known scale for rating the severity of depressive symptoms. Scores on this item were recorded prior to starting one of two antidepressants, and recorded subsequently in serial assessments over both the acute phase (eight weeks) and the continuation phase (next four months) of antidepressant treatment.

The subjects included within this investigation form a sub-group from a larger sample of patients, who had participated in a multi-centre double-blind randomised controlled trial, supported by the pharmaceutical company Bristol-Myers Squibb, which has been reported previously (Baldwin *et al*, 1996; Baldwin *et al*, 2001). Recruitment into the acute phase of the overall treatment study started in October 1992: the continuation phase of the study was completed in September 1994. The method and results of the wider study are summarised briefly below.

My involvement in the overall study included the following activities -

- offering advice on the overall study protocol
- submitting the protocol to a local research ethics committee
- producing the rating scale training videos
- training investigators in use of the assessment interview and rating scales
- recruiting patients from my outpatient clinic
- communicating with investigators via a study newsletter
- analysing the data in association with employees of Bristol-Myers Squibb
- presenting the results to the study investigators
- preparing the final study report
- preparing the results for publication
- publishing the results in peer-reviewed journals

There were three main objectives to the current investigation. It has been claimed that sexual dysfunction may be more apparent or troublesome to patients during the continuation phase of antidepressant treatment (Hirschfeld, 1999). As such, the first objective was to examine changes in item 14 of the HAM-D over acute and continuation treatment, to see whether temporal changes in that

item mirror temporal changes in overall depressive symptoms in antidepressant-treated patients. As the literature review indicates that drugs with 5-HT_2 antagonist properties (nefazodone, mirtazapine) may be associated with less sexual dysfunction than SSRIs (e.g. paroxetine) (Montejo *et al*, 2001; Baldwin, 2001), the second objective was to ascertain whether paroxetine and nefazodone differed in their effects on item 14, in either acute or continuation treatment. The third and related objective was to examine the incidence of sexual dysfunction during treatment with nefazodone or paroxetine, by examining reports of treatment-emergent adverse events related to sexual function.

METHOD FOR OVERALL STUDY

Study design

The overall study was a multi-centre double-blind parallel-group randomised controlled trial of the efficacy and tolerability of nefazodone and paroxetine in the acute and continuation treatment of patients fulfilling DSM-III-R criteria for either non-psychotic major depression or bipolar disorder, currently depressed. The participating patients underwent a 1-4 week washout period to ensure an adequate drug-free interval, followed by eight weeks of double-blind treatment (acute phase). Patients who responded to acute treatment could undergo a further 16 weeks of double-blind treatment (continuation phase).

To be considered for participation in the study, patients had to have a minimum score of 18 on the 17-item version of the HAM-D (Appendix 2.1), and a rating of at least moderately ill on the Clinical Global Impression Severity of Illness Scale (CGI-S) (Guy, 1976) at baseline (Appendix 2.2). There were a range of exclusion criteria, such as pregnancy or lactation, serious risk of suicide, presence of psychosis, current alcohol or drug abuse or dependence, unstable physical illness, and failure to respond to more than two previous courses of antidepressant treatment.

Double-blind treatment

Patients were randomly assigned to receive nefazodone (200-600 mg/day) or paroxetine (20-40 mg/day) using a 'double-dummy' technique to preserve the blind. During acute treatment, the dosage of nefazodone was raised to 200 mg b.d. at day 8, after which it could be raised further dependent upon improvement and tolerability. The paroxetine dosage could be raised at day 15 to 30 mg/day, and at day 29 to 40 mg/day, again depending upon efficacy and tolerability. Treatment compliance was assessed using a daily diary and weekly capsule count. During continuation treatment, the daily dosage of double-blind treatment was reduced whenever possible, to help identify the minimal dose that maintained efficacy.

Efficacy assessments

During acute treatment, antidepressant efficacy was evaluated by completion of the HAM-D at all study visits; the Hamilton Rating Scale for Anxiety (HAM-A) (Hamilton, 1959) at baseline and weeks 2 and 8; the CGI-S at every visit and the Clinical Global Impression of Improvement (CGI-I) at each visit after randomisation; the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) at baseline and weeks 4 and 8, and a Patient Global Assessment (PGA) at each visit. Patients were considered to have responded to acute treatment if they achieved a score of 1 (very much improved) or 2 (much improved) on the CGI at week 8. During continuation treatment, efficacy was assessed by completion of the HAM-D, HAM-A, MADRS, CGI-S, CGI-I, and PGA at monthly visits. Patients were considered to have responded to continuation treatment if the CGI-I rating at endpoint was at least 'much improved', compared to baseline.

Statistical methods

The data from each centre were pooled for analysis, using a model to accommodate the possibility of a study centre effect. For acute treatment, efficacy analyses were performed in all patients who had received study medication and who had undergone at least one efficacy evaluation during double-blind treatment. Two sets of analyses were performed - a last observation carried forward (LOCF) analysis, using data carried forward from the previous visits when no observation was recorded; and an observed case (OC) analysis, using only actual observations at each visit. A two-way analysis of variance (ANCOVA) was performed, to test for baseline comparability as well as differences between treatments in efficacy measures (Altman, 1991). For continuation treatment, only within-treatment group analyses were made. Tabulations were done to determine whether the response shown at the end of the acute phase was maintained.

METHOD FOR CURRENT INVESTIGATION

Hypothesis

The study hypothesis was that nefazodone treatment would show significant advantages over paroxetine treatment in sexual interest, as assessed by item 14 of the HAMD. The null hypothesis to be tested was there would be no significant differences between nefazodone and paroxetine on this item during acute or continuation treatment.

Change in severity of overall depressive symptoms and genital symptoms

To determine the change in severity of depressive symptoms, I examined the raw data for each of the 108 patients who entered both the acute and continuation phases of the study. Using the computer software package STATA version 7.0 (StataCorp, 2001), I then calculated the mean total 17-item HAM-D score and standard deviation of that score at each visit, for both treatment groups, using an observed

case analysis. The difference between groups in mean HAM-D scores at each visit was then determined, together with the standard error and 95% confidence intervals for that difference. Significance values were then calculated using two-tailed t-tests. A similar method was used to examine the change in item 14 of the HAM-D.

As the CGI scales provide another measure of illness severity and improvement, I also examined the raw data for the CGI-I for each of the 108 patients. The CGI-I score at a visit compares the patient's overall clinical condition to that present at the baseline assessment. As such no CGI-I values are available for the baseline visit. I adopted the same approach to calculate the mean CGI-I scores and standard deviation of that score in both treatment groups, and the difference between groups in mean CGI-I scores, standard error and 95% confidence intervals, as with the HAM-D scores, again using an observed case analysis. Finally, the pattern of change in the overall symptom and genital symptom severity in both treatment groups was examined, to see if the timing of improvements differed.

Treatment-emergent sexual adverse events

To determine the incidence of troublesome sexual dysfunction associated with treatment, I examined the raw data for both the acute and continuation phases of the study, to identify those adverse events that were reported by study investigators and which could represent change in sexual function. Each adverse event could be characterised by the investigator according to the time of onset, duration, and severity; in addition, investigators had an opportunity to record whether they felt the adverse event was related to double-blind treatment, and whether treatment was necessary for that event.

ETHICAL CONSIDERATIONS

The study was conducted in accordance with the Declaration of Helsinki as adopted by the 18th World Medical Assembly 1964 and subsequent amendments: Tokyo (1975), Venice (1983), and Hong Kong (1989). The study was approved by the local research ethics committee for each study centre.

No ethical problems were foreseen for the participation of patients in the study. Both nefazodone and paroxetine had proven efficacy in major depression, at the doses used in the study; and the protocol permitted dosage changes according to the efficacy and tolerability of study treatment, reflecting standard clinical practice. The duration of acute treatment (eight weeks) was sufficient to allow assessment of efficacy; responders to acute treatment could enter continuation therapy (four months), reflecting treatment recommendations at the time of the study. Patients attended appointments frequently and regularly; assessments of efficacy and tolerability were comprehensive; and participation could only occur after the provision of written informed consent.

RESULTS FOR OVERALL TREATMENT STUDY

Dosage of study medication

At the end of acute treatment, the mean modal dose for paroxetine was 33 mg/day and for nefazodone was 476 mg/day; at the end of continuation treatment, the mean modal dose was 32 mg/day for paroxetine and 430 mg/day for nefazodone.

Efficacy of acute treatment

Two hundred and six patients at 20 centres received study medication in the acute phase; 114 (55%) women and 92 (45%) men, aged between 19 and 74 years. Of these 206 patients, 105 received nefazodone and 101 received paroxetine. In both groups, the HAM-D total scores (LOCF analysis) reduced significantly: by 9.7 in the nefazodone-treated group, and by 10.5 in the paroxetine-treated group. At the end of acute treatment, 100 (58%) nefazodone-treated patients, and 96 (60%) paroxetine-treated patients had responded to study medication (rated as either 1 or 2 on the CGI-I; intention-to-treat LOCF analysis). There were no significant differences between treatment groups on any outcome measure. Table 2.1 gives details of the demographic and clinical characteristics for all patients who participated in the acute treatment study; Table 2.2 gives the results on the efficacy measures. Figure 2.1 shows the decline in severity of depressive symptoms during double-blind acute treatment.

Efficacy of continuation treatment

One hundred and eight patients entered the continuation phase; 57 (53%) women and 51 men (47%), aged between 20 and 71 years. Of these 108 patients, 55 (51%) received nefazodone and 53 (49%) received paroxetine. Three (6%) of the paroxetine-treated and four (7%) of the nefazodone-treated patients were withdrawn due to lack of efficacy. Thirty-six (68%) of the paroxetine-treated and 37 (67%) of the nefazodone-treated patients completed the study.

There were no clinically relevant differences in antidepressant activity between nefazodone and paroxetine at any stage during continuation treatment. The improvement from baseline of the rating scale scores was either maintained or enhanced throughout the continuation period. In the LOCF analysis, at the end of the study 47 (85.5%) nefazodone-treated patients and 42 (79.25%) paroxetine-treated patients were judged to have responded to double-blind treatment.

RESULTS FOR CURRENT INVESTIGATION

Study sample

Table 2.3 gives details for the sample of 108 patients who underwent both acute and continuation treatment. The age and gender distributions in the sample were similar to those in the overall treatment group. The baseline mean 17-item total HAM-D scores (nefazodone, 25.25; paroxetine, 25.70) were similar, and slightly but not significantly higher than those in the overall treatment study sample. There

Table 2.1.

Clinical and demographic characteristics - all randomised patients

Characteristic	Nefazodone (n = 105)	Paroxetine (n= 101)	Total (n = 206)
Mean age (yrs)	38.3	37.9	38.1
Age range (yrs)	19-74	19-64	19-74
Gender, N (%)			
Men	42 (40)	50 (50)	92 (45)
Women	63 (60)	51 (50)	114 (55)
Major depression, N (%)			
Unipolar, single episode	45 (43)	52 (51)	97 (47)
Unipolar, recurrent	59 (56)	49 (49)	108 (52)
Bipolar, depressed	1 (1)	0 (0)	1 (0.5)

Table 2.2

Efficacy variables in evaluable patients - acute treatment study (ITT, LOCF analysis)

Measure		Nefazodone mean	Paroxetine mean	95% confidence interval for treatment difference*
HAM-D				
	Baseline	24.6	24.8	
	Change	-9.7	-10.5	-1.4 to 3.1
HAM-A				
	Baseline	19.0	18.3	
	Change	-6.5	-8.0	-0.7 to 3.8
MADRS				
	Baseline	33.1	33.1	
	Change	-13.2	-15.7	-0.7 to 5.7
CGI-S				
	Baseline	4.5	4.5	
	Change	-1.4	-1.5	-0.3 to 0.5
CGI-I				
	% responders **	58	60	-15.8 to 11.8

* treatment difference defined as change in score from baseline for nefazodone minus the change in score from baseline for paroxetine

** response defined as much or very much improved

Table 2.3

Demographic and clinical characteristics of patients entering both treatment phases

Characteristic	Nefazodone (n = 55)	Paroxetine (n = 53)	Total (n = 108)
Mean age (yrs)	39.0	38.6	38.8
Age range (yrs)	20-71	22-55	20-71
Gender, N (%)			
Men	27 (49)	24 (45)	51 (47)
Women	28 (51)	29 (55)	57 (53)
Mean number of depressive episodes	1.2	1.5	1.3
Duration of present episode (months), N (%)			
< 3	16 (29)	18 (34)	34 (31)
3-6	18 (33)	20 (38)	38 (35)
6-12	8 (15)	4 (8)	12 (11)
> 12	13 (24)	11 (21)	24 (22)
Major depression			
Unipolar, single episode	25 (45)	26 (49)	51 (47)
Unipolar, recurrent	29 (53)	27 (51)	56 (52)
Bipolar	1 (2)	0 (0)	1 (1)
Previous antidepressants for this episode			
Yes, N (%)	41 (75)	41 (77)	82 (76)
No, N (%)	14 (25)	12 (23)	26 (24)

were no differences between treatment groups in the sample at baseline assessment in either demographic or clinical characteristics, and there were similar proportions of patients with single or recurrent depressive episodes.

Efficacy of double-blind treatment

There was a gradual reduction in the severity of depressive symptoms, measured by the mean total 17-item HAM-D score at each visit. Table 2.4 gives the mean scores at each visit in both treatment groups. There were no significant differences between treatment groups at any assessment, although there was a non-significant trend ($p = 0.06$) towards greater efficacy with nefazodone at month 6. The pattern of change in mean total HAM-D score in acute and continuation treatment in the 108 patients was similar, as shown in Figure 2.2.

Change in genital symptoms

The severity of genital symptoms reduced in both treatment groups, over the course of the study. Figure 2.3 shows that the pattern of change was somewhat different. With nefazodone, there was a steady decline in score to 31.2% of the original value, but with paroxetine an early increase in the first four weeks of double-blind treatment was followed by a later decline, to 58.7% of the value at baseline. There were significant differences between treatment groups, with fewer genital symptoms for nefazodone, at week 2 (p-value 0.04), week 4 (0.04), week 6 (0.04), week 8 (0.01), month 3 (0.02), month 5 (0.002) and month 6 (0.01). The magnitude of the difference in mean score at these weeks ranged between 0.29 and 0.46. Table 2.5 gives the mean item 14 score and standard deviation for each visit for both treatment groups, together with the difference in mean score and standard error, confidence intervals and p-values.

Change in overall illness severity

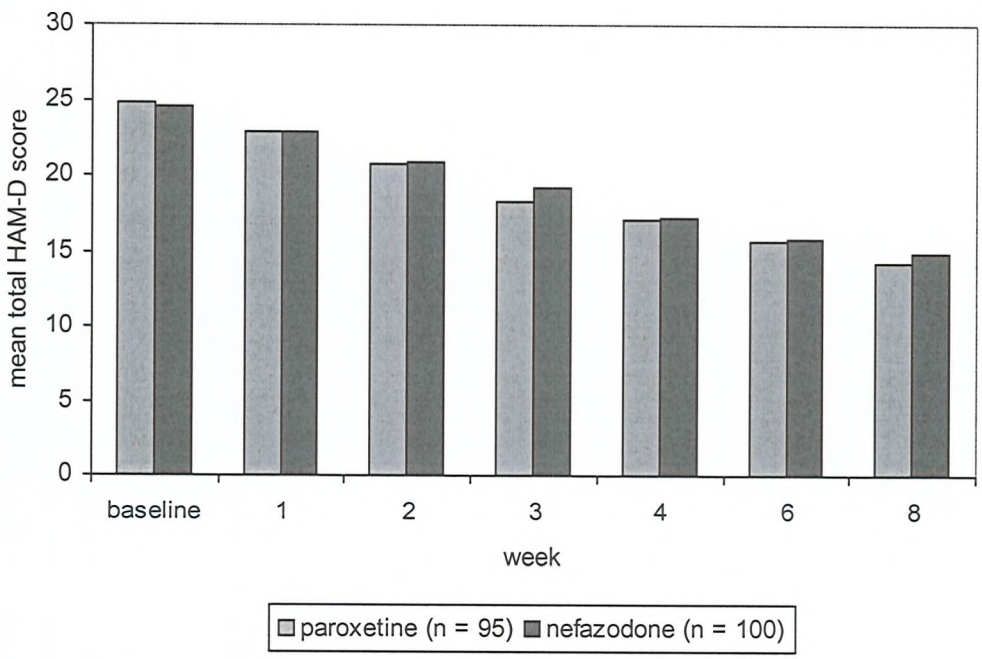
The mean CGI-I score declined steadily from week 1 (reflecting an improvement in overall condition) in both treatment groups. The overall change in score was similar (2.09 with nefazodone, 1.88 with paroxetine). Table 2.6 gives the mean CGI-I score and standard deviation for each visit in both groups, and the difference in mean score and standard error with confidence intervals and p-values. There were no significant differences between treatment groups in CGI-I score at any assessment. Figure 2.4 shows a strikingly similar pattern of change in CGI score in the two treatment groups.

Adverse events associated with treatment

There were no major differences in the profile of adverse events relating to sexual function in the treatment groups. Adverse events were reported by the majority of patients in both treatment groups, in both the acute and continuation phases of the study, but adverse events relating to sexual dysfunction

Figure 2.1

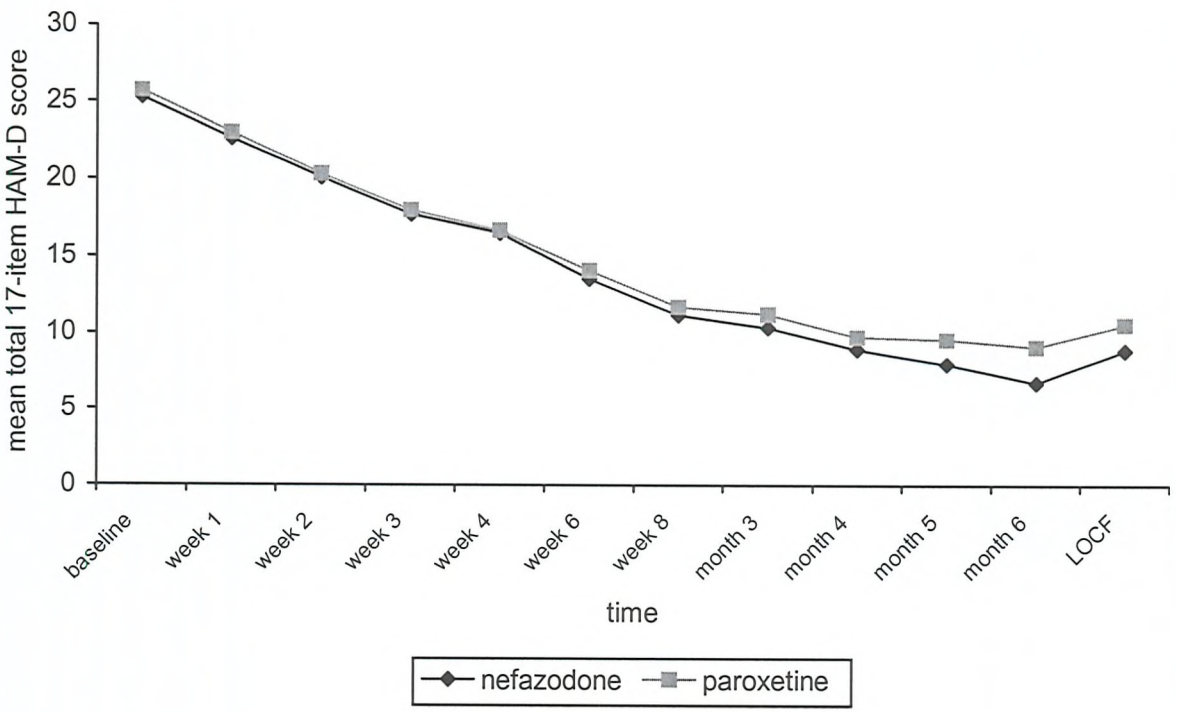
Change in mean total 17-item HAM-D score in acute treatment - overall sample ITT, LOCF analysis



Note that x-axis is not to scale

Figure 2.2

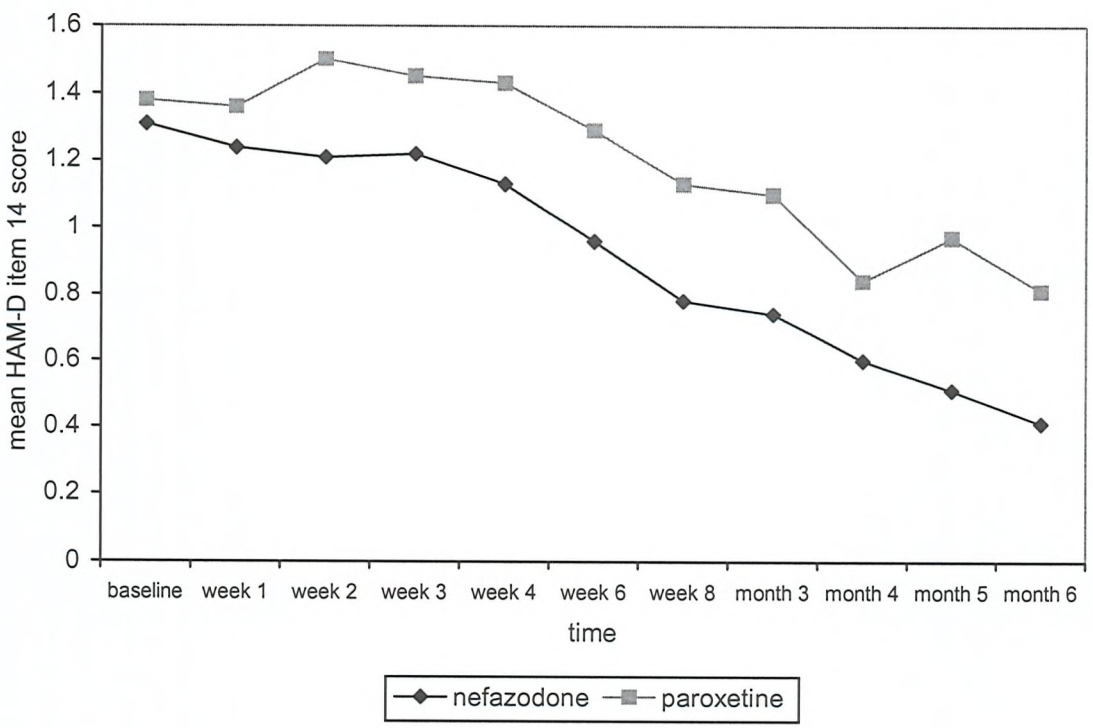
Mean total 17-item HAM-D scores in study sample (OC analysis)



Note that x-axis is not to scale

Figure 2.3

Mean HAM-D item 14 (genital symptoms) in study sample (OC analysis)



Smaller numbers indicate lesser severity of genital symptoms

Note that x-axis is not to scale

Table 2.4 **Mean 17-item HAM-D total scores in patients undergoing acute and continuation treatment**

	Nefazodone			Paroxetine			Difference between treatments				
Time	n/N	Mean	SD	n/N	mean	SD	Diff mean	SE (n)	95% CI Lower	95% CI Upper	P-value
Baseline	55/55	25.25	3.99	53/53	25.70	4.15	-0.44	0.78	-2.00	1.11	0.57
Week 1	54/55	22.61	4.30	50/53	22.98	4.31	-0.37	0.84	-2.04	1.31	0.66
Week 2	52/55	20.08	4.59	50/53	20.34	5.22	-0.26	0.97	-2.18	1.65	0.76
Week 3	52/55	17.72	5.38	49/53	17.98	5.94	-0.26	1.12	-2.47	1.96	0.81
Week 4	51/55	16.53	5.96	51/53	16.68	6.57	-0.15	1.22	-2.57	2.27	0.90
Week 6	55/55	13.55	5.52	49/53	14.10	5.73	-0.55	1.09	-2.71	1.61	0.61
Week 8	55/55	11.20	5.96	53/53	11.75	5.77	-0.55	1.13	-2.79	1.68	0.62
Month 3	43/50	10.38	6.26	45/49	11.27	6.63	-0.88	1.32	-3.50	1.73	0.50
Month 4	41/45	8.96	6.11	39/44	9.77	5.35	-0.82	1.22	-3.24	1.61	0.50
Month 5	34/39	7.97	5.22	39/41	9.59	5.23	-1.61	1.32	-4.23	1.01	0.22
Month 6	37/37	6.73	3.88	36/36	9.14	6.44	2.41	1.24	-4.87	0.06	0.06

n/N number of recorded observations / patients remaining at that assessment
SD standard deviation
SE standard error
CI confidence interval

All calculations given to two decimal points

Table 2.5 HAM-D item 14 (genital symptoms) in 108 patients undergoing acute and continuation treatment

	Nefazodone			Paroxetine			Difference between treatments				
Time	n/N	Mean	SD	n/N	mean	SD	Diff mean	SE (n)	95% CI Lower	95% CI Upper	P-value
Baseline	55/55	1.31	0.74	53/53	1.38	0.63	-0.07	0.13	-0.33	0.19	0.61
Week 1	54/55	1.24	0.73	50/53	1.36	0.72	-0.12	0.14	-0.40	0.16	0.40
Week 2	53/55	1.21	0.74	50/53	1.50	0.68	-0.29	0.14	-0.57	-0.01	0.04
Week 3	54/55	1.22	0.72	49/53	1.45	0.71	-0.23	0.14	-0.51	0.05	0.11
Week 4	53/55	1.13	0.79	53/53	1.43	0.67	-0.30	0.14	-0.58	-0.02	0.04
Week 6	55/55	0.96	0.82	52/53	1.29	0.70	-0.31	0.15	-0.60	-0.01	0.04
Week 8	55/55	0.78	0.69	53/53	1.13	0.73	-0.35	0.14	-0.62	-0.08	0.01
Month 3	47/50	0.74	0.67	49/49	1.10	0.82	-0.36	0.15	-0.66	-0.05	0.02
Month 4	45/45	0.60	0.58	44/44	0.84	0.83	-0.24	0.15	-0.54	0.06	0.12
Month 5	39/39	0.51	0.51	39/41	0.97	0.76	-0.46	0.14	-0.75	-0.17	0.00 #
Month 6	37/37	0.41	0.50	35/36	0.81	0.74	-0.41	0.15	-0.70	-0.11	0.01

n/N number of recorded observations / patients remaining at that assessment

SD standard deviation

SE standard error

CI confidence interval

p = 0.002

All calculations given to two decimal points

Table 2.6 CGI-I scores in 108 patients undergoing acute and continuation treatment

	Nefazodone			Paroxetine			Difference between treatments				
Time	n/N	Mean	SD	n/N	mean	SD	Diff mean	SE (n)	95% CI Lower	95% CI Upper	P-value
Week 1	52/55	3.52	0.78	51/53	3.55	0.67	-0.03	0.14	-0.31	0.26	0.84
Week 2	53/55	3.06	0.66	50/53	2.96	0.75	0.10	0.14	-0.18	0.37	0.49
Week 3	54/55	2.81	1.08	49/53	2.71	0.94	0.10	0.20	-0.30	0.50	0.62
Week 4	53/55	2.79	1.23	53/53	2.83	1.19	0.04	0.23	-0.50	0.43	0.87
Week 6	55/55	2.22	0.94	52/53	2.29	0.89	-0.07	0.18	-0.42	0.28	0.69
Week 8	55/55	1.93	0.63	53/53	1.91	0.66	0.02	0.12	-0,22	0.27	0.86
Month 3	45/50	2.02	1.06	48/49	1.90	1.13	0.13	0.23	-0.33	0.58	0.58
Month 4	45/45	1.78	0.95	43/44	1.81	0.82	0.04	0.19	-0.41	0.34	0.85
Month 5	39/39	1.61	0.71	41/41	1.83	0.71	-0.21	0.18	-0.58	0.15	0.25
Month 6	37/37	1.43	0.65	36/36	1.67	0.96	-0.23	0.19	-0.61	0.15	0.22

n/N number of recorded observations / patients remaining at that assessment
SD standard deviation
SE standard error
CI confidence interval

All calculations given to two decimal points

Table 2.7 Reported adverse events relating to sexual function in the study sample of 108 patients

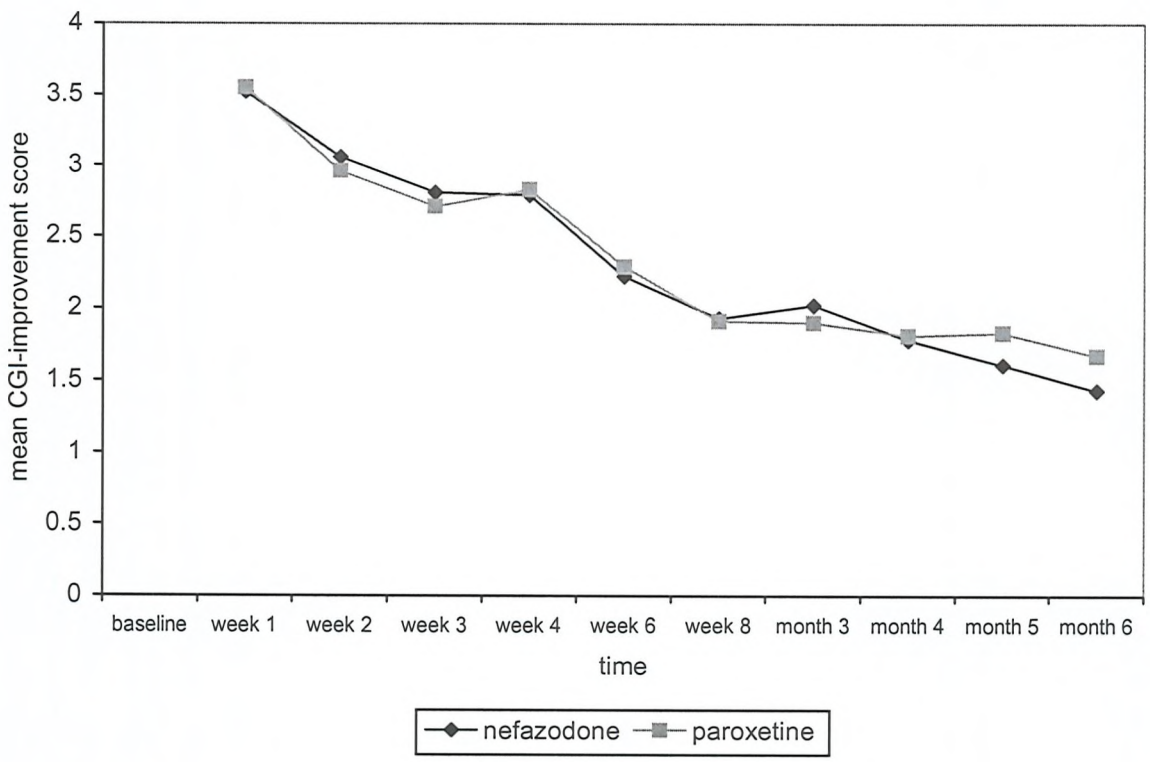
	Nefazodone (n =55)		Paroxetine (n = 53)	
	Acute treatment	**Continuation**	**Acute**	**Continuation**
Patients reporting at least 1 adverse event, N (%)				
Mild	23 (41.8)	20 (50.9)	32 (60.4)	32 (60.4)
Moderate	32 (58.2)	34 (61.8)	31 (58.5)	36 (67.0)
Severe	19 (34.5)	23 (41.8)	18 (34.0)	21 (39.6)
Adverse events relating to sexual function				
Abnormal ejaculation (N)	1 (mild)	1 (mild)	1 (severe)	1 (severe)
Breast pain (N)	1 (mild)	-	-	-
Psychosexual dysfunction (N)	-	1 (moderate)	1 (mild)	1 (mild)
Impotence (N)	-	-	-	1 (moderate)
Duration of adverse event, action				
Abnormal ejaculation	Persisted, monitor *	Persists, monitor *	20 days, none *	Persists, reduce dose *
Breast pain	3 days, none **	-	-	-
Psychosexual dysfunction	-	Persists, treated **	40 days, none *	Persists, reduce dose *
Reduced libido	-	-	-	Persists, none *

* considered related to study drug

** not considered related to study drug

Figure 2.4

Mean CGI-I (improvement) scores in study sample (OC analysis)



Smaller numbers indicate greater improvement

Note that x-axis is not to scale

were described only infrequently. In view of the small numbers, no statistical comparisons were made. Table 2.7 gives details of the reported adverse events that were available in the raw data set.

DISCUSSION

Findings of the overall treatment study

The findings of the overall double-blind, parallel-group, multi-centre, flexible-dose, randomised controlled trial indicate that nefazodone and paroxetine had similar efficacy and tolerability in the treatment of psychiatric outpatients fulfilling DSM-III-R criteria for major depressive episodes. The study treatments differed in pharmacological properties - paroxetine is an SSRI, nefazodone possesses both SSRI and 5-HT_2 antagonist actions - but these differences were not associated with differences in overall efficacy and tolerability, in either acute or continuation treatment.

Findings of the current investigation

The study findings in the sub-group of 108 patients who entered both acute and continuation treatment, indicate that nefazodone and paroxetine differ significantly in their effects on sexual function, as estimated by changes in item 14 (genital symptoms) of the HAM-D. The null hypothesis can therefore be rejected. Treatment with nefazodone was associated with a consistent decline in mean item 14 scores throughout the study; but with paroxetine mean scores increased during the first four weeks of treatment. The difference between the study treatments in mean item 14 score was significant at weeks 2, 4, 6 and 8; and months 3, 5 and 6. This difference between treatment groups was not the result of differences in overall antidepressant efficacy, as the mean total 17-item HAM-D scores and mean CGI-I scores did not differ significantly, at any point, in either acute or continuation treatment.

There were no obvious differences between study treatments in the reporting of adverse events related to sexual function, probably due to the low incidence of events in both treatment groups. An analysis of clinical trial databases for nefazodone and other antidepressants indicate that nefazodone is associated with a low incidence of treatment-emergent sexual adverse events (Preskorn, 1995); but the low number of reports in this study suggests that this is an insensitive measure of sexual dysfunction associated with antidepressant treatment.

Study weaknesses

The overall study has a number of weaknesses. There was no placebo-control group, so technically the antidepressant efficacy of the study treatments was not proven; it can only be concluded that they did not differ in their effects on depressive symptoms as measured by change in mean HAMD scores. Use of a placebo-control may have allowed a more sensitive differentiation between study treatments:

comparator-control studies tend to minimise differences between antidepressant treatment (Baldwin *et al*, 2003). A multi-centre study such as this runs the risk of treatment-by-centre interactions, but efforts were made to minimise this by concerted inter-rater reliability meetings with training in all outcome measures; by supervised rigorous adherence to the study protocol; and by a statistical model that anticipated possible 'centre effects'.

The principal weakness in the current investigation is the reliance on a single and rather limited measure of sexual function. Item 14 is a three-point scale (0, 1 or 2), used to assess not only reduced libido but also other aspects of sexual function such as erectile failure and anorgasmia. It is also used to record disturbances in menstrual function in women, even though weekly ratings of this aspect are of dubious value. Item 14 is a composite measure, and does not allow characterisation of the type of disturbance of sexual function that may be present. Furthermore, the clinical relevance of a difference in score of between 0.29 and 0.46 is uncertain.

Differences between study treatments in effects on sexual function

The findings of the overall study need to be placed in their temporal context. At the time of the overall treatment study, it was felt that nefazodone might have fewer adverse effects on sexual function than the SSRI fluoxetine, but this supposition was based on examination of the clinical trial database for adverse events, rather than on changes on a rating scale (Preskorn, 1995; Baldwin, 1996).

A contemporaneous second double-blind, parallel-group, flexible-dose, multicentre, randomised controlled trial with nefazodone, using the SSRI sertraline as an active comparator, found that nefazodone had advantages over sertraline in some aspects of sexual function, on both item 14 of the HAM-D and a specific rating scale for sexual function (Feiger *et al*, 1996). A subsequent investigation found that nefazodone was significantly superior to sertraline in preventing the re-emergence of sexual dysfunction in non-depressed patients who had experienced previous sexual problems during treatment of depression with sertraline (eventually reported by Ferguson *et al*, 2001). As such, it seemed clear that nefazodone did indeed have advantages over sertraline, in terms of causing less sexual dysfunction during treatment of depression.

However, it was not known whether nefazodone might have advantages over other SSRIs, in causing less sexual dysfunction during the treatment of depression. The findings of the current investigation suggest that this may well be the case. Nefazodone first became available for use in clinical practice in the United Kingdom in 1995, and tended to be used as a second-line treatment in depressed patients who had developed unacceptable changes in sexual function with SSRIs. Nefazodone was prescribed much less frequently than other novel antidepressants, and for largely commercial reasons the manufacturers withdrew it in March 2003.

Implications for clinical practice and research

The findings of the current investigation support the contention that prescription of drugs with 5-HT_2 antagonist properties may be particularly indicated in those depressed patients for whom preserved sexual function is a major concern, for whom an SSRI might otherwise be recommended (Hirschfeld, 1999). In the United Kingdom, this currently means that mianserin, mirtazapine and trazodone may be drugs of choice in this clinical situation, providing there are no other reasons (e.g. concerns about potential for weight gain, drowsiness, or previous blood dyscrasias) that militate against their use.

Future research into the propensity of antidepressants to cause sexual dysfunction should not rely on the incidence of treatment-emergent adverse events related to sexual function, as the number of such events reported within a randomised controlled trial is too small to allow differentiation between treatments. In addition, reliance on change in the score on item 14 of the HAM-D, although sensitive to change and able to differentiate between treatments, is inappropriate as the sole approach to characterising the range and severity of sexual problems occurring during antidepressant treatment. For these reasons, the studies described in the subsequent chapters in this thesis have all employed a specific rating scale for assessing the components of sexual function and satisfaction during treatment with antidepressants.

CHAPTER 3 : POINT PREVALENCE OF SEXUAL PROBLEMS DURING ANTIDEPRESSANT TREATMENT

AIM OF THE INVESTIGATION

The findings of the randomised controlled trial with nefazodone and paroxetine (described in chapter 2) suggested that depressed patients reported treatment-emergent sexual problems only infrequently. I was concerned that patient self-report of treatment-emergent adverse events was an unreliable measure of possible adverse sexual effects of antidepressants, and wished to determine whether routine use of rating scales assessing sexual function might be a better method for investigating this area of clinical practice.

The main aim of the study was to determine whether questioning patients about their sexual function was possible within the setting of my routine clinical practice. I also wished to estimate the prevalence and determine the nature of reported sexual problems among patients taking antidepressant drugs. I wished to ascertain whether study participants exhibited a range of impairments in the sexual response cycle, and to see whether the prevalence of sexual problems was related to the presence of a history of sexual abuse or assault, co-morbid physical illness or concomitant prescribed medication. As the study was essentially a pilot study of the assessment of sexual function, involving less than 100 patients, I did not employ complex statistical analysis.

My role in this investigation included the following activities -

- developing the study protocol
- submitting the protocol to the local research ethics committee
- training a research assistant in use of the diagnostic interview and rating scales
- analysing the data
- presenting the preliminary results at a scientific meeting
- preparing the final study report
- preparing the results for publication

METHOD

The investigation involved collection of data from a consecutive sample of patients attending routine outpatient clinic appointments within the Mood Disorders Service in Southampton. The patients were interviewed between October 1997 and September 1998. Typically, each patient had already undertaken a 30-60 minute appointment before the study was mentioned and consent to participation

was sought. All data was collected by a research colleague or me at the end of routine outpatient appointments. I supervised this colleague and examined the data for each patient at the end of each clinic.

Inclusion and exclusion criteria

The inclusion criteria for participation in the study were limited, in an attempt to include a representative sample of patients. Study participants had to be currently receiving care within the Mood Disorders Service, to be taking at least one antidepressant, and to able to understand the procedures involved in the study. The sole exclusion criterion was that an interview would not be undertaken if it was considered likely to cause unnecessary upset to the patient.

Diagnostic interview

All patients underwent a structured clinical assessment using the Mini-International Neuropsychiatric Interview (MINI) (English version 5.0) (Sheehan *et al*, 1998). The MINI contains a series of questions based on diagnostic criteria for mental disorders, and generates psychiatric diagnoses according to the DSM-IV and ICD-10 systems. The medical case-notes for each patient were reviewed to establish the primary clinical diagnosis.

Assessment of sexual function

The presence of sexual difficulties during treatment with antidepressant drugs was assessed in three different ways. Firstly, all patients were asked in general terms to describe any side effects or problems that they may have experienced during treatment. Secondly, they were asked to complete a simple sexual function and enjoyment questionnaire, designed in consultation with the patient self-help charitable organisation Depression Alliance. A previous version of this questionnaire was included in the booklet '*Depression and Your Sex Life*', written by me and published by Depression Alliance in 1996. The scale exists in different forms for men and women, both scales including five items. Patients were asked to compare their current to their normal level of sexual functioning. The MINI is shown in Appendix 3.1; the male and female versions of the sexual function questionnaire are shown in Appendices 3.2 and 3.3, respectively.

Ethical considerations

The protocol for this study was approved by the Southampton Joint Ethics Committee on 5th June 1997 and by the University of Southampton on 11th June 1997. No ethical problems were foreseen for the participation of patients in the study.

RESULTS

Study sample

Two patients were excluded from possible participation in the study. The first was considered too distressed to be able to undertake completion of the questionnaires, and discussion of sexual matters with the second patient would have further complicated an already troubled patient-doctor relationship. These two patients aside, all attending patients were approached about potential participation in the study.

A total of 84 patients agreed to participate in the study. One patient was inadvertently interviewed twice, and data from the second interview are excluded from analysis. The remaining 83 patients (41 men, 42 women) had a mean age of 40.1 years, with an age range of 19-70 years. Reflecting the nature of the Mood Disorders Service, the principal clinical diagnosis in most patients was of either a mood (n=49) or an anxiety disorder (n=24). Three patients had obsessive-compulsive disorder. A total of six patients had other medical conditions (chronic fatigue syndrome, obsessional personality disorder, complex partial seizures, schizoaffective disorder [2 patients], and frontal lobe syndrome): in one patient the diagnosis was unclear. A clinical vignette describing each patient is included in Appendix 3.4. Table 3.1 gives data for each of the participating patients.

MINI Diagnoses

As expected in a secondary care mood disorders patient sample, there was substantial psychiatric co-morbidity, most patients having more than one current MINI diagnosis. A total of 234 MINI diagnoses were recorded in the overall sample (105 in men, average number of diagnoses 2.6; 125 in women, average number 3.0). The most common current MINI diagnoses were major depressive episode (51 patients), social phobia (42) and panic disorder with agoraphobia (34). A total of 57 patients had no lifetime (i.e. previous) MINI diagnosis. The most common lifetime diagnoses were bipolar disorder (10 patients), mood disorder with psychotic features (9) and panic disorder (9). The demographic characteristics, primary clinical diagnoses and current MINI diagnoses are shown in Table 3.2.

Table 3.1 Individual patient data

Patient	Gender	Age	Clinical diagnosis	Current MINI diagnoses	Lifetime MINI diagnoses	Current physical illness	Anti-depressant	Other psychotropics	Other drugs	Sexual abuse	Sexual partner	Current sexual Problems
P001	M	41	Chronic fatigue syndrome	Major depressive episode, bipolar disorder, panic disorder with agoraphobia, obsessive-compulsive disorder, post-traumatic stress disorder	Mood disorder with psychotic features	Chronic fatigue syndrome[a]	RIMA	-	-	Y	N	Arousal Ejaculation Enjoyment
P002	F	51	Recurrent depressive disorder	Major depressive episode, agoraphobia, social phobia, post-traumatic stress disorder	-	COPD[a], Incontinence[a]	SNRI	Phenothiazine[b] Benzodiazepine[b] Anticholinergic Anticonvulsant[b]	Steroid[b] Theophylline H2 antagonist[b] Opiate/NSAID[b]	Y	N	Desire Arousal Orgasm
P003	M	62	Bipolar affective disorder	-	-	-	SNRI	Lithium	-	N	Y	Desire Arousal Enjoyment
P004	F	55	Recurrent depressive disorder	-	-	Chronic vulvitis[a]	SSRI	Benzodiazepine	H2 antagonist[b] Steroid[b]	N	Y	Desire Arousal
P005	M	46	Bipolar affective disorder	Major depressive episode, agoraphobia, social phobia	Bipolar disorder	-	SNRI	Anticonvulsant	-	N	Y	Desire Arousal Orgasm Enjoyment
P006	F	35	Bipolar affective disorder	-	Bipolar disorder, panic disorder, mood disorder with psychosis	-	SSRI	Lithium	Oral contraceptive[b]	N	Y	Desire Arousal Orgasm Enjoyment
P007	M	34	Panic disorder with agoraphobia	Panic disorder with agoraphobia, social phobia	-	-	SSRI	-	-	N	N	Arousal Orgasm
P008	M	32	Obsessive-compulsive disorder	Obsessive-compulsive disorder, generalised anxiety disorder	-	-	SSRI	-	-	N	N	None
P009	F	48	Depressive episode	Major depressive episode, social phobia, specific phobia, obsessive-compulsive disorder, alcohol dependence	-	-	SNRI	Lithium	-	Y	Y	Orgasm
P010	M	46	Panic disorder with agoraphobia	Panic disorder, major depressive episode, social phobia, specific phobia, obsessive-compulsive disorder	Bipolar disorder, mood disorder with psychotic features	Sensorineuronal deafness	TCA	Benzodiazepine	-	N	Y	Desire Arousal Orgasm Enjoyment

Patient	Gender	Age	Clinical diagnosis	Current MINI diagnoses	Lifetime MINI diagnoses	Current physical illness	Anti-depressant	Other psychotropics	Other drugs	Sexual abuse	Sexual partner	Sexual Problems
P011	F	40	Recurrent depressive disorder	Major depressive episode, panic disorder with agoraphobia	-	Hiatus hernia	5-HT_2 antagonist	-	Proton pump inhibitor[b] Cisapride	Y	Y	Desire Arousal Orgasm Enjoyment
P012	F	40	Bipolar affective disorder	Current post-traumatic stress disorder	Bipolar disorder, mood disorder with psychosis, panic disorder	-	TCA	Lithium Substituted benzamide[b]	-	Y	Y	Arousal
P013	M	37	Obsessive-compulsive disorder	Major depressive episode, obsessive-compulsive disorder	-	-	SSRI	5-HT_{1a} partial agonist	-	N	N	Orgasm
P014	F	37	Recurrent depressive disorder	Major depressive episode, panic disorder with agoraphobia, social phobia, specific phobia	-	-	5-HT_2 antagonist	-	-	N	Y	Desire Arousal Orgasm Enjoyment
P015	F	29	Post-traumatic stress disorder	Major depressive episode, agoraphobia, social phobia, post-traumatic stress disorder	Panic disorder	Psoriasis[a]	5-HT_2 antagonist	-	Immuno-suppressant	N	Y	Desire Arousal Orgasm Enjoyment
P016	F	24	Depressive episode with psychosis	Major depressive episode, bipolar disorder, panic disorder with agoraphobia, social phobia, obsessive-compulsive disorder	-	-	SNRI	Phenothiazine[b] Benzodiazepine	-	Y	Y	Desire Arousal Orgasm Enjoyment
P017	F	35	Social phobia	Social phobia, agoraphobia, obsessive-compulsive disorder	-	-	SSRI	-	-	N	Y	Desire Arousal Orgasm Enjoyment
P018	M	34	Social phobia	Major depressive episode, agoraphobia, social phobia	Alcohol dependence	Gilbert's syndrome	SSRI	-	-	N	Y	Desire
P019	M	33	Recurrent depressive disorder	Generalised anxiety disorder	-	-	SSRI	-	-	N	N	Orgasm Enjoyment
P020	M	26	Social phobia	Agoraphobia, social phobia, specific phobia	-	-	SSRI	-	-	N	Y	Desire Orgasm
P021	F	35	Dysthymic disorder	Major depressive episode, panic disorder with agoraphobia, social phobia, specific phobia, post-traumatic stress disorder	Bipolar disorder	-	SSRI	Phenothiazine[b]	-	Y	N	Arousal Orgasm Enjoyment

Patient	Gender	Age	Clinical diagnosis	Current MINI diagnoses	Lifetime MINI diagnoses	Current physical illness	Anti-depressant	Other psychotropics	Other drugs	Sexual abuse	Sexual partner	Sexual Problems
P022	M	38	Panic disorder	Panic disorder with agoraphobia	-	-	SSRI	-	-	N	Y	Orgasm
P023	F	38	Depressive episode with psychosis	Major depressive episode	-	Asthma[a]	TCA	Lithium Liothyronine Tryptophan Thioxanthene[b] Anticholinergic	-	N	Y	Desire Arousal Orgasm Enjoyment
P024	M	31	Panic disorder	Panic disorder with agoraphobia, drug dependence	-	-	SSRI	-	-	N	Y	None
P025	M	70	Recurrent depressive disorder	Major depressive episode	Panic disorder	Osteoporosis, back pain[a]	SSRI	Lithium	paracetamol	N	N	Discussion refused
P026	M	42	Recurrent depressive disorder	Major depressive episode with psychosis, panic disorder with agoraphobia, obsessive-compulsive disorder, alcohol dependence, drug dependence, post-traumatic stress disorder	-	-	SSRI	Benzodiazepine Opiate[b]	NSAID	N	N	Desire Arousal Orgasm Enjoyment
P027	M	19	Panic disorder	Panic disorder	-	-	SSRI	Benzodiazepine	-	N	Y	Desire Arousal Orgasm Enjoyment
P028	M	50	Recurrent depressive disorder	Agoraphobia, social phobia	Panic disorder	Migraine	TCA	Lithium	-	N	Y	Desire Arousal Enjoyment
P029	F	50	Recurrent depressive disorder with psychosis	Dysthymia, panic disorder with agoraphobia, social phobia, anorexia nervosa	Mood disorder with psychosis	Hypo-thyroidism	SSRI	Phenothiazine[b] Anticholinergic	Thyroxine	N	Y	Desire Arousal Orgasm Enjoyment
P030	F	41	Depressive episode	Major depressive episode, panic disorder, social phobia	-	-	SSRI	-	-	N	Y	Desire Pain Arousal Orgasm Enjoyment
P031	F	29	Panic disorder with agoraphobia	Panic disorder with agoraphobia, social phobia	-	-	TCA	-	-	N	Y	Orgasm
P032	M	34	Panic disorder	Alcohol dependence	Panic disorder with agoraphobia	Cardiac disease[a]	SSRI	-	Anti-arrhythmic	N	Y	Desire Arousal Orgasm Enjoyment
P034	F	62	Recurrent depressive disorder	Panic disorder, social phobia, post-traumatic stress disorder	-	Recent femoral fracture, pain[a]	SNRI	-	NSAID	N	Y	None

Patient	Gender	Age	Clinical diagnosis	Current MINI diagnoses	Lifetime MINI diagnoses	Current physical illness	Anti-depressant	Other psychotropics	Other drugs	Sexual abuse	Sexual partner	Sexual Problems
P035	M	44	Panic disorder	Major depressive episode, panic disorder with agoraphobia, social phobia	-	-	SSRI	Phenothiazine[b]	-	N	Y	Desire Arousal Enjoyment
P036	M	56	Obsessional personality disorder	Dysthymia, social phobia, post-traumatic stress disorder	-	Myocardial ischaemia[a]	MAOI	Benzodiazepine[b]	NSAID ACE inhibitor[b] Proton pump inhibitor[b]	N	N	None
P037	M	51	Recurrent depressive disorder	Major depressive episode, panic disorder, generalised anxiety disorder	-	Renal calculi	TCA	-	-	N	Y	Arousal Orgasm
P038	M	37	Recurrent depressive disorder	-	-	-	TCA	-	-	N	Y	Desire
P039	F	43	Recurrent depressive disorder	Agoraphobia, generalised anxiety disorder	-	-	5-HT_2 antagonist	-	-	N	Y	Desire Arousal Orgasm Enjoyment
P040	M	30	Complex partial seizures	Major depressive episode with psychosis, panic disorder with agoraphobia, social phobia, obsessive-compulsive disorder	Bipolar disorder	Temporal lobe epilepsy[a]	SSRI	-	Anticonvulsant[b]	N	Y	Desire Arousal Orgasm Enjoyment
P041	F	42	Recurrent depressive disorder	Major depressive episode, panic disorder, social phobia, post-traumatic stress disorder	-	Acne, hypo-thyroidism, hypertension	SNRI	Lithium	Thyroxine Thiazide[b] Tetracycline	Y	N	Refused discussion
P042	M	22	Depressive episode	Agoraphobia, social phobia, obsessive-compulsive disorder	-	-	TCA	-	-	N	N	None
P043	M	52	Depressive episode	Major depressive episode	-	Meniere's disease	SSRI, 5-HT_2 antagonist	-	-	N	Y	Desire Arousal Enjoyment
P044	F	39	Panic disorder	Agoraphobia, social phobia	Panic disorder	-	SSRI	-	Quinine	N	Y	Desire
P045	F	50	Recurrent depressive disorder	Major depressive episode, panic disorder with agoraphobia, obsessive-compulsive disorder	-	-	5-HT_2 antagonist	Phenothiazine[b]	-	N	N	Refused discussion
P046	F	25	Depressive episode	Major depressive episode, panic disorder with agoraphobia, alcohol dependence	Bipolar disorder	Recurrent patellar dislocation, chest infection[a]	TCA	-	Penicillin	N	Y	Desire Arousal Orgasm Enjoyment
P047	F	36	Depressive episode	Major depressive episode, panic disorder	-	-	SSRI	Phenothiazine	Opiate/NSAID[b]	Y	Y	Desire Arousal Orgasm Enjoyment

Patient	Gender	Age	Clinical diagnosis	Current MINI diagnoses	Lifetime MINI diagnoses	Current physical illness	Anti-depressant	Other psychotropics	Other drugs	Sexual abuse	Sexual partner	Current sexual Problems
P048	F	22	Dysthymic disorder	Dysthymia, panic disorder with agoraphobia	-	-	SSRI	-	-	N	N	Arousal Orgasm Enjoyment
P049	M	51	Recurrent depressive disorder	Major depressive episode, alcohol dependence	Bipolar disorder, mood disorder with psychosis	Back pain[a], psoriasis[a]	SSRI	-	NSAID	N	N	Desire Arousal Enjoyment
P050	F	38	Recurrent depressive disorder	Major depressive episode, bipolar disorder, social phobia, specific phobia	Mood disorder with psychosis	-	SSRI	Lithium Cyclopyrrolone Phenothiazine[b]	-	N	N	Desire Arousal Orgasm Enjoyment
P051	F	19	Post-traumatic stress disorder	Major depressive episode, social phobia	-	Acne	SSRI	-	Tetracycline	N	N	None
P052	M	48	Recurrent depressive disorder	Bipolar disorder, alcohol dependence	-	Alcoholic hepatitis	5-HT_2 antagonist	-	-	Y	Y	Arousal Orgasm
P053	F	30	Schizo-affective psychosis	Bipolar disorder, panic disorder, specific phobia, obsessive-compulsive disorder, psychosis, post-traumatic stress disorder	-	Hypertension	SNRI	Anticholinergic Atypical antipsychotic	Thiazide[b] Thyroxine	Y	N	Desire Arousal Orgasm Enjoyment
P054	F	44	Social phobia	Major depressive episode, panic disorder with agoraphobia, social phobia	Mood disorder with psychosis	Type II diabetes mellitus[a]	SSRI	-	Oral contraceptive[b]	N	N	None
P055	F	35	Recurrent depressive disorder	Major depressive episode, panic disorder with agoraphobia, social phobia	-	-	SSRI	Benzodiazepine	-	N	N	Desire Arousal Orgasm Enjoyment
P056	F	41	Recurrent depressive disorder	Major depressive episode, panic disorder, social phobia	-	-	TCA	Lithium Phenothiazine[b] Liothyronine	-	Y	Y	Desire Arousal Orgasm Enjoyment
P057	F	56	Recurrent depressive disorder	Major depressive episode, panic disorder with agoraphobia, social phobia, obsessive-compulsive disorder	-	-	5-HT_2 antagonist	-	Steroid	N	Y	Desire Arousal Orgasm Enjoyment
P058	F	35	Panic disorder	Panic disorder	-	-	TCA	Thioxanthene[b]	-	N	Y	Desire Arousal Orgasm Enjoyment

Patient	Gender	Age	Clinical diagnosis	Current MINI diagnoses	Lifetime MINI diagnoses	Current physical illness	Anti-depressant	Other psychotropics	Other drugs	Sexual abuse	Sexual partner	Current sexual problems
P059	F	30	Obsessive-compulsive disorder	Major depressive episode, panic disorder, social phobia, obsessive-compulsive disorder	-	-	TCA	-	-	N	N	Desire Arousal Orgasm Enjoyment
P060	M	31	Depressive disorder	Major depressive episode, agoraphobia, specific phobia, alcohol dependence	-	Non-epileptic seizures	SSRI	-	Anti-migraine analgesic	N	Y	Orgasm
P061	M	50	Social phobia	Social phobia	-	'Irritable bowel syndrome'	SSRI	-	-	N	Y	None
P062	M	38	Recurrent depressive disorder	Dysthymia, panic disorder with agoraphobia, alcohol dependence	Bipolar disorder, mood disorder with psychosis	-	SSRI	-	-	N	N	Arousal Orgasm
P063	F	37	Recurrent depressive disorder	Major depressive episode, panic disorder with agoraphobia, social phobia, obsessive-compulsive disorder	Bipolar disorder	-	SSRI	-	-	N	Y	Desire Arousal Orgasm Enjoyment
P064	F	21	Social phobia	Bipolar disorder, panic disorder with agoraphobia, social phobia, specific phobia	-	-	SSRI	-	-	N	Y	Orgasm Enjoyment
P065	M	49	Recurrent depressive disorder	Major depressive episode, panic disorder with agoraphobia	Mood disorder with psychosis, antisocial disorder	Myocardial ischaemia[a]	SSRI 5-HT_2 antagonist	Thioxanthene[b]	NSAID	N	Y	Desire Arousal Orgasm Enjoyment
P066	M	23	Unclear	Major depressive episode, agoraphobia, social phobia	-	-	SSRI TCA	Phenothiazine[b]	-	N	N	Arousal Orgasm Enjoyment
P067	M	49	Depressive disorder	Major depressive episode, panic disorder with agoraphobia	-	Asthma	TCA	-	Salbutamol inhaler	N	N	Desire Arousal Enjoyment
P068	M	47	Dysthymic disorder	Major depressive episode, agoraphobia	-	-	SNRI	-	-	N	Y	Desire Arousal Orgasm Enjoyment
P069	M	55	Dysthymic disorder	Major depressive episode, bipolar disorder, agoraphobia, generalised anxiety disorder	-	Cardio-myopathy [a], hypotension	TCA	Butyrophenone[b] Benzodiazepine Anticholinergic	-	N	Y	Desire Orgasm Arousal Enjoyment
P070	M	33	Post-traumatic stress disorder	Major depressive episode, panic disorder with agoraphobia, social phobia, obsessive-compulsive disorder, post-traumatic stress disorder	Mood disorder with psychosis	-	SNRI	-	-	N	N	Arousal

Patient	Gender	Age	Clinical diagnosis	Current MINI diagnoses	Lifetime MINI diagnoses	Current physical illness	Anti-depressant	Other psychotropics	Other drugs	Sexual abuse	Sexual partner	Current sexual Problems
P071	M	46	Frontal lobe syndrome	Major depressive episode, post-traumatic stress disorder	Panic disorder	Frontal damage[a], anosmia	SSRI	-	-	N	N	Desire Arousal Orgasm Enjoyment
P072	F	57	Recurrent depressive disorder	Major depressive episode, agoraphobia	-	Hypo-thyroidism	TCA	-	Thyroxine	N	Y	Desire Arousal Orgasm Enjoyment
P073	F	36	Panic disorder	Major depressive episode, panic disorder, social phobia, specific phobia, obsessive-compulsive disorder	-	-	SSRI	-	-	Y	Y	Desire Arousal Orgasm Enjoyment
P074	M	49	Panic disorder	Major depressive episode, panic disorder with agoraphobia, social phobia	-	Nasal polyposis	TCA	Benzodiazepine[b]	Beta-blocker[b]	N	Y	Arousal Orgasm Enjoyment
P075	F	40	Recurrent depressive disorder	Major depressive episode, panic disorder with agoraphobia, social phobia, specific phobia	-	-	TCA	Thioxanthene[b] Benzodiazepine[b]	-	N	Y	Desire Arousal Orgasm Enjoyment
P076	M	50	Panic disorder	Major depressive episode, panic disorder with agoraphobia, social phobia	bipolar disorder, psychotic syndrome	-	TCA	Lithium Phenothiazine[b] Benzodiazepineb	-	N	Y	Desire Arousal Ejaculation Enjoyment
P077	M	31	Panic disorder	Major depressive episode, panic disorder with agoraphobia	-	-	5-HT_2 antagonist	-	-	N	Y	None
P078	M	41	Depressive episode	Major depressive episode, panic disorder with agoraphobia, social phobia, alcohol dependence	-	Venous ulceration	SSRI	-	-	N	Y	Desire Arousal Orgasm Enjoyment
P079	M	50	Depressive episode	Major depressive episode, panic disorder with agoraphobia, social phobia	-	-	SSRI	Cyclopyrrolone	-	N	Y	Desire Arousal Orgasm Enjoyment
P080	F	42	Schizo-affective disorder	Major depressive episode, agoraphobia, generalised anxiety disorder	Panic disorder	-	SSRI	-	-	N	Y	Desire Arousal Orgasm Enjoyment
P081	F	49	Recurrent depressive disorder	Dysthymia, agoraphobia, social phobia	Panic disorder	Hypo-thyroidism	NaRI	-	Thyroxine	Y	N	Desire Arousal Orgasm Enjoyment

Patient	Gender	Age	Clinical diagnosis	Current MINI diagnoses	Lifetime MINI diagnoses	Current physical illness	Anti-depressant	Other psychotropics	Other drugs	Sexual abuse	Sexual partner	Current sexual Problems
P082	F	44	Recurrent depressive disorder	Generalised anxiety disorder	-	-	SSRI	-	-	N	Y	Desire Arousal Orgasm Enjoyment
P083	F	31	Social phobia	Major depressive episode, panic disorder with agoraphobia, social phobia, generalised anxiety disorder	-	-	SSRI	-	-	Y	N	Desire Arousal Orgasm Enjoyment

A medical condition associated with sexual dysfunction
B medication (other than antidepressants) associated with sexual dysfunction

Table 3.2

Study sample demographic and clinical characteristics

	Men	Women	Total sample
N	41	42	83
Mean age (yrs)	41.7	38.6	40.1
Age range (yrs)	19-70	19-62	19-70
Primary clinical diagnosis			
Depressive disorder	18	27	45
Anxiety disorder	14	10	24
Bipolar illness	2	2	4
Obsessive-compulsive disorder	2	1	3
Other	4	2	6
Unclear	1	-	1
Current MINI diagnosis			
Major depressive episode	25	26	51
Social phobia	17	25	42
Panic disorder with agoraphobia	17	17	34
Obsessive-compulsive disorder	8	10	18
Agoraphobia	9	8	17
Panic disorder	3	9	12
Post-traumatic stress disorder	4	7	11
Specific phobia	2	8	10
Alcohol dependence	7	2	9
Generalised anxiety disorder	4	4	8
Bipolar disorder	3	4	7
Dysthymia	2	3	5
Other	4	2	6
None	2	2	4
Total	105	125	230
Average number MINI diagnoses	2.6	3.0	2.8

Psychotropic drug treatment

Patients were taking antidepressants from a range of classes, in keeping with the nature of the study. Three patients were taking two antidepressant drugs, one usually being used to counteract insomnia associated with the other. Forty-four patients were taking an SSRI, and nineteen patients were taking a TCA. Ten patients were taking the serotonin-noradrenaline re-uptake inhibitor venlafaxine; and in another 10, the 5-HT_2 antagonists nefazodone or mirtazapine. Two patients were taking a monoamine oxidase inhibitor and one patient the noradrenaline reuptake inhibitor reboxetine.

Thirty-four patients were taking at least one psychotropic drug, in addition to an antidepressant. A total of 18 patients were taking an antipsychotic drug: in four patients this was for psychotic symptoms, in the remaining patients they were being used for anxiety symptoms that had proved resistant to other treatment approaches. Fourteen patients were taking a benzodiazepine, principally as a hypnotic; 11 patients were taking lithium, and five patients were taking an anticholinergic drug (all to counteract extra-pyramidal adverse effects of antipsychotic drugs). Seven patients were taking other psychotropic drug classes (liothyronine [2 patients]; a cyclopyrrolone [2 patients]; 5-$HT1_a$ partial agonist; anticonvulsant; l-tryptophan; opiate). Among the 34 patients who were taking psychotropic drugs in addition to an antidepressant, these drugs could have contributed to sexual dysfunction in 22 patients. Table 3.3 gives details of prescribed psychotropic medication.

Co-morbid physical illness and concomitant medication

A total of 34 patients had a total of 62 current physical health problems. In 17 patients, these problems could have contributed to any sexual problems, either through pain (n=3), uncertainty regarding cardiac health (n=4), urogenital problems (n=2), breathlessness (n=3), unsightly skin conditions (n=2), fatigue (n=1), brain disease (n=2): two patients had two possible contributory conditions. Twenty-seven patients were taking medication for their physical ill health; of these 21 were taking one medicine alone. In 11 patients, these concomitant medications for physical problems could have contributed to any sexual problems. Table 3.3 also gives details of physical health problems and medication used to treat physical illness.

Reported sexual problems

A total of 14 patients (2 men, 12 women) reported a history of sexual abuse. Fifty-five patients (26 men, 29 women) had a current sexual partner. When asked whether they had experienced any recent sexual difficulties, 37 patients (19 men, 18 women) replied positively. When asked to complete the sexual function questionnaire, 10 patients reported no sexual problems, 10 described a single problem, and 60 reported multiple problems. Three patients declined to complete the questionnaire. Taken together, the 80 patients who completed the questionnaire described a total of 223 current sexual problems, an

Table 3.3

Prescribed medication and physical health

	Men	Women	Total sample
N	41	42	83
Antidepressant class			
SSRI	24	20	44
TCA	10	9	19
SNRI	4	6	10
5-HT2 antagonist	4	6	10
MAOI	2	-	2
Other	-	1	1
Concomitant psychotropic drug			
Antipsychotic drug	5	13	18
Benzodiazepine	8	6	14
Lithium	4	7	11
Other	4	3	7
Anticholinergic	1	4	5
No concomitant drug	26	23	49
Physical ill health	17	17	34
likely to cause sexual problems			17
Drugs for physical illness			
Yes	10	17	27
Single drug	9	12	21
Two drugs	-	3	3
Three drugs	1	2	3
likely to cause sexual problems			11

Table 3.4

Reported sexual problems

	Men	Women	Total sample
N (%)	41 (49.4)	42 (50.6)	83 (100)
History of sexual abuse (%)	2 (2.4)	12 (14.5)	14 (16.9)
Current sexual partner (%	26 (63.4)	29 (69.0)	55 (66.3)
Direct report of sexual problems	19 (46.3)	18 (42.9)	37 (44.6)
Questionnaire description of sexual problems			
No problems (%)	6 (14.6)	4 (9.5)	10 (12.0)
Single problem (%)	6 (14.6)	4 (9.5)	10 (12.0)
Multiple problems (%)	28 (68.3)	32 (76.2)	60 (72.3)
Refused discussion (%)	1 (2.4)	2 (4.8)	3 (3.6)
Type of sexual problem			
Desire	22	30	52
Arousal	27	32	59
Ejaculation	2	-	2
Orgasm	23	33	56
Pain	0	1	1
Satisfaction	23	30	53

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average of 2.8 problems per patient. Patient-reported problems occurred with similar frequency in all phases of the sexual response cycle (desire, arousal, orgasm). Table 3.4 gives details of the sexual problems reported by the sample.

Sexual function and enjoyment questionnaire responses

Very few patients described improvements in any aspect of their current sexual function, compared to normal. Only 17 of the completed questionnaire items, from a total of 415 items, indicated an improvement over normal levels in an area of sexual functioning. Most patients described considerable impairments in sexual function: 260 responses to individual items showed either minor or major impairment in an area of sexual functioning. The distribution of scores on individual questionnaire items is shown in Figure 3.1 to Figure 3.5 for men, and Figure 3.6 to Figure 3.10 for women.

The findings from the sub-group of 41 male patients appear to indicate that aspects of function are affected adversely less often than in women. In men, out of a maximum of 205 items, 75 items (36.6%) were rated as showing no change: in the sample of 42 women, 37 out of 210 items (17.6%) indicated no change compared to normal sexual functioning. Female patients also appeared to describe greater severity of impairment: in women 113 out of the 147 (76.9%) questionnaire items indicating an impairment were at the more severe end, whereas the figure for men was 76 out of 113 (67.2%). The questionnaire responses for the sub-groups of male and female patients are shown in Table 3.5.

Effects of psychiatric co-morbidity

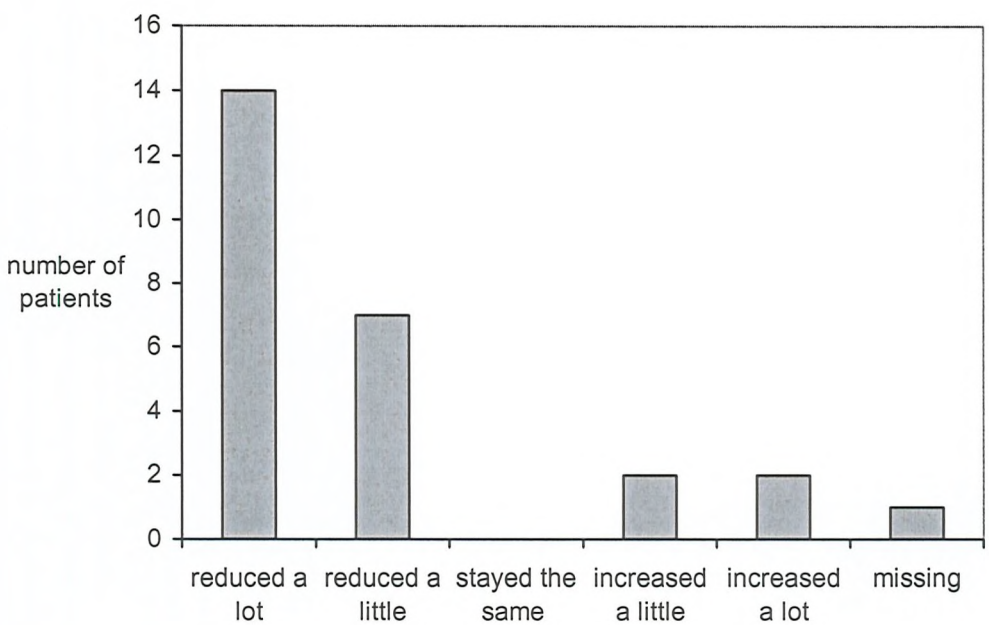
The presence of sexual problems appears related to the number of current MINI diagnoses. The more MINI diagnoses (i.e. increasing co-morbidity), the greater the likelihood of patients describing multiple sexual problems. Out of the total of 40 patients who described problems in all areas of the sexual response, 26 (65%) had three or more current MINI diagnoses, and 16 of the 24 patients with four or more current MINI diagnoses described impairments in four or more areas of sexual function. Table 3.6 shows the relationship between increasing co-morbidity and descriptions of sexual problems.

Effects of psychotropic polypharmacy

There was no clear relationship between the number of prescribed psychotropic drugs and the number of patient-described sexual problems. Most patients who were taking three or more psychotropic drugs reported multiple changes in sexual function, but in the 49 patients who were taking only one psychotropic drug (the antidepressant), 22 (44.9%) described changes in four or more areas of sexual function. Table 3.7 shows the relationship between number of prescribed drugs and presence of sexual problems.

Figure 3.1

Sexual function and enjoyment questionnaire item 1 scores in male patients



Compared to your normal sexual functioning, has your desire for sex changed?

Figure 3.2

Sexual function and enjoyment questionnaire item 2 scores in male patients

Compared to your normal sexual functioning, how easy is it to achieve your normal erection?

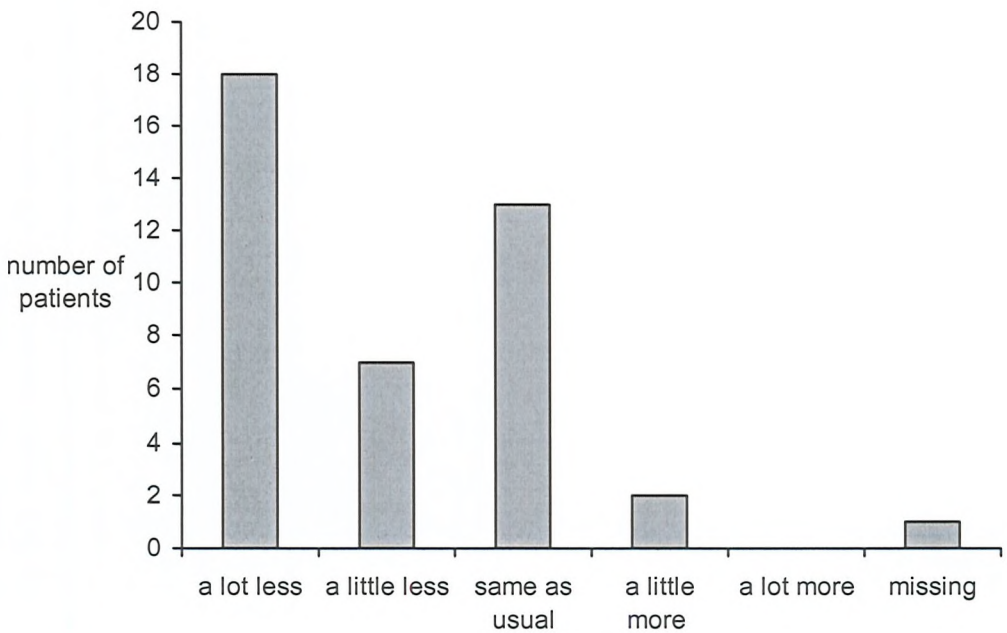


Figure 3.3

Sexual function and enjoyment questionnaire item 3 scores in male patients

Compared to your normal sexual functioning, has your ability to maintain an erection changed?

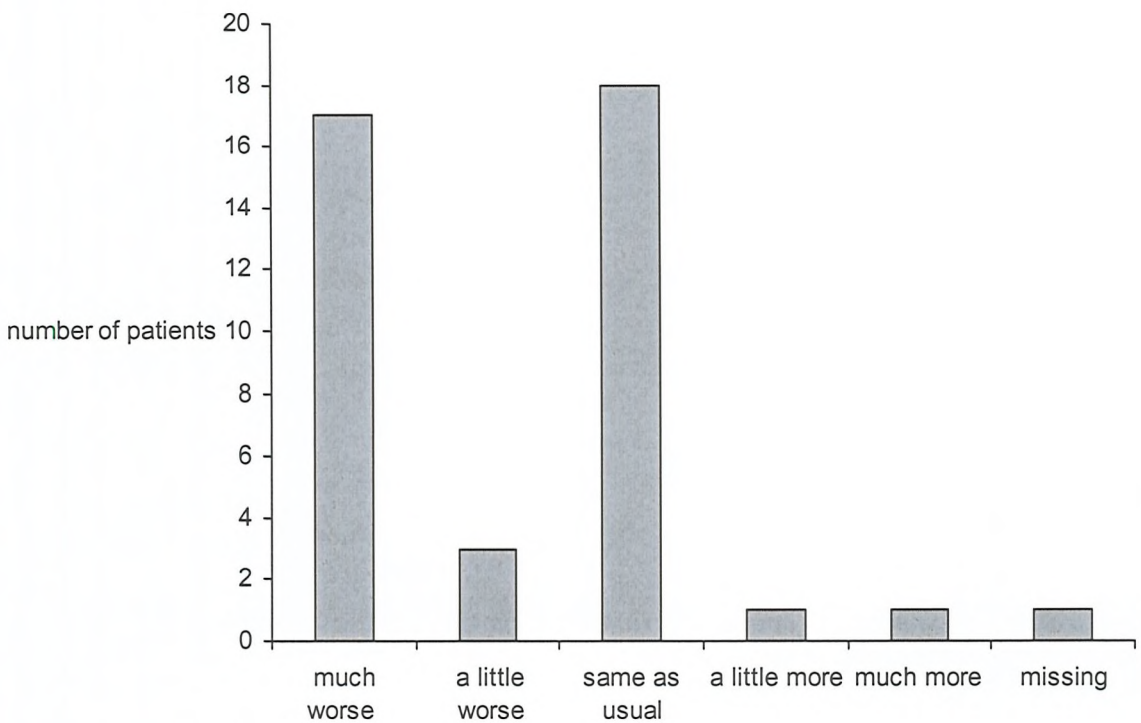


Figure 3.4

Sexual function and enjoyment questionnaire item 4 scores in male patients

Compared to your normal sexual functioning, has your ability to ejaculate changed?

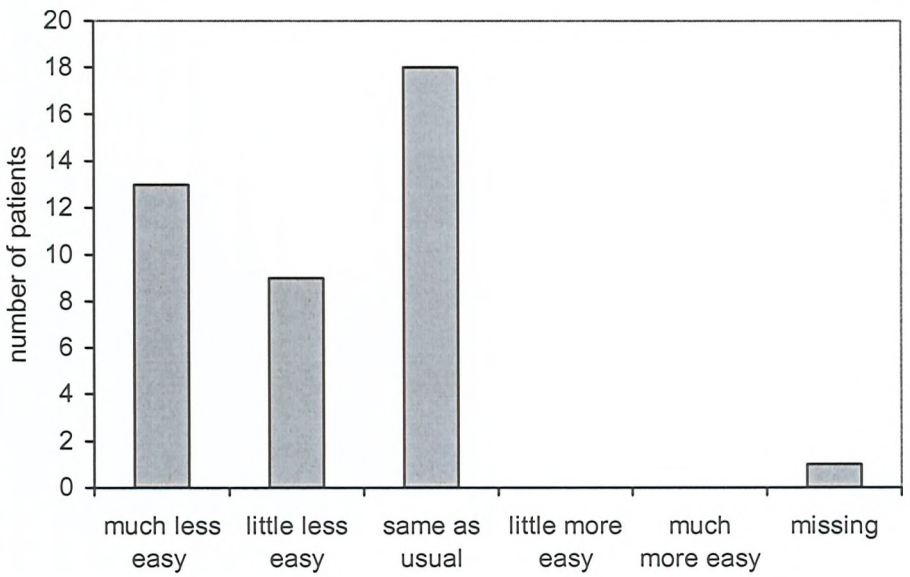
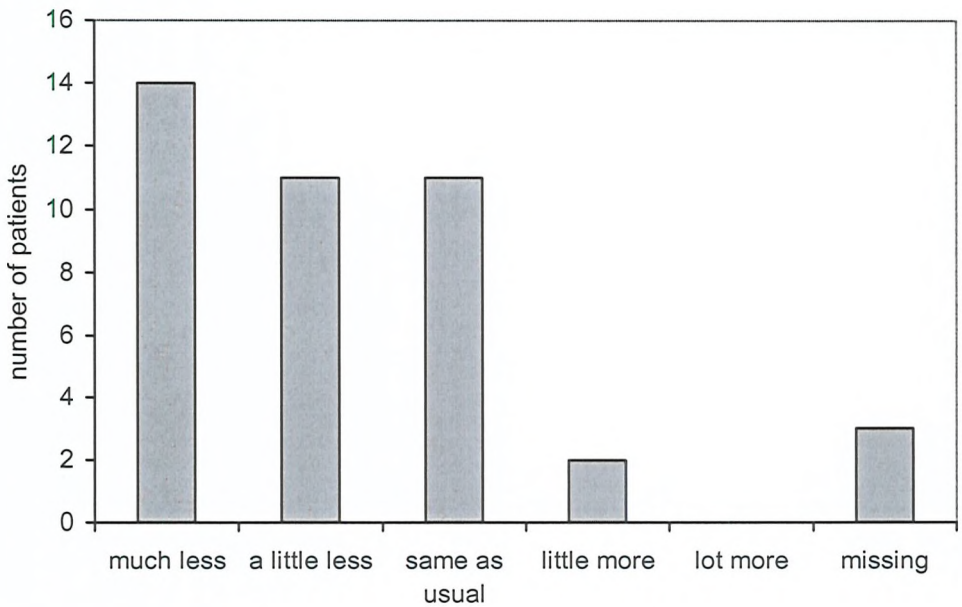


Figure 3.5

Sexual function and enjoyment questionnaire item 5 scores in male patients



Compared to your normal sexual functioning, can you enjoy sex?

Figure 3.6

Sexual function and enjoyment questionnaire item 1 score in female patients

Compared to your normal sexual functioning, has your desire for sex changed?

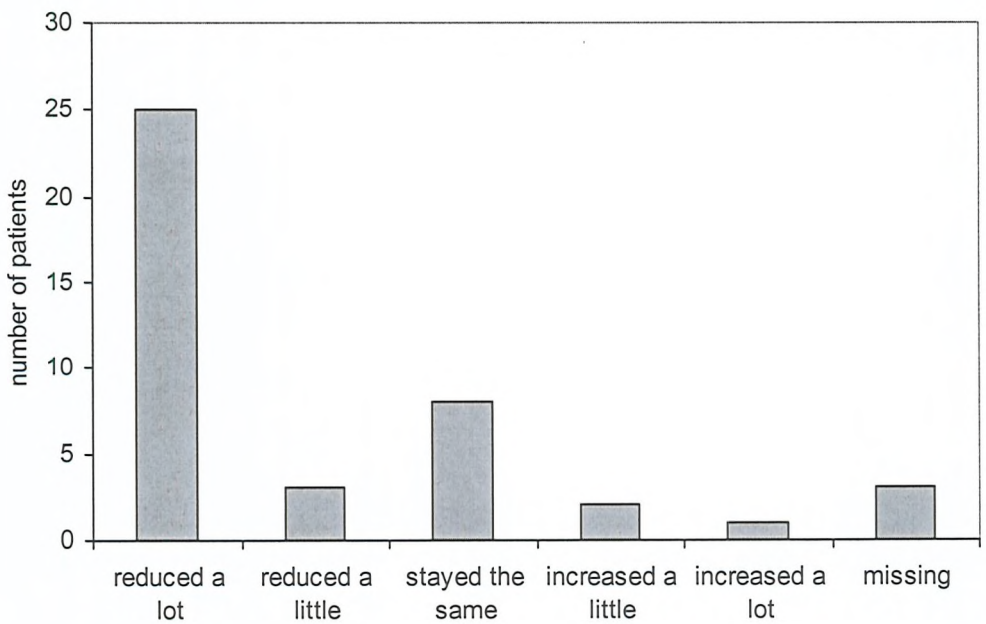


Figure 3.7

Sexual function and enjoyment questionnaire item 2 score in female patients

Compared to your normal sexual functioning, do you become aroused as you used to?

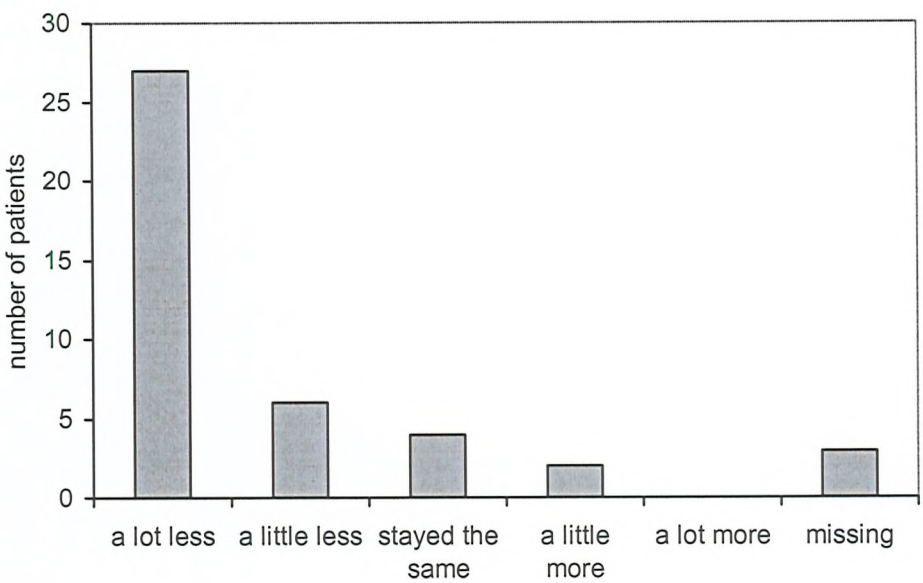


Figure 3.8

Sexual function and enjoyment questionnaire item 3 score in female patients

Compared to your normal sexual functioning, has your ability to achieve orgasm changed?

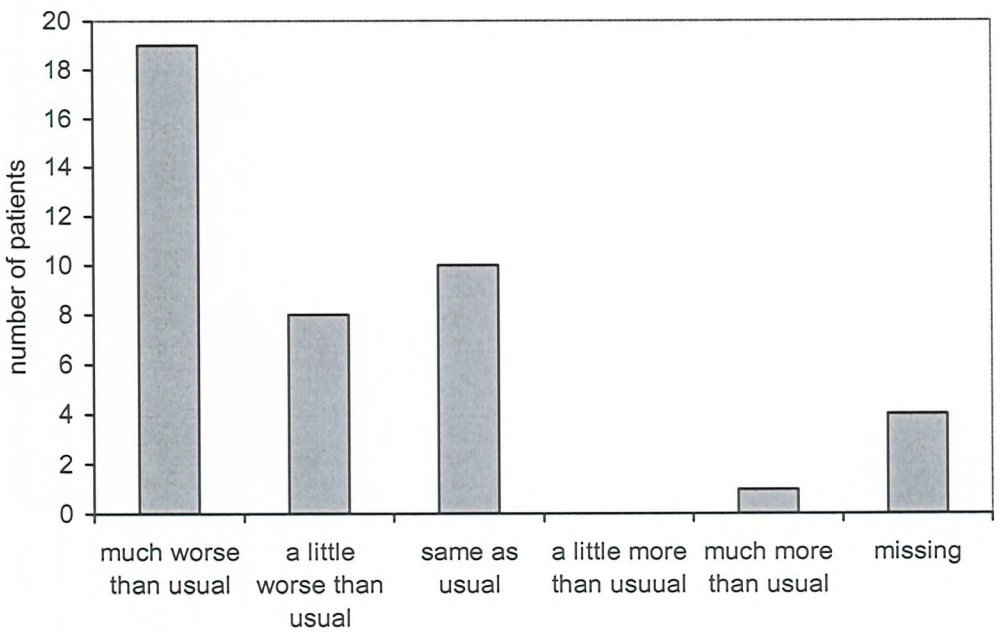


Figure 3.9

Sexual function and enjoyment questionnaire item 4 score in female patients

Compared to your normal sexual functioning, are you satisfied with the intensity of your orgasm?

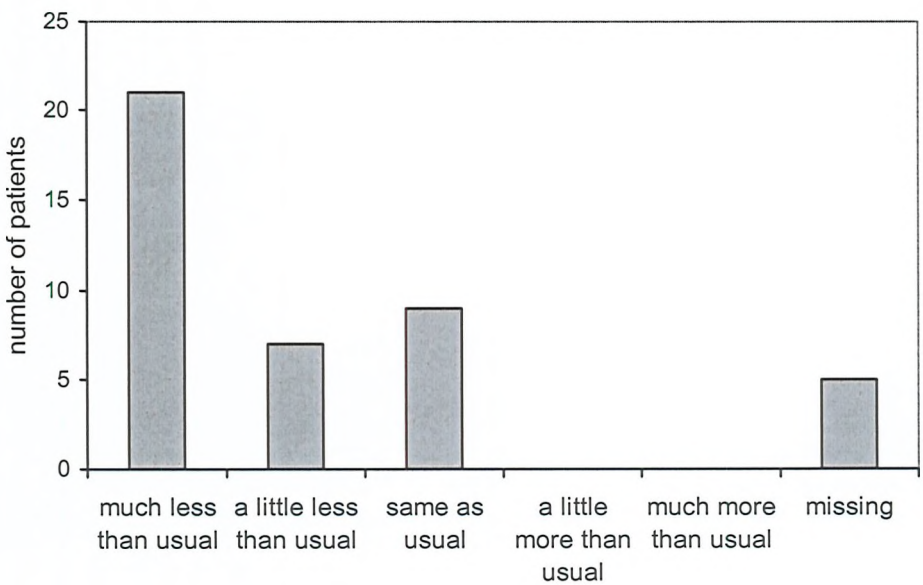


Figure 3.10

Sexual function and enjoyment questionnaire item 5 score in female patients

Compared to your normal sexual functioning, can you enjoy sex?

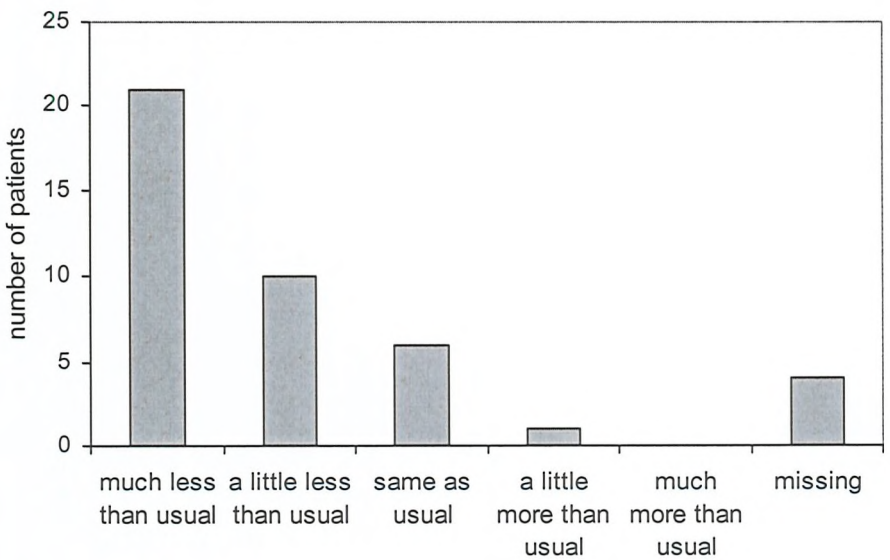


Table 3.5

Sexual function and enjoyment questionnaire scores grouped by gender

		-2	-1	0	+1	+2	9
		← Increasing impairment			Increasing improvement →		missing
Male patients (n=41)							
Item 1	Desire	14	7	15	2	2	1
Item 2	Achieve erection	18	7	13	2	0	1
Item 3	Maintain erection	17	3	18	1	1	1
Item 4	Ejaculate	13	9	18	0	0	1
Item 5	Enjoyment	14	11	11	2	0	3
Female patients (n=42)							
Item 1	Desire	25	3	8	2	1	3
Item 2	Arousal	27	6	4	2	0	3
Item 3	Achieve orgasm	19	8	10	0	1	4
Item 4	Intensity of orgasm	21	7	9	0	0	5
Item 5	Enjoyment	21	10	6	1	0	4

Table 3.6

Association between current MINI diagnoses and sexual problems

	Number of sexual problems					
Number of current MINI diagnoses	none	one	two	three	four or more	missing
None	0	1	1	1	1	0
One	1	2	2	1	5	1
Two	5	4	0	4	8	0
Three	4	1	3	3	10	1
Four or more	0	3	1	3	16	1

Table 3.7

Association between numbers of current psychotropic drugs and sexual problems

	Number of sexual problems					
	0	1	2	3	4 or more	missing
Number of psychotropic drugs						
1	9	8	6	4	22	0
2	1	2	1	6	8	3
3	0	1	0	1	5	0
4 or more	0	0	0	1	5	0

DISCUSSION

Overall findings

This study confirms previous findings (Monteiro *et al*, 1987; Harrison *et al*, 1986; Baldwin, 2001) that the method of enquiry is a major importance in the detection of possible sexual problems. In this consecutive sample of 83 outpatients with mood and anxiety disorders, 37 (44.6%) reported sexual problems when given the opportunity to describe any possible changes in sexual function, but 70 (84.3%) described changes in sexual functioning when completing a questionnaire. It is of course possible that some patients did not regard any changes as being problematic.

Similar proportions of male and female patients reported sexual problems directly (men, 46.3%; women 42.8%), or described them in a questionnaire (men 82.93%; women 85.7%), so there was no evidence that the genders differed in their readiness to mention problems. Isolated sexual problems were uncommon. When sexual dysfunction was present, most patients described impairments in more than one aspect of the sexual response, in line with previous research (Bancroft, 1989).

Twelve women and two men (together comprising 16.8% of the total sample) reported a lifetime history of sexual abuse. This figure accords with the findings of epidemiological and case-control studies indicating that sexual abuse in childhood is a common antecedent of psychopathology in adult life, particularly in women (McMillan *et al* 2001; Wise *et al*, 2001).

Study weaknesses

The patient sample was taken from a specialist secondary care service, and the findings are unlikely to be applicable to the wider population of antidepressant-treated patients in clinical practice. Clearly, the small size of the overall sample does not permit detailed meaningful comparisons between sub-groups of patients. Although the MINI is often used to characterise patients being considered for potential participation in randomised controlled trials, it was developed for use principally in epidemiological studies in community and primary care settings. In secondary care settings it may generate many diagnoses per patient, and clinical judgement is required to make the principal clinical diagnosis. The sexual function and enjoyment questionnaire was developed originally as a means for helping patients to mention a potentially sensitive subject in clinical practice, and its psychometric properties had not been delineated before use in this study. Finally, although patients were asked about their compliance with psychotropic drugs and drugs used to treat any physical illness, it cannot be assumed that the patients were taking their medication.

Acceptability of assessments

The finding that only three patients declined to discuss their sexual function supports previous research, indicating that patients are prepared for, and often welcome such a discussion (Ende *et al*, 1984). However, this patient sample was under my consultant care, and a satisfactory doctor-patient relationship had already been established. Nevertheless, as most patients completed the questionnaire readily, typically taking only ten minutes, with a low rate of missing data (only 26 missing items out of a total of 415), it seems suitable for further study in similar populations.

Findings on sexual function and enjoyment questionnaire

The finding that very few patients reported an improvement in sexual function above their normal level of functioning is not unexpected. There is little evidence to suggest that mood or anxiety disorders facilitate or enhance sexual function (Matthew and Weinman, 1982); likewise there is minimal evidence indicating that treatment with antidepressant drugs can enhance sexual function above pre-morbid levels of functioning (Kennedy *et al*, 1996; Phillip *et al*, 1999).

Causes of sexual problems

Although sexual problems were present in most patients, a cross-sectional study such as this is unable to identify possible causes of sexual dysfunction. It cannot be assumed that the sexual problems are associated with antidepressant treatment, or with the presence of depression. Many patients were prescribed a number of psychotropic and other drugs that have been reported to cause sexual problems, and no enquiries were made into pre-morbid sexual functioning. The incidence of treatment-emergent sexual dysfunction can only be estimated through a follow-up study with baseline and repeated assessments.

The presence of sexual dysfunction appears related to the presence of psychiatric co-morbidity, as patients with multiple current MINI diagnoses had higher rates of multiple sexual problems. However, some patients with no or only one current MINI diagnosis described multiple sexual problems, and some patients with multiple MINI diagnoses described no or single sexual problems. Co-morbidity does not necessarily equate to greater overall severity of psychopathological symptoms. There was no striking association between the use of multiple psychotropic drugs and the number of sexual problems: many patients taking only one psychotropic drug described multiple sexual problems, whereas some patients taking many drugs had no sexual problems.

The vignettes indicate that most patients who reported problems or changes in their sexual function had many possible causes for such a change, both longitudinally (e.g. childhood sexual abuse, rape) and cross-sectionally (e.g. current psychiatric illness, psychotropic drug treatment). This observation reinforces the need for longitudinal research in defined patient groups, and lead to the desire to conduct a five-year follow-up study in this cohort of patients, as described in Chapter 8 of this thesis.

CHAPTER 4 : CHANGES IN SEXUAL FUNCTION DURING ANTIDEPRESSANT TREATMENT

AIM OF THE INVESTIGATION

The findings of the double-bind randomised controlled trial comparing nefazodone and paroxetine (described in chapter two) indicate that antidepressants differ significantly, in their effects on an aspect of sexual function, as measured by item 14 ('genital symptoms') of the HAM-D. That study also demonstrated that the differential effect on sexual function was not the result of a difference in the overall efficacy of antidepressant treatment. However as described above item 14 is an inappropriate measure of all aspects of the sexual response. The sexual function and satisfaction scale described in chapter three was developed originally as a means by which depressed patients could report any sexual problems they might experience, to facilitate discussion of a sensitive issue with their doctors. The findings of study three suggest that the scale can be used in clinical practice, to delineate the range and severity of sexual problems experienced by patients treated with antidepressants. Being a point prevalence study, however, study three was unable to show whether the scale was able to detect changes in sexual function during antidepressant treatment.

The aims of the current study were to examine two aspects of the measurement of the effects of antidepressant treatment on sexual function and satisfaction. The first was to investigate whether the scale could be used serially, during acute treatment of depressed patients. The second aim was to determine whether the scale might reveal differences in effects on sexual function, between two antidepressants with differing pharmacological properties.

The subjects included within this investigation took part in an international multi-centre double-blind parallel-group fixed-dose randomised controlled trial, comparing the SSRI paroxetine with a serotonin-noradrenaline re-uptake inhibitor (SNRI), in the acute treatment of patients with major depressive episodes. Recruitment into the acute phase of the overall treatment study started in April 1998. A pharmaceutical company supported the overall treatment study. My roles in the overall study included -

- offering advice on the study protocol
- discussing use of the sexual function scale with the study sponsors
- acting as the UK study co-ordinator
- preparing training videos for the depression rating scales
- training the study investigators in use of the sexual function scale
- discussing the results with the study sponsors
- presenting the study results at international meetings

The findings of the overall treatment study have been submitted for publication in a peer-reviewed scientific journal. In the current investigation, I examined the raw data relating to scores on the sexual function scale, the HAM-D, MADRS, and CGI. I also collated all comments on use of the sexual function scale, recorded by the study investigators, and translated into English when necessary.

METHOD FOR THE OVERALL INVESTIGATION

Study design

The overall study was an international multi-centre double-blind parallel-group fixed-dose randomised controlled trial of the efficacy and tolerability of the SNRI and paroxetine in the acute treatment of outpatients fulfilling DSM-IV criteria for a non-psychotic major depressive episode. The diagnosis was confirmed by reference to the Mini International Neuropsychiatric Interview (MINI) which is a brief structured interview (Sheehan *et al*, 1997). The participating patients underwent a 1-3 week washout period to ensure an adequate drug-free interval, followed by six weeks of double-blind treatment. Assessment visits occurred at baseline, after 1, 2, 4 and 6 weeks of double-blind treatment, and then one week later in the patients who stopped study treatment. Patients who responded to acute treatment could undergo a further 18 weeks of double-blind treatment (continuation phase). The continuation phase of the study is not included within this chapter.

To be considered for participation in the study, patients had to have a minimum score of 20 on the MADRS at baseline. There were a number of exclusion criteria, such as pregnancy or lactation, serious risk of suicide, current alcohol or drug abuse or dependence, major personality disorder, unstable physical illness, concomitant medication with various drugs, and failure to respond to two or more previous courses of antidepressant treatment.

Double-blind treatment

Patients were randomly assigned to receive the SNRI or paroxetine (20 mg mane) using a double-dummy technique to preserve the blind. The dosage of double-blind treatment was kept constant throughout the study. Treatment compliance was assessed by a capsule count at each patient assessment.

Assessments of efficacy and sexual function

Antidepressant efficacy was evaluated by completion of the 17-item HAM-D and MADRS at all study visits, the CGI-S at every visit and the CGI-I at each visit after randomisation. Patients were considered to have responded to treatment if they achieved a score of 1 ('very much improved') or 2 ('much improved') on the CGI-I at study end-point, and showed a decrease of at least 50% in the HAM-D and MADRS total scores, compared to baseline. Sexual function and satisfaction was assessed using the sexual function and enjoyment questionnaire (first used in chapter three) at each study visit.

Statistical methods

The data from each centre were pooled and analysed on an intention to treat last observation carried forward basis (ITT-LOCF). The ITT set included all patients who received at least one dose of the study drug and who had at least one evaluation performed while undergoing double-blind treatment. Data were analysed using SAS version 6.12 for Windows, the statistical significance level being set at 5% for all tests. Changes in the total score on the HAM-D and MADRS between baseline and endpoint were compared between the two treatment groups by Student's t-test. Responder rates were compared between treatment groups by a chi-square test.

METHOD FOR THE CURRENT INVESTIGATION

Hypothesis

Treatment studies with SSRIs and the SNRI venlafaxine indicate that both can be associated with the development of sexual dysfunction: in the absence of good comparative data, the null hypothesis relating to sexual function was that the SNRI in this investigation and paroxetine would not differ significantly in effects on sexual function, as assessed by item 14 of the HAMD and by items on the sexual function and enjoyment questionnaire.

Change in severity of depressive and genital symptoms

To determine the change in severity of depressive and genital symptoms, I examined the raw data for each of the patients who were recruited into the acute phase of the treatment study. Using the software package STATA version 7.0, I calculated the mean total 17-item HAM-D score and standard deviation of that score at each visit for both treatment groups. The difference in mean HAMD-D scores at each visit was determined, together with the standard error and 95% confidence intervals for that difference. Significance values were calculated using two-tailed t-tests. A similar method was used to examine change in item 14 of the HAM-D. The CGI-I score at a visit compares the patient's overall condition to that at the baseline assessment, so I adopted the same approach to examine raw data for the CGI-I for each of the patients at subsequent visits.

Change in and comments on the sexual function and enjoyment questionnaire

At each visit, the questionnaire compares a patient's current with their usual level of sexual function and satisfaction. I examined the raw data for each of the recruited patients, and used a similar approach to the HAM-D scores, but analysed the scores separately for the sub-groups of male and female patients. Finally, I collated all the written comments made by investigators on the scale at any assessment, and examined the distribution of missing data at the baseline assessment, in all patients.

ETHICAL CONSIDERATIONS

The overall treatment study was conducted in accordance with the Declaration of Helsinki and its subsequent revisions. The study was approved by the local research ethics committee, either for each study centre or each country, according to local legal requirements.

No ethical problems were foreseen for the participation of patients in the study. Both treatments had proven efficacy in major depression, at the doses used in the study. The duration of acute treatment (six weeks) was sufficient to allow an assessment of efficacy; and responders to acute treatment could enter continuation treatment (lasting up to eighteen weeks), reflecting recommendations for the treatment of depression. Participation could only occur after the provision of written informed consent; patients attended appointments frequently and regularly; and assessments of efficacy and tolerability were comprehensive and relevant to clinical practice and patient concerns.

RESULTS FOR THE OVERALL TREATMENT STUDY

Patient population

Forty-two study centres in nine European countries recruited 305 patients. A total of 303 patients were randomised to double-blind treatment (SNRI, 150; paroxetine, 153). Sixty-two patients (SNRI, 29; paroxetine, 33) withdrew before completing acute treatment, principally due to adverse events (37 patients), withdrawal of consent (34 patients), or lack of efficacy (15 patients): some patients had more than one reason for withdrawal. The ITT-safety analysis included 300 patients (SNRI, 148; paroxetine 152), the efficacy analysis 299 patients (SNRI, 148; paroxetine, 151). The clinical characteristics of the overall treatment sample are shown in table 4.1. There were no significant differences in baseline features between the treatment groups.

Efficacy of double-blind treatment

The mean total 17-item HAM-D and MADRS scores declined steadily during acute treatment in both treatment groups. There were no significant differences between the two treatment groups, in terms of change in HAM-D or MADRS scores from baseline to day 42. The proportion of responders, assessed according to change from baseline in CGI-I, and HAM-D and MADRS scores was not significantly different. Table 4.2 summarises the efficacy results in the overall treatment study.

Tolerability of double-blind treatment

The tolerance profiles of the two treatments were similar. A similar proportion of patients in each treatment group reported at least one adverse event (SNRI, 77.7%; paroxetine 70.4%: p=0.15, chi-square test). The profile of adverse events was similar, but increased sweating was more common with SNRI treatment, and dizziness with paroxetine. No adverse events relating to sexual function were reported during double-blind treatment. Similar proportions of patients withdrew from the study because of adverse events (SNRI, 11.5%; paroxetine 13.2%).

Table 4.1

Demographic and clinical characteristics – ITT sample

Characteristic	SNRI	Paroxetine
N	148	151
Mean MADRS score (SD)	29.8 (5.5)	29.6 (5.0)
Mean 17-item HAM-D score (SD)	23.7 (4.2)	23.4 (4.3)
Previous treatment with antidepressant, n (%)	39 (26.3)	42 (27.8)

ITT	intention to treat
MADRS	Montgomery-Asberg Depression Rating Scale
SD	standard deviation
HAM-D	Hamilton Rating Scale for Depression

Table 4.2

Efficacy results - overall treatment study (ITT, LOCF analysis)

Measure	SNRI (n= 148)	Paroxetine (n=151)	p-value
Change in mean MADRS score	16.2	16.8	0.66
Change in mean HAM-D score	11.8	12.0	0.85
CGI-I responder (%) (score of 1 or 2 compared to baseline)	66.2	64.2	0.72
MADRS responder (%) (50% or more reduction from baseline score)	62.8	64.9	0.71
HAM-D responder (%) (50% or more reduction from baseline score)	58.1	60.3	0.70

ITT, LOCF	intention to treat, last observation carried forward
MADRS	Montgomery-Asberg Depression Rating Scale
HAM-D	Hamilton Rating Scale for Depression
CGI-I	Clinical Global Impression of Improvement

RESULTS FOR THE CURRENT INVESTIGATION

Patient population

Raw data were available for 305 recruited patients (89 men and 216 women; mean age 43.8 years, age range 20-78 years). Two randomised patients did not receive medication and are therefore excluded from further analysis. The study sample for this investigation comprises 89 men (of who 47 received SNRI and 42 paroxetine) and 214 women (103 received SNRI and 111 paroxetine). Data are reported using an observed case analysis.

Change in genital symptoms (item 14 of the HAM-D)

Genital symptoms were assessed in the 303 patients randomised to double-blind treatment. There was a gradual reduction in severity of genital symptoms over the course of the study in both treatment groups, in the overall sample and in the sub-groups of male and female patients. Table 4.3 gives the mean score on item 14 at each assessment. There was a significant difference between treatment groups after four weeks of treatment (day 28), with an advantage for SNRI treatment. The null hypothesis can therefore be rejected. However the difference between treatments was slight (0.22), and unlikely to be of clinical relevance. The change in mean score between baseline and study endpoint was similar (paroxetine, 0.31; SNRI, 0.32). Table 4.4 gives the mean scores and standard deviations, and the difference in mean score with the standard error, confidence intervals and p-value for the overall study sample. Separate analyses were not performed, for the sub-groups of male or female patients.

Change in sexual function

The analysis of sexual function and enjoyment questionnaire item scores was derived from the 303 patients randomised to double-blind treatment. Because the questionnaire contains a number of gender-specific items, the data from the sub-groups of male and female patients were analysed separately: no overall analysis in the total sample was performed. The mean scores by item for each study visit for men and women are shown in Table 4.5 and Table 4.6, respectively.

In male patients, there were no significant differences between treatment groups in the mean baseline sexual function item scores at the baseline assessment. Paroxetine was associated with greater difficulty in ejaculation, compared to baseline, in the first two weeks of treatment; SNRI treatment was associated with greater difficulty in achieving and maintaining erection in the first week of treatment. There were significant differences between the treatment groups at day 7 on both item 2 ($p=0.03$) and item 3 ($p<0.01$); at day 28 on item 1 ($p=0.01$), item 2 ($p=0.02$) and item 3 ($p=0.02$); and at day 42 on item 3 ($p=0.02$). All of these differences were in favour of paroxetine. Again the null hypothesis, of there being no difference between the two treatments in effects on sexual function, can be rejected. The

Table 4.3

Genital symptoms (item 14 of HAM-D) over the course of the study

	Paroxetine (N=153)			**SNRI (N=150)**		
	Male (n=42)	Female (n=111)	Total	Male (n=47)	Female (n=103)	Total
Baseline	1.31	1.52	1.46	1.40	1.39	1.39
Day 7	1.27	1.43	1.38	1.34	1.30	1.31
Day 14	1.15	1.35	1.29	1.15	1.18	1.17
Day 28	1.17	1.34	1.29	1.08	1.07	1.07
Day 42	1.02	1.20	1.15	1.02	1.10	1.07

HAM-D Hamilton Rating Scale for Depression

Table 4.4 Change in genital symptoms (HAM-D item 14 scores) - all patients

	Paroxetine (N=153)			SNRI (N=150)			Difference between treatments (paroxetine minus SNRI)				
Time	N	mean	SD	n	mean	SD	Diff mean	SE	95% CI Lower	95% CI Upper	P-value
Baseline	153	1.46	0.05	150	1.39	0.06	0.07	0.08	-0.09	0.23	0.37
Week 1	143	1.38	0.06	137	1.31	0.07	0.07	0.09	-0.10	0.24	0.41
Week 2	136	1.29	0.06	132	1.17	0.07	0.12	0.09	-0.06	0.30	0.19
Week 4	124	1.29	0.07	125	1.07	0.07	0.22	0.09	0.03	0.40	0.02
Week 6	146	1.15	0.06	148	1.07	0.09	0.07	0.09	-0.10	0.26	0.40

HAM-D	Hamilton Rating Scale for Depression
n	number of recorded observations
SD	standard deviation
SE	standard error
CI	confidence interval

All calculations given to two decimal points

Table 4.5

Mean scores on sexual function and enjoyment questionnaire scale by visit

Sub-group of 89 male patients

	Item 1 desire		**Item 2** achieve erection		**Item 3** maintain erection		**Item 4** ejaculation		**Item 5** enjoyment	
Day	PAR	SNRI	PAR	SNRI	PAR	SNRI	PAR	SNRI	PAR	SNRI
0	-1.27	-1.24	-0.95	-1.02	-0.83	-1.13	-0.44	-0.74	-1.21	-1.00
7	-0.68	-1.13	-0.71	-1.18	-0.47	-1.21	-0.57	-0.71	-0.81	-1.05
14	-0.65	-0.73	-0.62	-1.03	-0.67	-1.08	-0.47	-0.89	-0.67	-0.92
28	-0.17	-0.85	-0.2	-0.72	-0.41	-0.87	-0.15	-0.29	-0.41	-0.74
42	-0.36	-0.64	-0.31	-0.69	-0.21	-0.74	-0.32	-0.44	-0.45	-0.62

Table 4.6

Mean item scores on sexual function and enjoyment questionnaire by visit
Sub-group of 214 female patients

	Item 1 desire		**Item 2** arousal		**Item 3** achieve orgasm		**Item 4** intensity orgasm		**Item 5** enjoyment	
Day	PAR	SNRI	PAR	SNRI	PAR	SNRI	PAR	SNRI	PAR	SNRI
0	-1.41	-1.38	-1.48	-1.28	-1.23	-1.22	-1.23	-1.26	-1.39	-1.33
7	-1.20	-1.13	-1.24	-1.18	-1.14	-1.10	-1.13	-1.15	-1.11	-1.21
14	-0.84	-0.83	-0.99	-0.99	-1.02	-1.07	-1.00	-1.09	-1.02	-1.04
28	-0.88	-0.57	-0.99	-0.70	-0.97	-0.77	-0.92	-0.86	-0.97	-0.81
42	-0.77	-0.64	-0.82	-0.75	-0.85	-0.78	-0.87	-0.78	-0.87	-0.75

change in individual mean item scores over time in paroxetine-treated and SNRI-treated male patients is shown in Figure 4.1 and Figure 4.2, respectively.

In female patients, there were no significant differences between treatment groups in the mean item scores, either at baseline or at subsequent assessments. For this reason, the data from the two treatment groups are combined, and the change in individual mean item scores in women is shown in Figure 4.3. Double-blind treatment was associated with a gradual improvement in all aspects of sexual function.

Comments on the sexual function and enjoyment questionnaire

Inspection of the comments made by the study investigators suggests that the questionnaire was much harder to introduce in female than in male patients. Comments on problems in use of the questionnaire were recorded for only two men, but for 15 women. Analysis of the missing data for items at the baseline assessment supports the observation that the questionnaire may be harder to utilise in female depressed patients, as items were missing in around four times as many women as in men. Female patients appeared to have more difficulty in providing answers to scale items relating to orgasm and sexual enjoyment than to sexual desire and arousal. Table 4.7 summarises the data relating to use of the sexual function scale.

DISCUSSION

Findings of the overall treatment study

The findings of the overall international, multi-centre, double-blind, parallel-group, fixed-dose, randomised controlled trial indicate that the SNRI and paroxetine had similar efficacy and tolerability in the treatment of patients fulfilling DSM-IV criteria for major depressive episodes. As in the controlled comparison of nefazodone and paroxetine, the difference between treatments in pharmacological properties in this study was not associated with differences in overall efficacy or tolerability, in the acute treatment of depressed patients. This finding supports the general observation that SSRI and SNRI antidepressants have similar overall efficacy in the treatment of outpatients with depressive episodes of moderate severity (Anderson *et al*, 2001).

Findings of the current investigation

The principal finding is that the sexual function and enjoyment questionnaire can be used serially to assess change in sexual function and satisfaction during antidepressant treatment, in male and female patients. In men and women, mean scores on all scale items increased between the baseline and endpoint assessments, indicating improvement in most aspects of sexual function. In male patients, the individual items showed differing patterns of change over time, suggesting that the items measure

Figure 4.1

Change from baseline in sexual function and enjoyment questionnaire scores

Male patients treated with paroxetine (n=42)

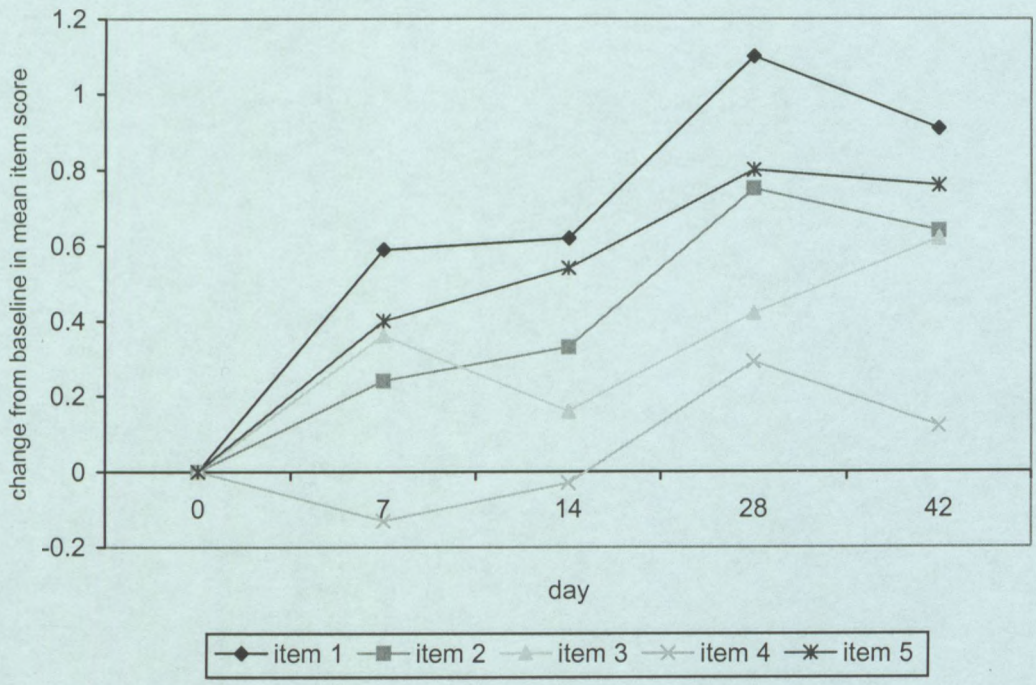


Figure 4.2

Change from baseline in sexual function and enjoyment questionnaire scores

Male patients treated with SNRI (n=47)

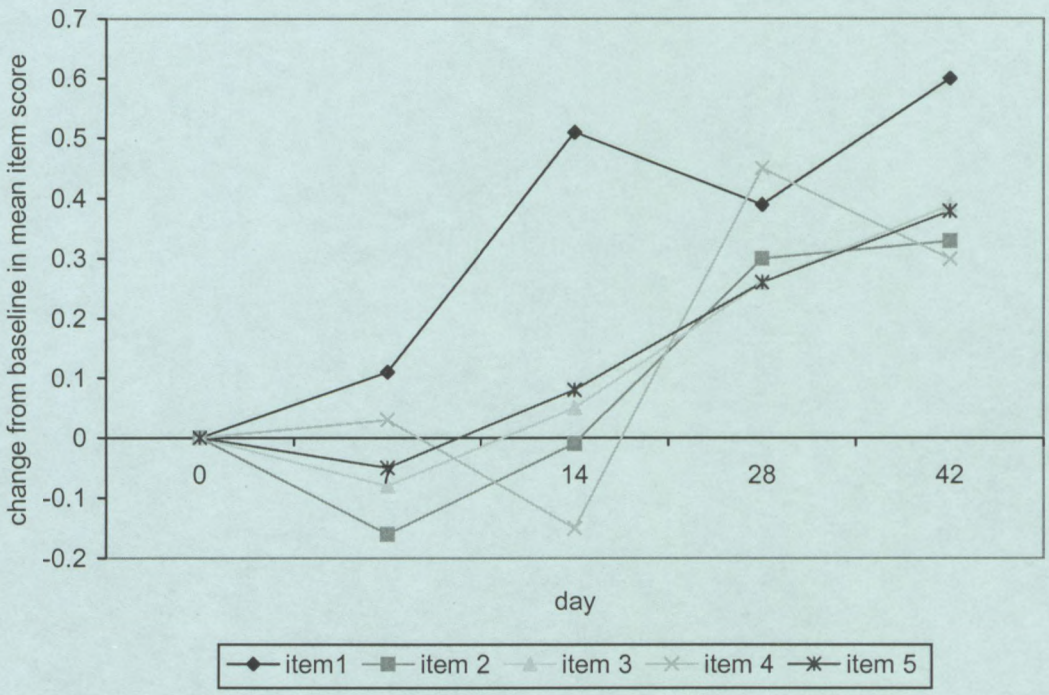


Figure 4.3

Change from baseline in sexual function and enjoyment questionnaire scores

All female patients (n= 214)

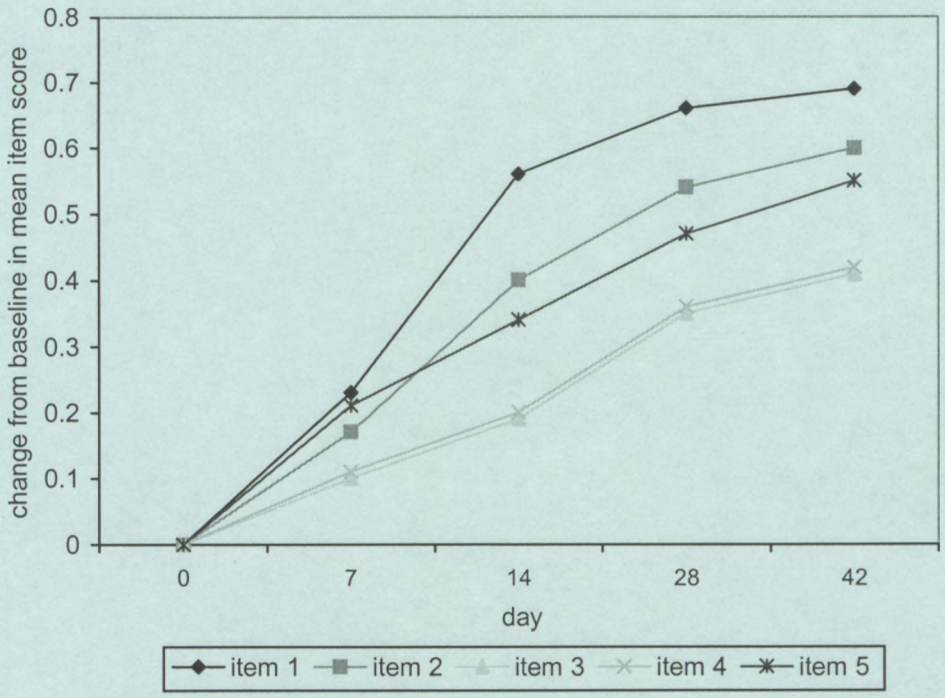


Table 4.7

Use of the sexual function and enjoyment questionnaire

	Men (N = 89)	Women (N = 214)	Total (N = 303)
Missing data at baseline N, (%)			
Item 1 desire	2 (2.2)	24 (11.2)	26 (8.6)
Item 2 achieve erection / arousal	3 (3.3)	26 (12.1)	29 (9.6)
Item 3 maintain erection / achieve orgasm	3 (3.3)	30 (14.0)	33 (10.9)
Item 4 ejaculation / intensity of orgasm	4 (4.4)	31 (14.5)	35 (11.6)
Item 5 enjoyment	4 (4.4)	34 (15.9)	38 (12.5)
Absence of sexual partner hinders ratings, N (%)	1 (1.1)	6 (2.8)	7 (2.3)
Does not engage in sexual activity, N (%)	0	6 (2.8)	6 (2.0)
Patient was too embarrassed to discuss sex, N (%)	1 (1.1)	1 (0.5)	2 (0.7)
Discussion of sex was culturally inappropriate, N (%)	0	2 (0.9)	2 (0.7)

differing aspects of sexual function. In female patients, items 3 and 4 showed a very similar pattern of change, suggesting that they may be effectively measuring the same aspect (i.e. achievement and satisfaction with intensity of orgasm). The comments made by the study investigators suggest that the scale can be used readily in men; but in female patients the number of missing data and the recorded comments suggest that use of the scale is more testing.

The findings in the patients who were randomised to double-blind study medication indicate that the treatments differed somewhat in their effects on sexual function. There was an advantage for SNRI treatment in one measure at one assessment in the overall sample, and advantages for paroxetine on six measures over three assessments in the sub-group of male patients. However, the most striking finding is that acute treatment of depression resulted in improvement in sexual function and satisfaction in both treatment groups, particularly so in women.

Study weaknesses

As in the controlled comparison of nefazodone and paroxetine, the overall treatment study has a number of weaknesses. These include the absence of a placebo control group, and the large number of study centres. Again, efforts were made to reduce the risk of treatment-by-centre interactions by inter-rater reliability meetings with training in all outcome measures. In addition, compliance with study medication cannot be assumed: compliance was assessed by capsule counts, but this is known to be a rather poor measure of treatment adherence (Demyttenaere, 1997).

The current investigation also had a number of potential weaknesses. The first is that the sexual function and enjoyment questionnaire was not developed originally to assess change, but was intended instead to be a checklist of symptoms that patients might complete prior to consulting health professionals. The second is that the scale was developed through discussion between medical colleagues and patients in the United Kingdom, and the scale may therefore be affected by national or cultural differences in the expression of sexual function. A third potential weakness is that the gender distribution of the overall sample (70% of the sample were women) may affect the confidence that can be placed in the results of analyses of sexual function in the sub-group of male patients.

However, as in the previous study, the findings of the study must be placed in temporal context. At the time the investigation was started, there was no generally accepted simple measure for serially assessing sexual function and satisfaction during antidepressant treatment. Since then, a number of scales similar to the scale have been developed and studied within the setting of randomised controlled trials. Further chapters in this thesis describe the effect of antidepressant treatment on two other sexual function rating scales.

Differences between study treatments in effects on sexual function

SNRI treatment was associated with a significantly greater improvement in mean score of item 14 (genital symptoms) of the HAM-D at day 28, in the overall sample of male and female patients. However, this difference was slight and unlikely to be clinically relevant: furthermore there were no other significant differences between study treatments in this item at other points in the study.

By contrast, the findings relating to mean scores on the sexual function scale items in male patients suggest that SNRI treatment was associated with significantly more impairment on some items at some points. Again, the difference in mean score was rather small, the maximum difference between study treatments being 0.68 on item 1 at day 28, and the clinical relevance of this difference is uncertain. The number of male patients (n=89 at baseline) and the number of tested items (five items at each of five assessments) reduces the confidence that can be placed in the findings. It seems reasonable to infer that the relative disadvantage for SNRI treatment in male patients results from its noradrenaline re-uptake inhibitory properties. The findings in the larger number of female patients (n=214) indicate that the study treatments did not differ significantly in their effects on sexual function.

Implications for clinical practice and research

The overall findings of the randomised controlled trial indicate that there were few differences between SNRI treatment and paroxetine in the acute treatment of outpatients with major depressive episodes of moderate severity. Further analysis of the database has indicated that the SNRI had significantly greater efficacy than paroxetine in the sub-group of patients with pronounced psychomotor retardation at the baseline assessment, and might therefore be preferred to paroxetine in such patients, in those countries where both are available.

The findings of the current investigation indicate that sexual function can be assessed over time in depressed patients, and that sexual function improves with time, presumably as depressive symptoms resolve. The institution of antidepressant treatment does not appear to worsen overall sexual function, although some male patients will experience greater difficulty with some antidepressants in the first weeks of treatment. It is of course possible that antidepressant treatment might reduce the degree of improvement in sexual function that might otherwise occur if depressed patients respond to non-pharmacological treatment.

The results of the current investigation confirm some findings described in previous chapters, namely that reports of treatment-emergent adverse effects are an inappropriate measure of the effects of antidepressant treatment on sexual function. Whilst it may be that disturbed sexual function is only reported by those patients for whom it is indeed a problem, the scores on both item 14 of the HAM-D and the sexual function scale indicate that sexual function was impaired at baseline in nearly all

patients. The effects of antidepressants on sexual function can only be evaluated if assessments are made before treatment is started.

Further research is needed to examine the psychometric properties of the questionnaire. In particular it would be interesting to examine how scores on this scale compare with those on other measures of sexual function and satisfaction. Chapter eight of this thesis includes an investigation of the relationships between scores on the scale and on the Arizona Sexual Experiences Scale.

Finally, the findings of the randomised controlled trials described in chapter two and in this chapter, indicate that antidepressants can differ significantly, in their effects on sexual function. This phenomenon is examined further in the next chapter of the thesis, which describes a further randomised controlled trial comparing paroxetine with the noradrenaline re-uptake inhibitor reboxetine, and in chapter six, which describes a randomised controlled trial comparing paroxetine with another SSRI, escitalopram.

CHAPTER 5 : COMPARISON OF THE EFFECTS OF SELECTIVE NORADRENERGIC AND SEROTONERGIC ANTIDEPRESSANTS ON SEXUAL FUNCTION

AIM OF THE INVESTIGATION

The findings of the randomised controlled trial comparing nefazodone and paroxetine (chapter two) indicate that antidepressants can differ significantly in their effects on an aspect of sexual function, as measured by item 14 (genital symptoms) of the HAM-D. This observation is supported by the findings of the randomised controlled trial comparing paroxetine with an SNRI (chapter four), which shows that antidepressants can differ not only in their effects on item 14, but also in their effects on other aspects of sexual function, as measured by the DASEX scale. Both of these studies also demonstrate that the varying effect on sexual function was not the result of a difference in the overall efficacy of antidepressant treatment.

Nefazodone differs from paroxetine, through having 5-HT_2 antagonist properties in addition to 5-HT re-uptake inhibitory effects; the SNRI studied in chapter four differs from paroxetine, through inhibiting the re-uptake of both serotonin and noradrenaline. Neither treatment study could examine the effects on sexual function of antidepressants with a primarily noradrenergic mechanism of action. This chapter reports the relevant findings from a multi-centre randomised controlled trial, comparing paroxetine with the selective noradrenaline re-uptake inhibitor reboxetine.

The pre-clinical pharmacological properties of reboxetine have been described elsewhere (Baldwin and Carabal, 1999). Analysis of the clinical trial database with reboxetine suggests that it is associated with a low burden of treatment-emergent sexual side effects, impotence being the most common (5%, compared to 0% with placebo) (Baldwin *et al*, 2000). The recently published results of a randomised placebo-controlled trial indicate that reboxetine and the SSRI fluoxetine differ, in their effects on sexual function (Clayton *et al*, 2003). Using the Rush Sexual Inventory, RSI (Zajecka *et al*, 1997) (Appendix 5.1), reboxetine treatment was found to be associated with a significantly greater improvement in sexual satisfaction than was seen with fluoxetine; by contrast, fluoxetine treatment was associated with significantly worse sexual function than that seen with placebo. This finding is supported by the results of a randomised double-blind controlled trial comparing reboxetine and the SSRI citalopram (Bodlund *et al*, 2003), in which reboxetine was associated with fewer adverse effects on sexual function, as assessed by the Swedish language version of the Sexual Function Scale (Bodlund, 1998).

The aims of the current study were to examine two further aspects of the effects of antidepressant treatment on sexual function and satisfaction. The first was to examine changes in scores on certain RSI items during the acute treatment of depressed patients. The second was to determine whether the

RSI might reveal differences in effects on sexual function, between two antidepressants with markedly different pharmacological properties.

The patients included within this investigation took part in an international multi-centre double-blind parallel-group flexible-dose randomised controlled trial, comparing reboxetine and paroxetine in the acute treatment of patients with major depressive episodes. The overall treatment study was supported by the Pharmacia pharmaceutical company. My roles in the overall study included -

- offering advice on the study protocol
- acting as the UK study co-ordinating investigator
- gaining approval from a regional multi-centre research ethics committee (May 1999)
- gaining approval from the local research ethics committee (September 1999)
- recruiting patients from my outpatient clinic

The results of the overall treatment study are being prepared for submission for publication in a peer-reviewed scientific journal. In the investigation described in this chapter, I examined the data relating to scores on the HAM-D, MADRS, CGI and certain items of the RSI.

METHOD FOR THE OVERALL STUDY

Study design

The overall study was an international double-blind parallel-group multi-centre randomised controlled trial comparing the efficacy and tolerability of reboxetine and paroxetine in the acute treatment of patients fulfilling DSM-IV criteria for a non-psychotic major depressive episode. The participating patients underwent 4-28 day washout period (dependent upon previous antidepressant treatment), prior to randomisation and eight weeks of double-blind treatment. Assessment visits occurred at baseline and at weekly intervals during double-blind treatment. Those patients who responded to treatment could undergo a further 16 weeks of double-blind treatment (continuation phase). This chapter does not include a consideration of the continuation phase.

To be considered for participation in the study, patients had to have a score of between 22 and 35 on the 21-item version of the HAM-D at baseline. As usual, there were a number of exclusion criteria, including pregnancy or lactation, serious risk of suicide, current alcohol or drug abuse or dependence, unstable or serious physical illness, concomitant medication with various drugs, and failure to respond to two or more courses of antidepressant treatment.

Double-blind treatment

Patients were randomly assigned to receive reboxetine (4 mg b.d.) or paroxetine (20 mg mane) using a double-dummy technique to preserve the blind. The dosage of double-blind treatment could be

increased at day 28, such that the dose for reboxetine would be 4 mg mane and 6 mg nocte, and that for paroxetine 20 mg b.d. Treatment compliance was assessed by a capsule count at each patient assessment.

Assessments of efficacy and sexual function

Antidepressant efficacy was assessed by completion of the 21-item HAM-D and MADRS at all study visits, the CGI-S at every visit and the CGI-I at each visit after randomisation. There were two additional efficacy assessments: the Medical Outcomes Study SF-36 (a self-completed quality of life scale) (Ware *et al*, 1992) and the Social Adaptation Self-Evaluation Scale (a self-completed measure of social function and adaptation) (Bosc *et al* 1997). Patients were considered to have responded to treatment if the HAM-D score decreased by at least 50%, compared to baseline; and to have entered symptomatic remission if the HAM-D score dropped to 10 or less. Sexual function and satisfaction was assessed by the RSI, completed at baseline, day 28 and day 56.

Statistical analysis

The overall data from each study centre were pooled and analysed on an intention to treat last observation carried forward (ITT LOCF) basis. The ITT set includes all patients randomised into the trial who received at least one dose of the study drug and who had at least one evaluation performed while undergoing double-blind treatment. For continuous variables, such as the HAM-D and MADRS, testing for difference between treatments was performed using a two-way analysis of variance that included treatment, investigator and treatment-by-investigator terms. Categorical data, such as response and remission were analysed using the Cochran-Mantel-Haenszel test, stratified by investigator.

METHOD FOR THE CURRENT INVESTIGATION

Hypothesis

The results of two randomised controlled trials (Clayton *et al*, 2003; Bodlund *et al*, 2003) indicate that reboxetine may have advantages over SSRIs, in effects on sexual function. The study hypotheses therefore were reboxetine would have significant advantages over paroxetine in effects on sexual function, as assessed by item 14 of the HAMD and the visual analogue items of the RSI. The null hypothesis being tested was there would be no significant differences between treatments on these measurements.

Change in severity of overall depressive symptoms and genital symptoms

Data entry and analysis followed a similar pattern to the approach described in previous chapters. To determine the change in severity of depressive symptoms, I examined the raw data from each of the patients entered by investigators from study centres in the United Kingdom. Using the computer software package STATA version 7.0, I then calculated the mean total 17-item HAM-D score and

standard deviation of that score at each visit, for both treatment groups, using an observed case analysis. The difference between groups in mean HAM-D scores at each visit was then calculated, together with the standard error and 95% confidence intervals for that difference. Significance values were then calculated using two-tailed t-tests. A similar method was used to examine the change in item 14 of the HAM-D.

As the CGI scales provide another measure of illness severity and improvement I also examined the raw data for the CGI-I in each of the patients. As before, the CGI-I was used to compare the patient's overall clinical condition to that present at the baseline assessment, and as such no CGI-I values are available for the baseline visit. As in previous chapters I calculated the mean CGI-I score and standard deviation for that score in both treatment groups, and the difference between groups in mean CGI-I scores, standard error and 95% confidence intervals.

The effects of double-blind treatment on sexual function were assessed through examination of the change in mean score on the visual analogue items of the RSI. Using STATA version 7.0, I calculated the mean score on each of these five items, for both treatment groups. The difference in mean score was calculated, together with the standard error and confidence intervals. Significance values were estimated using two-tailed t-tests.

Treatment-emergent sexual adverse events

As in previous chapters I examined the raw data for the acute phase of the study to identify adverse events that were reported by study investigators and which could represent a change in sexual function. Wherever possible, each adverse event was characterised according to the nature of the event, the time of onset, duration, and severity; as before, study investigators had an opportunity to record whether the adverse events was related to double-blind treatment, and whether treatment was necessary for that event.

ETHICAL CONSIDERATIONS

The overall treatment study was conducted in accordance with the Declaration of Helsinki and its subsequent revisions. The study was approved by the local or regional research ethics committees, either for each study centre or each country, according to local legal requirements.

No ethical problems were foreseen for the participation of patients in the study. Both reboxetine and paroxetine had proven efficacy in major depression, at the doses used in the study. The duration of acute treatment (eight weeks) was sufficient to allow an assessment of efficacy; and responders to acute treatment could enter continuation treatment (lasting up to sixteen weeks), reflecting recommendations for the treatment of depression. The study protocol permitted dosage changes

according to the efficacy and tolerability of treatment, reflecting standard clinical practice. Participation could only occur after the provision of written informed consent; patients attended appointments frequently and regularly; and assessments of efficacy and tolerability were comprehensive and relevant to clinical practice and patient concerns.

RESULTS FOR THE CURRENT INVESTIGATION

The combined data from all study centres has not yet been analysed fully, and as such this section describes only the data obtained from study centres in the United Kingdom. The reduction in patient numbers means that many items of the RSI cannot be evaluated meaningfully, and hence only the general items and visual analogue items are described.

Study sample

Table 5.1 gives demographic and clinical details for the sample of 70 patients who were recruited in United Kingdom study centres and underwent double-blind treatment with reboxetine or paroxetine. The age and gender distributions were similar in the two treatment groups (reboxetine, 20 men and 15 women, mean age 38.0 years; paroxetine, 20 men and 16 women, mean age 45.3 years). The baseline mean 17-item HAM-D total scores (reboxetine, 24.0; paroxetine, 23.7) were similar.

Not all patients completed the RSI at baseline assessment. In those that did, more patients in the paroxetine treatment group had previously experienced sexual dysfunction whilst taking other medication (reboxetine 10.7%; paroxetine 25.9%). The treatment groups contained similar proportions who had undergone genitourinary surgical or medical procedures (reboxetine, 27.6%; paroxetine, 25.0%). More patients in the reboxetine treatment group had undergone non-routine investigation of their reproductive organs (reboxetine, 13.8%; paroxetine 3.6%). Very few patients had been evaluated for sexual dysfunction (reboxetine, 1 patient; paroxetine, 2 patients) or treated for sexual dysfunction (one patient in the paroxetine treatment group).

Efficacy of double-blind treatment

There was a gradual reduction in the severity of depressive symptoms in both treatment groups, measured by the mean total 17-item HAM-D score at each visit, using an observed case analysis. Table 5.2 gives the mean score at each visit in both treatment groups. There were no significant differences between treatment groups at any assessment.

Change in genital symptoms (item 14 of the HAM-D)

In both treatment groups, the severity of genital symptoms first increased and then subsequently reduced over the course of the treatment study, although the pattern of change was rather different.

Table 5.1

Demographic and clinical characteristics at baseline

	Reboxetine	Paroxetine	Total
Number	34	36	70
Gender			
Male, n (%)	20 (58.8)	20 (55.6)	40 (57.1)
Female, n (%)	14 (41.2)	16 (44.4)	30 (42.9)
Mean age, years (SD)	38.0 (10.5)	45.3 (11.9)	41.7 (11.8)
Age range, years	21-60	23-63	21-63
17-item HAM-D score, mean (SD)	24.0 (3.8)	23.7(4.0)	23.8 (3.9)
Sexual dysfunction with medication			
No, n (%)	25 (89.3)	20 (74.1)	45 (81.8)
Yes, n (%)	3 (10.7)	7 (25.9)	10 (18.2)
Genitourinary surgical or medical procedure			
No, n (%)	21 (72.4)	21 (75.0)	42 (73.7)
Yes, n (%)	8 (27.6)	7 (25.0)	15 (26.3)
Non-routine investigation of reproductive organs			
No, n (%)	25 (86.2)	27 (96.4)	52 (91.2)
Yes, n (%)	4 (13.8)	1 (3.6)	5 (8.8)
Evaluated for sexual dysfunction			
No, n (%)	28 (96.6)	26 (92.9)	54 (94.7)
Yes, n (%)	1 (3.4)	2 (7.1)	3 (5.3)
Treated for sexual dysfunction			
No, n (%)	29 (100.0)	27 (96.4)	56 (98.3)
Yes, n (%)	0 (0.0)	1 (3.6)	1 (1.7)

Table 5.2 **17-item HAM-D total scores in patients acute double-blind treatment with reboxetine or paroxetine (observed case analysis)**

	Reboxetine			Paroxetine			Difference between treatments				
Time	N	Mean	SD	n	mean	SD	Diff mean	SE (n)	95% CI Lower	95% CI Upper	P-value
Baseline	34	24.03	3.81	36	23.67	3.96	0.36	0.93	-1.49	2.22	0.70
Week 1	33	21.97	5.13	36	21.06	5.14	0.91	1.24	-1.55	3.38	0.46
Week 2	29	20.31	4.94	34	18.68	6.12	1.63	1.42	-1.20	4.47	0.25
Week 3	28	18.25	6.40	32	15.90	6.20	2.34	1.63	-0.92	5.60	0.16
Week 4	26	14.50	7.14	31	14.51	5.54	-0.02	1.68	-3.38	3.35	0.99
Week 5	24	14.08	7.19	31	14.87	6.26	-0.79	1.82	-4.43	2.86	0.67
Week 6	21	13.05	6.67	29	13.86	6.81	-0.81	1.93	-4.70	3.07	0.68
Week 7	20	12.35	5.91	30	13.6	6.97	-1.25	1.90	-5.06	2.56	0.51
Week 8	21	9.90	6.20	30	11.67	6.22	-1.76	1.77	-5.31	1.79	0.32

n number of recorded observations
SD standard deviation
SE standard error
CI confidence interval

All calculations given to two decimal points

With reboxetine, there was an increase over the baseline value at weeks 1, 2 and 3, followed by a steady decline in score over the rest of the treatment period to a score approximately 50% of the original value. With paroxetine, an increase in severity over baseline values was seen until the penultimate study assessment. There were no significant differences in mean values between the treatment groups, although there were non-significant trends with advantages for reboxetine at week 7 (p=0.097) and week 8 (p=0.06). The magnitude of the difference in mean score was small (0.38 at week 7, 0.43 at week 8). Table 5.3 gives the mean item 14 score and standard deviation for each visit for both treatment groups, together with the difference in mean score and standard error, confidence intervals and p-values.

Change in overall illness severity

The mean CGI-I score declined from week 1 in both treatment groups, reflecting an improvement in overall clinical condition. The overall change in score was similar (1.49 with reboxetine, 1.32 with paroxetine). Table 5.4 gives the mean CGI-I score and standard deviation for each visit in both groups, and the difference in mean score and standard error with confidence intervals and p-values. There were no significant differences between treatment groups in CGI-I score at any assessment.

Change in Rush Sexual Inventory visual analogue scores

As indicated earlier not all patients completed the RSI at the baseline assessment, and the number of observations at subsequent assessments declined during double-blind treatment. The visual analogue items are not gender-specific and the data from male and female patients are combined. Table 5.5 gives the mean scores on the relevant RSI items at baseline, and after 4 and 8 weeks of double-blind treatment.

The pattern of change in individual items shows marked differences between treatment groups. The mean score on the item assessing frequency of pleasurable sexual thoughts increased steadily with reboxetine treatment, but with paroxetine an initial decrease was followed by a much smaller increase (figure 5.1). The item measuring ability to become sexually excited showed increases in mean score in both treatment groups, although the change with paroxetine was slight (7.1% increase, compared to 66.5% with reboxetine) (figure 5.2). The mean score on the item assessing frequency of desires to initiate sexual activity increased in both groups, although again the change was much less with paroxetine than with reboxetine (10.2% increase, compared to 64.4%) (Figure 5.3). The mean score on the item assessing frequency of initiation of sexual activity increased in both treatment groups, with a relatively greater increase with reboxetine (61.9%, compared to 20.1% with paroxetine) (figure 5.4). Finally, the mean score on the item assessing overall degree of sexual satisfaction increased steadily during reboxetine treatment, but declined during treatment with paroxetine (figure 5.5).

Table 5.3 **HAM-D item 14 (genital symptoms) in patients undergoing double-blind acute treatment with reboxetine or paroxetine (observed case analysis)**

	Reboxetine			Paroxetine			Difference between treatments				
Time	N	Mean	SD	n	Mean	SD	Diff mean	SE (n)	95% CI Lower	95% CI Upper	P-value
Baseline	34	1.32	0.84	36	1.22	0.80	0.10	0.20	-0.29	0.49	0.61
Week 1	33	1.45	0.67	36	1.44	0.73	0.01	0.17	-0.33	0.35	0.95
Week 2	29	1.38	0.68	34	1.44	0.75	-0.06	0.18	-0.42	0.30	0.73
Week 3	28	1.39	0.74	32	1.38	0.79	0.02	0.20	-0.38	0.41	0.93
Week 4	26	1.23	0.71	31	1.32	0.83	-0.09	0.21	-0.51	0.32	0.66
Week 5	24	1.13	0.80	31	1.35	0.84	-0.23	0.22	-0.68	0.22	0.31
Week 6	21	1.10	0.70	29	1.27	0.84	-0.18	0.23	-0.63	0.27	0.43
Week 7	20	0.95	0.76	30	1.33	0.80	-0.38	0.22	-0.83	0.07	0.10 #
Week 8	21	0.67	0.73	30	1.10	0.84	-0.43	0.23	-0.89	0.02	0.06

n	number of recorded observations
SD	standard deviation
SE	standard error
CI	confidence interval
#	p = 0.0974

All calculations given to two decimal points

Table 5.4 Clinical Global Impression of Improvement in patients undergoing double-blind acute treatment with reboxetine or paroxetine (observed case analysis)

	Reboxetine			Paroxetine			Difference between treatments				
Time	n	mean	SD	n	mean	SD	Diff mean	SE (n)	95% CI Lower	95% CI Upper	P-value
Week 1	33	3.73	0.72	36	3.53	0.77	0.20	0.18	-0.16	0.56	0.27
Week 2	29	3.56	0.87	34	3.35	0.85	0.20	0.22	-0.24	0.63	0.36
Week 3	28	3.29	1.12	32	2.97	0.93	0.32	0.26	-0.21	0.85	0.24
Week 4	26	2.73	1.08	31	2.87	0.99	-0.14	0.27	-0.69	0.41	0.61
Week 5	24	2.71	1.12	31	2.64	0.84	0.06	0.26	-0.47	0.59	0.81
Week 6	20	2.45	1.00	29	2.41	1.01	0.04	0.29	-0.55	0.62	0.90
Week 7	20	2.75	1.12	29	2.69	1.17	0.06	0.33	-0.61	0.73	0.86
Week 8	21	2.24	1.22	29	2.21	0.94	0.03	0.31	-0.58	0.64	0.92

n number of recorded observations
SD standard deviation
SE standard error
CI confidence interval

All calculations given to two decimal points

Table 5.5 Rush Sexual Inventory visual analogue scores in patients undergoing double-blind acute treatment with reboxetine or paroxetine

	Reboxetine			Paroxetine			Difference between treatments				
Item	n	mean	SD	n	mean	SD	Diff mean	SE (n)	95% CI Lower, Upper		P-value
Sexual thoughts											
Baseline	26	34.38	30.04	28	31.64	32.18	2.74	8.49	-14.29	19.77	0.75
Week 4	19	48.94	31.17	23	29.87	30.20	19.08	9.50	-0.12	38.27	0.05
Week 8	10	60.80	24.44	16	38.75	32.53	22.05	12.00	-2.71	46.81	0.08
Sexual excitement											
Baseline	27	41.44	25.72	28	35.82	31.64	5.62	7.79	-10.01	21.25	0.47
Week 4	20	56.45	30.46	22	35.00	34.56	21.45	10.09	1.05	41.85	0.04
Week 8	10	69.00	36.04	16	38.38	35.85	30.63	14.48	0.74	60.51	< 0.05 #
Sexual desire											
Baseline	27	32.48	28.91	28	31.32	30.96	1.16	8.08	-15.06	17.38	0.88
Week 4	19	51.52	30.19	22	33.73	34.39	17.80	10.19	-2.80	38.40	0.09
Week 8	10	53.40	30.91	15	34.53	36.79	18.87	14.12	-10.36	48.09	0.19
Initiate sex											
Baseline	26	23.65	22.93	28	18.04	22.49	5.62	6.18	-6.79	18.02	0.37
Week 4	18	35.28	33.62	22	21.00	26.95	14.28	9.57	-5.10	33.65	0.14
Week 8	10	38.30	31.57	16	22.31	27.01	15.99	11.61	-7.98	39.96	0.18
Sexual satisfaction											
Baseline	26	32.00	29.44	27	29.96	32.75	2.04	8.57	-15.16	19.23	0.81
Week 4	18	46.44	38.33	21	29.43	32.94	17.02	11.41	-6.10	40.13	0.14
Week 8	10	50.10	36.58	16	32.44	30.30	17.66	13.22	-9.63	44.95	0.19

SD, standard deviation; SE, standard error; CI, confidence intervals. # p = 0.045

Figure 5.1

Change in Rush Sexual Inventory sexual thoughts visual analogue item

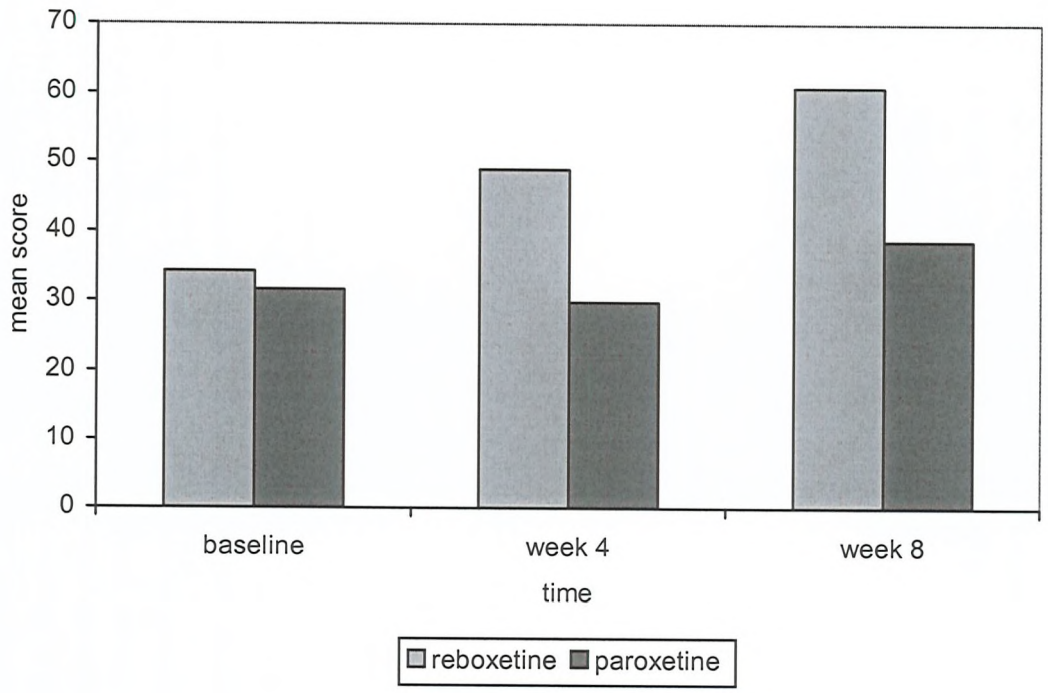


Figure 5.2

Change in Rush Sexual Inventory sexual excitement visual analogue item

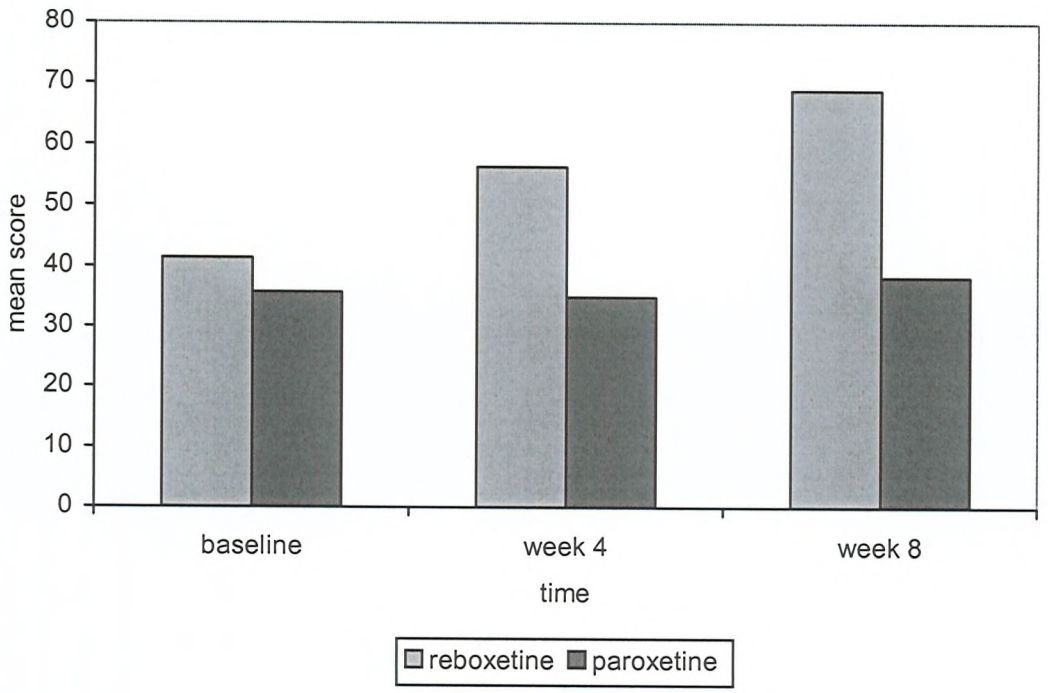


Figure 5.3

Change in Rush Sexual Inventory sexual desire visual analogue item

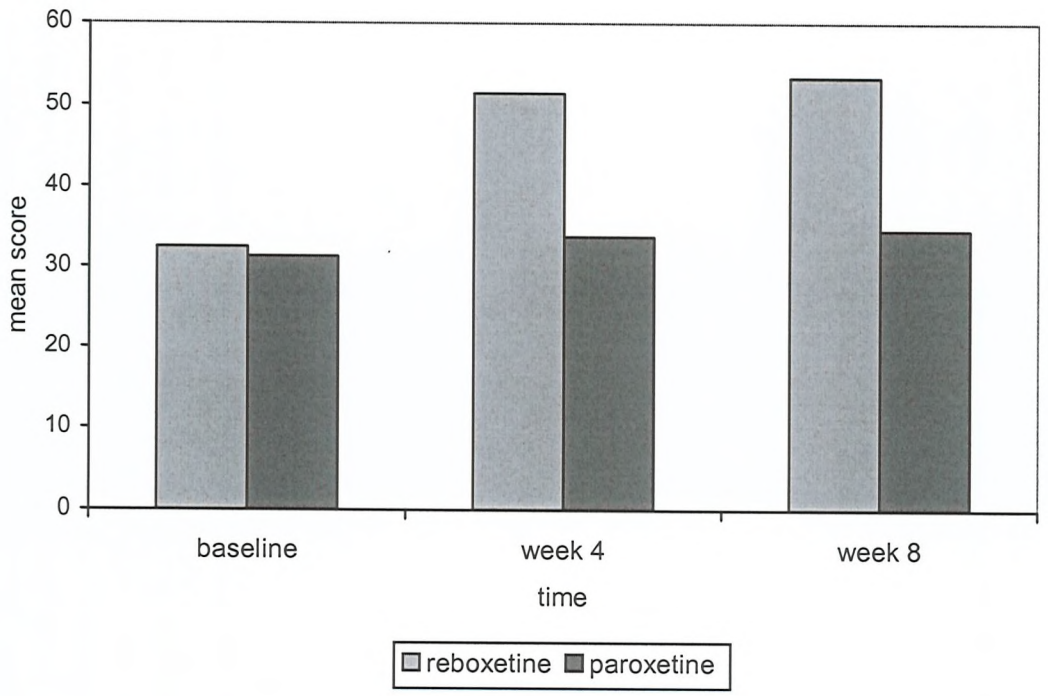


Figure 5.4

Change in Rush Sexual Inventory initiation of sex visual analogue item

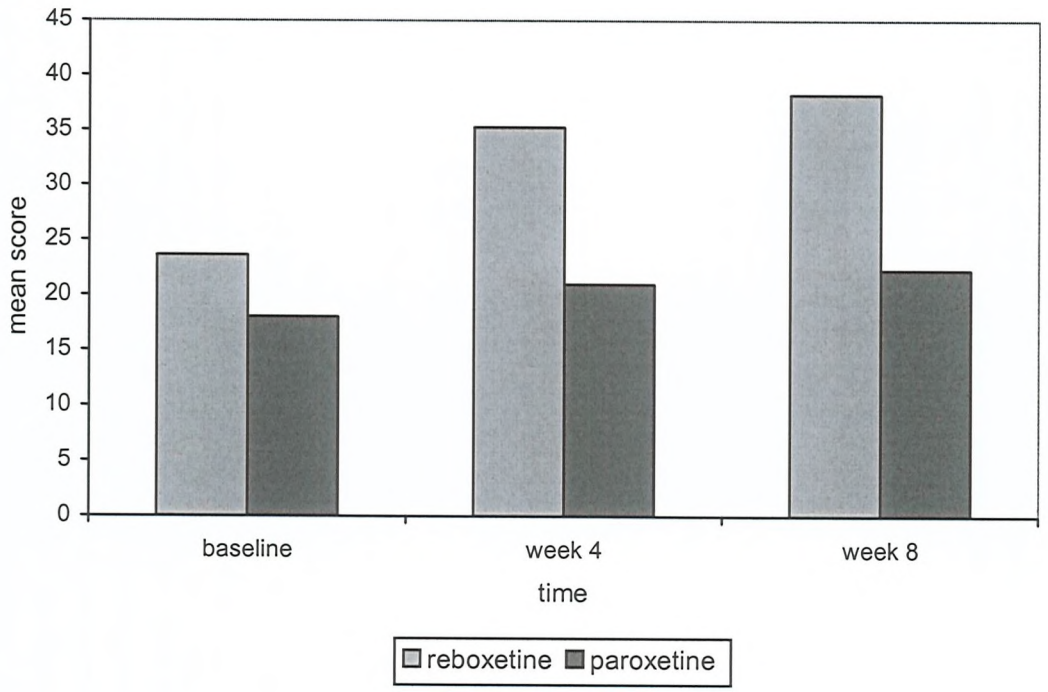
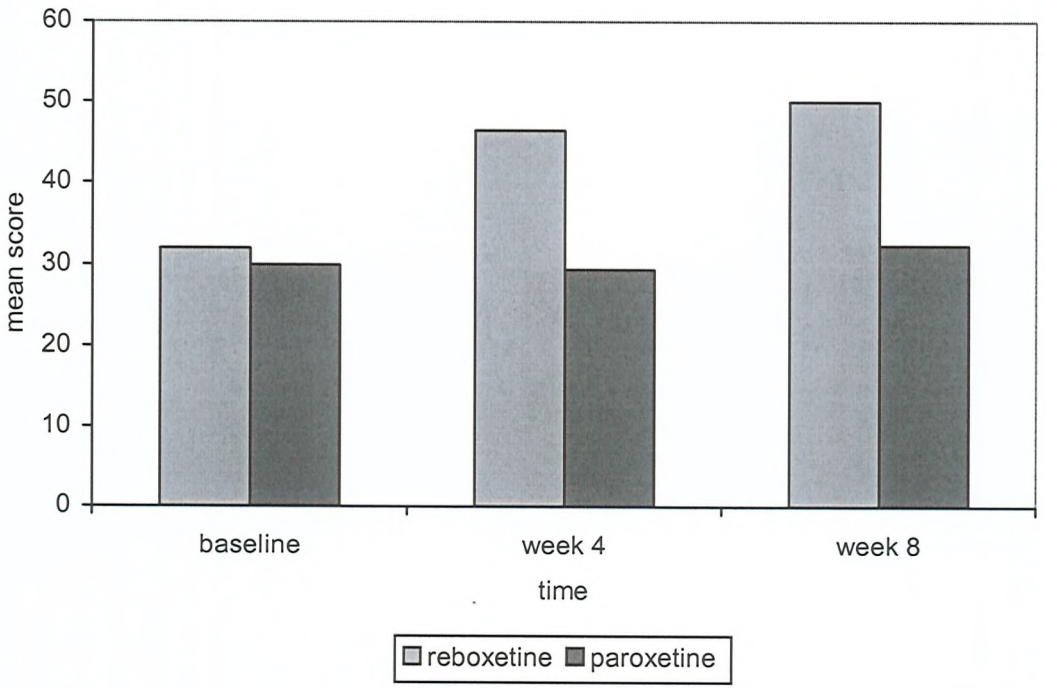


Figure 5.5

Change in Rush Sexual Inventory sexual satisfaction visual analogue item



There were significant differences between treatment groups, with advantages for reboxetine, at week 4 and week 8 on the item assessing ability to become sexually excited. In addition, there were non-significant trends, again with advantages for reboxetine, in the frequency of sexual thoughts at week 4 (p=0.05) and week 8 (p=0.08), and in the desire to initiate sexual activity at week 4 (p=0.09). The null hypothesis, that there would be no differences between treatments in effects on sexual function as assessed by the visual analogue items of the RSI, can therefore be rejected.

Adverse events associated with treatment

A total of 12 patients (six in each treatment group) reported a total of 13 adverse events relating to sexual function. Table 5.6 gives the nature of these events, together with details of their severity, the possible relation to double-blind treatment, any action that was required, and the clinical outcome. The time of onset of the event and its duration could not be ascertained in many reports. Reboxetine treatment appeared associated with problems in sexual desire and arousal, whereas paroxetine treatment appeared associated with problems in orgasm (inhibited ejaculation in men or anorgasmia in women). In view of the small numbers, no statistical comparisons were made.

DISCUSSION

Findings of the study

The findings of the current investigation in the sub-group of 70 patients from United Kingdom study centres who entered double-blind treatment indicate that reboxetine and paroxetine differ in their effects on sexual function, despite having similar overall antidepressant efficacy. The study provides further evidence that antidepressants of similar efficacy can differ in their effects on sexual function, as previously shown in the randomised controlled trials of nefazodone against paroxetine (reported in chapter two) and an SNRI against paroxetine (reported in chapter four). Relatively more reboxetine-treated patients withdrew from the study (13 from 34 patients, 38.2%) than did those receiving paroxetine (6 from 36 patients, 16.7%), due mainly to drop-outs due to adverse events, not related to sexual function.

Measures of sexual function and satisfaction showed increases in both treatment groups as severity of depressive symptoms declined, but the magnitude of the increase was consistently greater with reboxetine than with paroxetine. There was a significant advantage for reboxetine over paroxetine in the RSI item measuring ability to become sexually excited. In addition, there were non-significant trends favouring reboxetine on item 14 of the HAM-D at weeks 7 and 8 of double-blind treatment, and on the RSI items assessing frequency of sexual thoughts (weeks 4 and 8) and desire to initiate sexual activity (week 4). This difference was not the result of differences in overall antidepressant efficacy, as mean total 17-item HAM-D scores and mean CGI-I scores did not differ significantly at any point during double-blind treatment.

Table 5.6

Reported adverse events relating to sexual function

Reboxetine (n = 34)					Paroxetine (n = 36)				
Nature of adverse event	Severity	Related to treatment	Action taken	Outcome	Nature of adverse event	Severity	Related to treatment	Action taken	Outcome
Reduced libido	Mild	Yes	None	Unknown	Reduced libido	Moderate	Yes	None	Persists
Reduced libido	Severe	No	None	Persists	Impotence	Severe	Yes	None	Persists
Impotence	Moderate	Yes	None	Recovered	Delayed ejaculation	Mild	Yes	None	Persists
Impotence	Severe	Yes	Withdrawn	Persists	Delayed ejaculation	Severe	Yes	None	Persists
Premature ejaculation #	Moderate	Yes	None	Recovered	Anorgasmia	Severe	Yes	None	Persists
Abnormal sexual function #	Moderate	Yes	None	Recovered	Breast tenderness	Mild	No	None	Recovered
Testicular pain	Moderate	No	None	Recovered					

Reported by the same patient

The proportion of patients (12 patients, 14.3% of the total sample) who reported an adverse event related to sexual function was greater than in the acute treatment studies described previously in this thesis. One possible reason for this may be that the patients were sensitised to report untoward sexual events, through inclusion of the RSI as a study outcome measure. In addition, the study was conducted approximately seven years later than the randomised controlled trial of nefazodone and paroxetine, during which period doctors and patients may have become more aware of the possible effects of antidepressants on sexual function and satisfaction. The profile of adverse sexual events in this study reflects that seen in the clinical trial databases with reboxetine and paroxetine.

Study weaknesses

The current investigation has a number of weaknesses. The first is the small size of the study sample, which represents a sub-group from the total patient population recruited in the overall treatment study. It will be important to determine whether the advantages seen for reboxetine in this investigation are confirmed in the analysis of data obtained in the overall study, expected during the course of 2004. The second weakness is that the decline in patient numbers during the course of the investigation further reduces the confidence that can be placed in the study findings. For example, only 51 patients (72.9% of the original sample) provided data on item 14 of the HAM-D at study end-point; 54 patients (77.1%) provided data on the RSI visual analogue items at the baseline assessment, and only 26 patients (37.1%) did so at the end of the investigation. Previous chapters have already considered a further weakness, that a multi-centre study runs the risk of treatment-by-centre interactions, although again considerable efforts were made to minimise this by inter-rater reliability meetings with training in all outcome measures. The drawback of using item 14 of the HAM-D in assessing sexual function has been described in previous chapters.

Implications for clinical practice and research

The findings of the current investigation support the contention that prescription of SSRI antidepressants may not be the best option in those depressed patients for whom preserved sexual function is a major concern (Hirschfeld, 1999). If the findings are confirmed in the overall treatment study, it could be argued that reboxetine is preferable to paroxetine in such a patient group, providing there is no difference in antidepressant efficacy and other measures of treatment tolerability.

This study provides further evidence that the scores on the visual analogue items of the RSI change during the course of antidepressant treatment (supporting the findings reported by Clayton *et al*, 2003). The study also confirms that it is possible to distinguish the effects of two antidepressants with differing pharmacological properties using this instrument. The RSI has now shown these properties in two double-blind treatment studies comparing reboxetine with two different SSRI antidepressants (fluoxetine

and paroxetine). It is however a lengthy and somewhat intrusive instrument and further treatment studies might usefully compare the utility of the RSI with shorter measures of sexual function.

CHAPTER 6 : SEXUAL DYSFUNCTION DURING ANTIDEPRESSANT TREATMENT WITH TWO SELECTIVE SEROTONIN RE-UPTAKE INHIBITORS

AIMS OF THE INVESTIGATION

Findings from the randomised controlled trials described in chapters two, four and five indicate that antidepressant drugs differ significantly in effects on sexual function, and these variations do not result from differences in overall efficacy or tolerability of treatment. In chapter two, nefazodone, a drug with both 5-HT_2 antagonist and 5-HT re-uptake inhibitory properties, had advantages over the SSRI paroxetine, as measured by change in item 14 (genital symptoms) of the HAM-D. In chapter four, paroxetine had some advantages over the comparator SNRI, as measured by some items of the sexual function and enjoyment questionnaire at some points, in male patients. In chapter five, the selective noradrenaline re-uptake inhibitor reboxetine had advantages over paroxetine, on some visual analogue items of the Rush Sexual Inventory. This chapter examines in detail the effects of increased selectivity for 5-HT re-uptake on sexual function, assessed principally by the Arizona Sexual Experiences Scale (ASEX) (McGahuey *et al*, 2000).

The SSRI citalopram is a racemic mixture of two enantiomers, serotonin re-uptake inhibition being dependent upon the S-enantiomer (escitalopram). Escitalopram is the most selective SSRI available for use in clinical practice. Double-blind placebo-controlled randomised controlled trials with escitalopram demonstrate it has greater antidepressant efficacy than citalopram, and similar overall tolerability (Gorman *et al*, 2002; Baldwin, 2002). Paroxetine is a single enantiomer SSRI, efficacious in the short-term and long-term treatment of patients with major depression, panic disorder, obsessive-compulsive disorder, social anxiety disorder, post-traumatic stress disorder, and generalised anxiety disorder. It is used widely in primary and secondary care settings (Baldwin, 2000). Prior to this investigation, the relative efficacy and tolerability (including assessments of sexual function) of escitalopram and paroxetine had not been examined within the context of a randomised controlled trial.

This was a randomised, double-blind, flexible-dose, parallel-group, international (Austria, Belgium, France, Ireland, Italy, Lithuania, United Kingdom) multi-centre study to compare the efficacy and safety of escitalopram and paroxetine in the treatment of patients with major depression. Efficacy and safety were evaluated over an initial eight-week treatment period (acute phase), and a further nineteen-week period (continuation phase) in patients who had responded to acute treatment. The study also involved a systematic enquiry into sexual function. Other assessments included investigation of treatment-emergent and discontinuation-emergent adverse effects, and use of specific scales and tests to evaluate sleep and cognitive function, but these are not described in this chapter.

Lundbeck, the pharmaceutical company that manufactures citalopram and escitalopram, sponsored the study. As main principal investigator for this study, my role includes the following activities –

- demonstrating the need for the study
- developing the overall study protocol
- supporting the study protocol in a letter to UK local research ethics committees
- producing the rating scale training videos
- training investigators in use of the assessment interview and rating scales
- communicating with study investigators via Lundbeck and through a study newsletter
- analysing the data in association with employees of Lundbeck
- presenting the results to the study investigators
- assistance in preparing the final study report
- assistance in preparing the results for publication

METHOD

Study objectives

The primary objective was to evaluate the efficacy of the two compounds in acute treatment of patients with DSM-IV major depressive disorder. Secondary objectives included evaluations of efficacy in the continuation phase, tolerability and safety across the study, treatment-emergent sexual dysfunction, and discontinuation effects during a brief treatment interruption in the continuation phase and tapered drug withdrawal at the end of the study. This chapter is largely restricted to consideration of data relating to effects on sexual function, assessed with the ASEX scale and an additional one-item scale relating to recent sexual experiences (RSE), but necessarily includes relevant data on antidepressant efficacy assessed by the Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery and Åsberg, 1979). The schedule for assessments is shown in Table 6.1.

Study treatments

Screening of patients was followed by a single-blind placebo run-in lasting seven days. Patients who did not respond (>25% reduction in total MADRS score) were randomly assigned to receive escitalopram or paroxetine for an eight-week double-blind treatment period. The daily dosage was fixed in the first two weeks (escitalopram 10 mg, paroxetine 20 mg), but could be increased after 2 or 4 weeks, if patients had not responded. After completing double-blind treatment, patients who were considered much or very much improved could enter a double-blind continuation phase on the current dose, which remained fixed for the rest of the study.

Table 6.1 Schedule of study assessments

Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19*	20
	Screen	Baseline																		
Stage of study	Eligibility		Acute treatment					Continuation phase									Down taper		Follow-up	
Week	-1	0	2	4	6	8	12	16	Interruptions			20	23	27	28	29	30	31	32	34
Day	-7	-1	14	28	42	56	84	11	11	12	12	14	16	18	19	20	21	21	22	23
								2	6	0	4	0	1	9	6	3	0	7	4	8
Window (days)	3	3	3	3	3	3	7	7	1	1	1	3	7	7	1	1	1	1	1	3
Signed informed consent	X																			
Assign screening number	X																			
Assign randomisation number		X																		
Demographic details	X																			
Inclusion/exclusion criteria	X	X																		
Medical history	X																			
MINI interview	X																			
Vital signs/weight	X	X[1]				X[1]		X[1]	X	X	X			X[1]	X	X	X	X	X[1]	
Physical examination	X																			
Concomitant medicine	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory tests	X																			
Pregnancy test	X			X[2]		X[2]	X[2]	X[2]				X[2]	X[2]	X[2]					X[2]	
ECG	X																			

CGI-improvement			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
CGI-severity		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19*	20
	Screen	Baseline																		
Modified DESS checklist	X							X	X	X	X			X	X	X	X	X	X	
MADRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
HAD	X	X	X	X	X	X		X	X	X	X			X	X	X	X	X	X	
CFF		X		X		X		X	X	X	X			X	X	X	X	X	X	
CRT		X		X		X		X	X	X	X			X	X	X	X	X	X	
CFQ		X		X		X		X	X	X	X			X	X	X	X	X	X	
LESQ		X		X		X		X	X	X	X			X	X	X	X	X	X	
ASEX		X	X	X		X		X						X				X	X	
Sociodemographics		X																		
SF-36		X				X					X			X					X	
Resource use questionnaire		X				X						X							X	
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense medicine	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Check compliance		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

* all patients withdrawing prematurely from the study should be seen for a premature withdrawal visit (assessments as per visit 19) [1] weight measured at selected visits only [b2] in Austria, pregnancy tests were performed on an approximately monthly basis throughout the study

Inclusion criteria and exclusion criteria, and patient withdrawals

To be considered for participation, patients aged 18 years or older had to fulfil DSM-IV diagnostic criteria for major depressive disorder and have a total MADRS score between 22 and 40 at baseline. Exclusion criteria included pregnancy or lactation, serious risk of suicide, current alcohol or drug abuse or dependence, unstable or serious physical illness, concomitant medication with various drugs, and previous non-response to citalopram or paroxetine. Patients were excluded if they were using any agent to treat sexual dysfunction. Participating patients had to be withdrawn from the study if the investigator considered it to be in the best interests of the patient, when there was a significant risk of suicide, if the patient became pregnant, the randomisation code was broken, or the patient withdrew consent or became lost to follow-up. Patients could also be withdrawn after a serious adverse event.

Method of randomisation

Patients who entered the double-blind acute treatment phase of the study were randomly allocated to one of two treatment groups, according to a randomisation code generated by the study sponsor. This randomisation code also independently dictated to which interruption period (first or second) and which withdrawal period (early, late) the patient was allocated. The randomisation was balanced so that an equal proportion of patients from each treatment arm entered the interruption periods and the withdrawal phases. Block randomisation ensured that equal numbers of patients entered each treatment group.

Assessment of sexual function

The ASEX is a patient-completed questionnaire comprising five items that evaluate a patient's recent sexual experiences (McGahuey *et al*, 2000). Patients were asked to assess their experiences over the last week and respond on a six-point scale for each item. Different versions of the scale exist for men and women. By convention, sexual dysfunction is judged to be present when the total ASEX score is 19 or more, or when the score on any ASEX item is 5 or more, or when the scores on any 3 ASEX items are 4 or more. The ASEX questionnaires for men and women are shown in Appendices 6.1 and 6.2, respectively. As delayed orgasm or ejaculation is one of the more common sexual side effects of antidepressant treatment, an additional one-item scale assessing satisfaction with time to reach orgasm or ejaculation was included (Recent Sexual Experiences, RSE). This question was posed at the same assessment but presented on a separate form.

Adverse events

At each visit, adverse events reported spontaneously, or observed or elicited in response to a non-leading question were recorded. The intensity of any adverse event was described as mild, moderate or severe, and the relationship to the study drug of any event was described as probable, possible or not related. By definition a 'serious adverse event' was any untoward

medical occurrence, not necessarily caused by study treatment (including death, life-threatening illness, persistent disability, and congenital anomaly).

STATISTICAL METHODS

Sample size and power

As in most randomised controlled trials without a placebo treatment arm, the primary analysis was based on non-inferiority, with the hypothesis that the study treatments would not differ significantly in efficacy. A total of 150 patients per treatment arm were needed to provide 80% power to show non-inferiority in change from baseline to week 8 on the MADRS total score.

Analysis data sets

The sets of patients to be analysed were defined *a priori* as follows. The *all patients treated set* (APTS) included all randomised patients who took at least one dose of double-blind study medication. The *full analysis set* (FAS) comprised all randomised patients who took at least one dose of medication and had at least one post-baseline assessment of the primary efficacy variables. Finally, the *per protocol set* (PPS) included all the patients in FAS who received double-blind treatment up to the week 4 visit, who underwent at least one assessment with the primary efficacy variable at or after the week 4 visit, and who did not exhibit any major protocol violations.

Analysis of efficacy and safety

Data from all assessments was listed and summarised by treatment group using descriptive statistics. Summary statistics (mean, standard deviation, median, and range) was presented for continuous variables and counts and percentages for categorical variables. Unless otherwise stated, all statistical tests were two-sided, and carried out at the 5% level of significance. The statistical software used was SAS version 8.1.

The primary efficacy parameter was change from baseline to week 8 on the MADRS total score in the FAS using LOCF technique and nominal visits. The analysis was based on a general linear model for analysis of covariance (ANCOVA) with factors for treatment group and centre, with the baseline MADRS score as a covariate. The test of primary interest (i.e. the non-inferiority test of escitalopram versus paroxetine) was performed at the 5% level. The final estimates of efficacy included 90% confidence intervals of the estimated between-group differences. The non-inferiority of escitalopram was evaluated on the basis of the one-sided 95% confidence interval for the treatment difference. Non-inferiority was declared if the upper

limit of the confidence interval for the difference in change for baseline in MADRS total scores showed paroxetine at most 3 points better than escitalopram.

Overall treatment response was analysed separately by a logistic regression, for a 50% reduction from baseline to final assessment of MADRS total score. Secondary analyses also included analyses of CGI-S and CGI-I scores using the non-parametric Cochran-Mantel-Haenszel mean score statistic with modified scores and with the individual centre comprising the strata. These analyses were performed by statisticians employed by Lundbeck Ltd.

Sexual dysfunction

Absolute values and changes from screening to post-screening assessments of the ASEX (and the additional question) were summarised and analysed for both treatment groups. Changes in ASEX and RSE were assessed in both the acute and continuation phases of treatment. Separate analyses were performed in the sub-groups of male and female patients. The proportion of patients fulfilling the ASEX criteria for probable sexual dysfunction at each time point was noted. Comparisons were made between study treatments in ASEX score, change in ASEX score, and proportion with sexual dysfunction.

Concurrent illness, concomitant medication, adverse events and withdrawals

Concurrent illness was classified and presented according to ICD-10 terminology. Concomitant medication was categorised according to the WHO terminology using the World Health Organisation Drug Dictionary version 1998/04 or later. All adverse events were categorised and presented according to WHO terminology using a dictionary based on the World Health Organisation Adverse Reaction Terminology version 1998/04 or later. The incidence of all treatment-emergent adverse events was tabulated in each treatment group according to system organ class and preferred term. The number of patients who were withdrawn prematurely was tabulated by treatment group, by the reason for withdrawal and by other relevant variables.

ETHICAL CONSIDERATIONS

The study was conducted in accordance with the Declaration of Helsinki as adopted by the 18th World Medical Assembly 1964 and subsequent amendments: Tokyo (1975), Venice (1983), Hong Kong (1989), Somerset West, South Africa (1996) and Edinburgh, Scotland (2000). The study was approved in the United Kingdom by three local research ethics committees. Approval for study centres in other countries was gained either from national, regional or local research ethics committees, according to local arrangements.

No ethical problems were foreseen for the participation of patients in the study. Escitalopram and paroxetine had proven efficacy in major depression; the doses used were the lowest with proven efficacy; and the protocol permitted dosage changes according to the efficacy and tolerability of study treatment, reflecting standard clinical practice. The duration of acute treatment was sufficient to allow assessment of efficacy; responders to acute treatment could enter continuation therapy, reflecting current recommendations; and the design permitted assessment of common problems during antidepressant treatment (e.g. sexual dysfunction; sleep; discontinuation symptoms). The design included detailed evaluation of the effects of missed treatment and of tapering treatment at the end of the study. Patients attended appointments frequently and regularly; assessments of efficacy and tolerability were comprehensive; and participation could only occur after the provision of written informed consent.

RESULTS

Patient disposition

A total of 325 patients were randomised to double-blind treatment: two did not receive medication, so the 'all patients treated set' (APTS) consists of 323 patients (158 randomised to paroxetine, 165 to escitalopram). A total of 89 patients (54 paroxetine, 35 escitalopram) withdrew from the study, leaving 234 patients (104 paroxetine, 130 escitalopram) who completed double-blind treatment. The full analysis set (FAS) comprises 321 patients (156 paroxetine, 165 escitalopram), the per protocol set (PPS) includes 305 patients (148 paroxetine, 157 escitalopram). The details of patient disposition are shown in Table 6.2.

Patient demographics (APTS)

The APTS consists of 85 men and 238 women. The mean age for the overall APTS sample was 45.0 years, the age range 18 to 85 years. The vast majority of the sample was of Caucasian origin, reflecting the area in which the study was conducted. There were no significant differences between treatment groups. The demographic details of the overall sample and for each treatment group are summarised in Table 6.3.

Antidepressant efficacy

There were no significant differences between treatment groups in the baseline MADRS score. Double-blind treatment was associated with a steady reduction in MADRS score throughout the acute (days 0-

Table 6.2

Summary of patient disposition

	Paroxetine		Escitalopram		Total	
	N	(%)	N	(%)	N	(%)
Patients randomised (APRS)	159		166		325	
Patients treated (APTS)	158		165		323	
Patients completed	104	(65.8)	130	(78.8)	234	(72.4)
Patients withdrawn	54	(34.2)	35	(21.2)	89	(27.6)
Efficacy sets						
Full analysis set (FAS)	156		165		321	
Per protocol set (PPS)	148		157		305	

Table 6.3

Summary of patient demographics in All patients Treated Sample (APTS)

	Paroxetine	Escitalopram	Total
Number of patients	158	165	323
Male N (%)	40 (25.3)	45 (27.3)	85 (26.3)
Female N (%)	118 (74.7)	120 (72.7)	238 (73.7)
Mean age (years)	45.1	44.9	45.0
Median age (years)	45	43	44
SD (years)	13.2	14.7	14.0
Minimum age (years)	19	18	18
Maximum age (years)	76	85	85
Caucasian N (%)	157 (99.4)	163 (98.8)	320 (99.1)
Black N (%)	1 (0.6)	0 (0.0)	1 (0.3)
Other N (%)	0 (0.0)	2 (1.2)	2 (0.6)

56) and continuation phases (days 57-189) of the study in both treatment groups. There were no significant differences between treatment groups in the proportion of patients who responded to treatment (i.e. patients with a 50% or more reduction in MADRS scores from baseline values), during either the acute or continuation phases of treatment. Similarly, there were no significant differences between treatment groups in the proportion of patients who achieved symptomatic remission (i.e. a MADRS score of less than 12). The efficacy results (FAS, LOCF analysis) are summarised in Table 6.4.

Change from baseline in total ASEX score

There were minimal changes in total ASEX scores during the course of the study. In the LOCF analysis, the mean total ASEX score was increased from that at baseline during the first eight weeks of double-blind treatment, indicating deterioration in sexual function, in both groups. The mean total ASEX score then declined (indicating improvement in function) from week 8 until the end of the study, when it was minimally lower than that at baseline, in both treatment groups. A similar pattern was seen in the observed case analysis (OC), in both groups. Table 6.5 and Figures 6.1 and 6.2 show the mean total ASEX scores by assessment visit in the two treatment groups, for both the LOCF and OC data sets.

The institution of double-blind treatment was associated with an increase in mean total ASEX score, in both treatment groups. In the overall sample, the magnitude of the change appears only slight (representing around 5% of the total score) and is unlikely to be of clinical significance. However some patients in both treatment groups showed major changes in ASEX score. With paroxetine, the biggest drop in score from baseline was by 18 points, the biggest increase by 22 points: with escitalopram, the biggest drop in score from baseline was 21 points, and the greatest increase in ASEX score was 18 points. Table 6.6 shows the changes from baseline in mean total ASEX score, together with the minimum and maximum changes, for both the LOCF and OC data sets.

Differences between treatment groups in adjusted mean change in ASEX total score

There were no significant differences between escitalopram and paroxetine in the adjusted mean changes in ASEX total score in the total sample, in either the LOCF or the OC analysis. In the LOCF there was a non-significant trend for a greater increase in ASEX score from baseline to day 14 with escitalopram (1.09, standard error 0.28) than with paroxetine (0.49, standard error 0.29) ($p = 0.091$). A similar non-significant trend was seen in the OC analysis ($p = 0.086$). The differences between groups in change in adjusted ASEX score in the overall sample are unlikely to be of clinical significance. Table 6.7 gives the differences between treatment groups for both analyses; Figure 6.3 shows the difference for the LOCF analysis.

Differences between treatment groups in male patients

Table 6.4

Efficacy of double-blind treatment (FAS, LOCF analysis)

	Escitalopram	Paroxetine
N	165	156
Mean baseline MADRS score	29.68	29.68
Mean endpoint MADRS score		
Acute phase	12.12	11.22
Continuation phase	7.95	9.41
Responders to treatment (%)		
Acute phase	67.9	71.2
Continuation phase	84.8	78.8
Patients achieving symptomatic remission (%)		
Acute phase	56.4	61.5
Continuation phase	78.8	76.3

MADRS Montgomery-Asberg Depression Rating Scale

There were no significant differences in antidepressant efficacy between groups

Response defined as 50% or more reduction in MADRS score from baseline
Remission defined as MADRS score of less than 12

Table 6.5

Mean total ASEX scores during the study (FAS, LOCF and OC data sets)

Treatment group	Day	Last Observation Carried Forward				Observed Cases			
		N	Mean	SD	MDN	N	Mean	SD	MDN
Paroxetine	0	145	19.88	6.53	20	145	19.88	6.53	20
	14	145	20.58	6.23	20	147	20.54	6.23	20
	28	145	20.56	6.21	20	146	20.47	6.21	20
	56	145	20.20	6.23	20	145	19.86	6.13	20
	112	145	19.86	6.22	20	129	19.17	6.01	19
	189	145	19.51	6.52	19	120	18.84	6.39	18
Escitalopram	0	155	20.28	5.98	20	155	20.28	5.98	20
	14	155	21.52	5.78	22	158	21.52	5.78	22
	28	155	21.29	6.25	21	153	21.22	6.31	20
	56	155	20.89	6.46	21	147	20.82	6.42	21
	112	155	19.98	6.32	20	144	19.82	6.25	19
	189	155	19.64	6.54	19	139	19.52	6.44	19

SD standard deviation

MDN median

Figure 6.1

Mean total ASEX scores during study (FAS, LOCF)

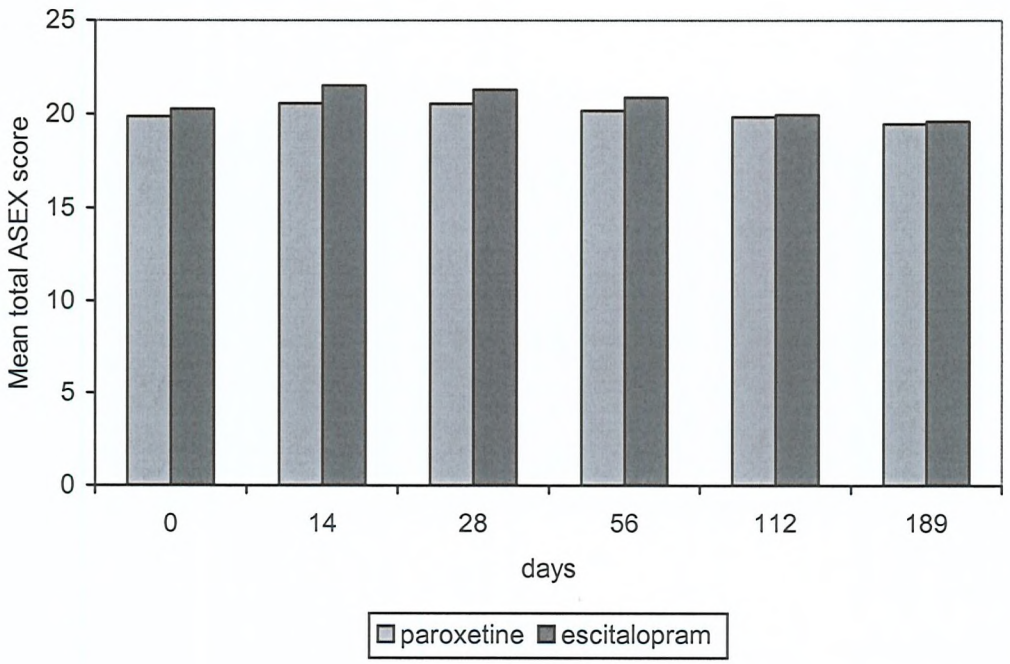


Figure 6.2

Mean total ASEX scores during the study (FAS, OC)

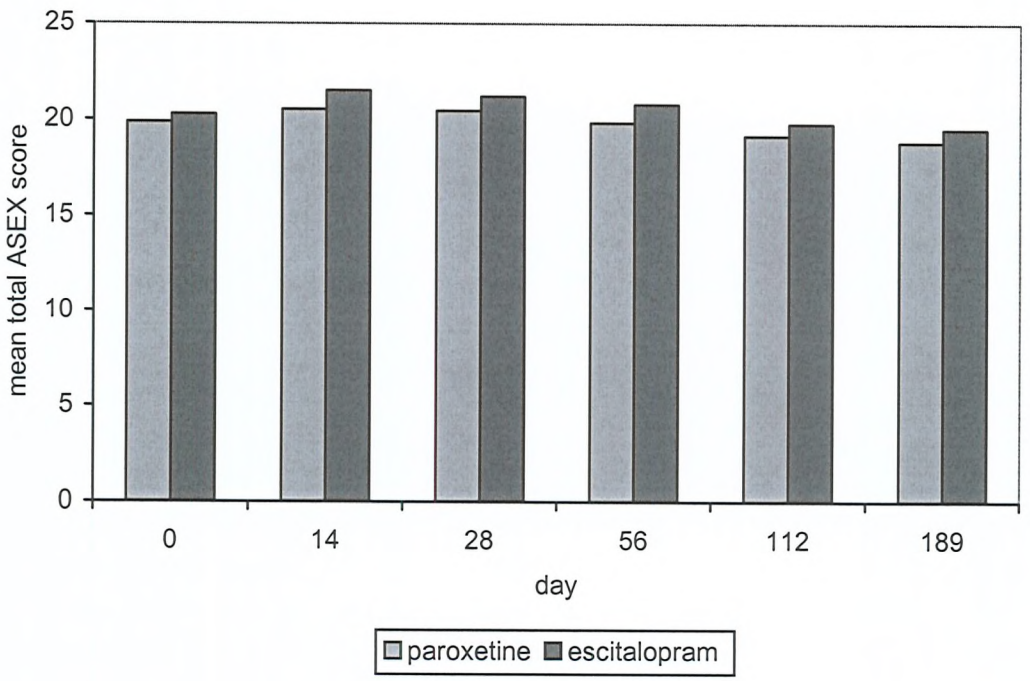


Table 6.6

Change from baseline in mean total ASEX score (FAS, LOCF and OC data sets)

Treatment group	Day	Last observation carried forward					Observed cases				
		N	Mean	SD	Minimum	Maximum	N	Mean	SD	Minimum	Maximum
Paroxetine	14	145	0.66	3.06	-6	+13	144	0.67	3.07	-6	+13
	28	145	0.63	4.40	-14	+22	142	0.65	4.45	-14	+22
	56	145	0.21	4.60	-17	+20	139	0.18	4.69	-17	+20
	112	145	-0.12	5.02	-18	+20	125	-0.46	4.91	-18	+17
	189	145	-0.52	5.40	-17	+20	116	-1.20	5.11	-17	+16
Escitalopram	14	155	1.14	3.31	-10	+18	155	1.14	3.31	-10	+18
	28	155	0.89	3.73	-12	+17	150	0.94	3.76	-12	+17
	56	155	0.50	4.63	-21	+17	144	0.52	4.68	-21	+17
	112	155	-0.52	4.40	-18	+14	139	-0.65	4.44	-18	+14
	189	155	-0.89	4.86	-18	+14	132	-1.14	5.00	-18	+14

LOCF last observation carried forward

OC observed case

SD standard deviation

Table 6.7

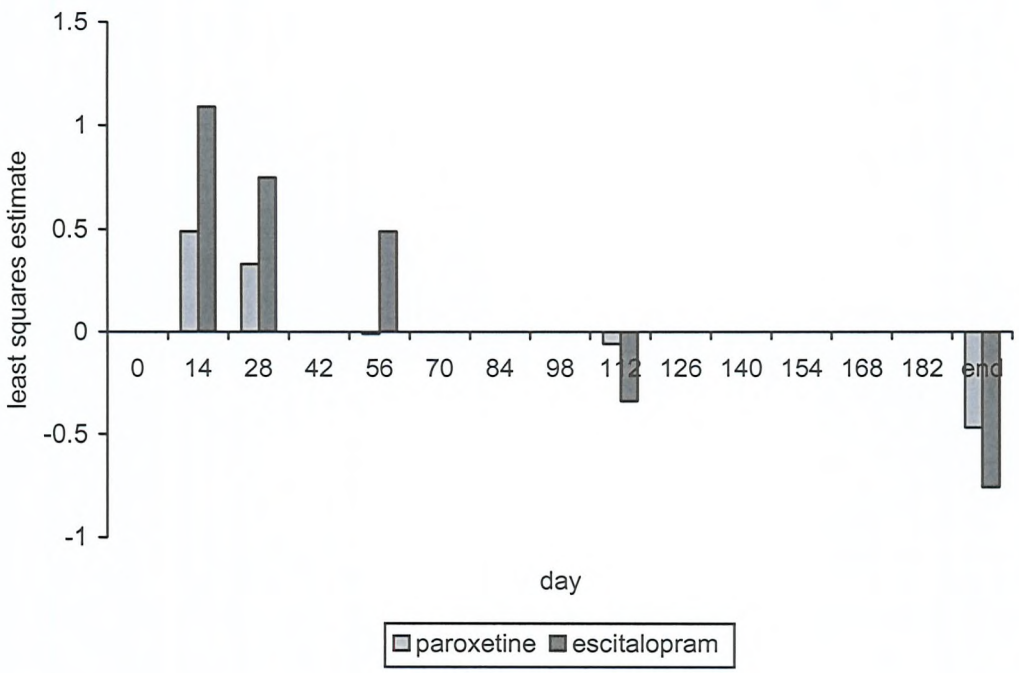
Treatment difference of adjusted mean changes in ASEX total score (FAS, LOCF and OC)

Analysis	Day	Paroxetine			Escitalopram			Difference between groups				
		N	Mean	SE	N	Mean	SE	Mean	SE	95% CI lower	95% CI upper	p-value
LOCF	14	145	0.49	0.29	155	1.09	0.28	-0.59	0.35	-1.28	0.09	0.091
	28	145	0.33	0.37	155	0.75	0.36	-0.42	0.44	-1.29	0.45	0.344
	56	145	-0.01	0.42	155	0.49	0.41	-0.50	0.50	-1.49	0.49	0.323
	112	145	-0/06	0.42	155	-0.34	0.41	0.29	0.50	-0.71	1.28	0.571
	129	145	-0.47	0.46	155	-0.76	0.45	0.28	0.55	-0.81	1.38	0.609
OC	14	144	0.49	0.29	155	1.09	0.28	-0.60	0.35	-1.29	0.09	0.086
	28	142	0.33	0.38	150	0.76	0.37	-0.43	0.46	-1.33	0.47	0.344
	56	139	-0.07	0.43	144	0.53	0.43	-0.61	0.52	-1.64	0.42	0.247
	112	125	-0.36	0.45	139	-0.32	0.44	-0.04	0.55	-1.13	1.04	0.935
	189	116	-1.14	0.53	132	-0.85	0.51	-0.28	0.63	-1.52	0.95	0.650

LOCF	last observation carried forward
OC	observed case
SE	standard error
95% CI	95% confidence interval

Figure 6.3

Adjusted mean changes from baseline in ASEX total score (FAS, LOCF analysis)
Male and female patients



There were 71 male patients in the total FAS sample. In the LOCF analysis, there was a non-significant advantage for escitalopram over paroxetine (p = 0.083) for change in ASEX score at day 56, but there were no significant differences between treatments at other time points. There were no significant differences or non-significant trends between groups in the OC analysis. Figure 6.4 shows adjusted mean changes in ASEX total score in male patients.

Differences between treatment groups in female patients

There were no significant differences or non-significant trends between the treatment groups in female patients. The pattern differed to that in male patients. In men, paroxetine was associated with a numerically greater increase in adjusted mean change in ASEX score than was escitalopram, over the course of the study. In women, escitalopram was associated with a numerically greater increase in the first eight weeks of the study, but with greater reductions in the continuation phase of treatment. Figure 6.5 shows adjusted mean changes in ASEX total score in female patients.

Proportion of patients with sexual dysfunction

The majority of patients had ASEX scores indicating the presence of probable sexual dysfunction, at all time points from baseline to endpoint, in both treatment groups, in both the LOCF and OC analysis. There were no significant differences in the proportion of patients with sexual dysfunction (men plus women) at baseline, being 69.9% with paroxetine, and 67.3% with escitalopram. In both treatment groups, the proportion with sexual dysfunction declined during both acute and continuation treatment (from 69.9% to 57.7% with paroxetine; from 67.3% to 57.0% with escitalopram). There were no significant differences or non-significant trends between the treatment groups. The proportion of patients with sexual dysfunction is given in Table 6.8 (LOCF and OC analyses), and shown in Figure 6.6 (LOCF analysis only).

ASEX single item scores

The mean scores on all the single ASEX items showed a steady decline during the study, in both treatment groups (OC analysis). Table 6.9 gives the mean score and standard deviation for each ASEX item over the course of the study in the total sample (i.e. including both male and female patients).

Change in ASEX item 1 (sex drive) in male and female patients

In the total sample there was a non-significant trend for a difference between treatments in the first four weeks of the study, there being a slight reduction with paroxetine and slight increase with escitalopram (p = 0.084 at day 14, p = 0.089 at day 28). This pattern was not apparent after the first four weeks of double-blind treatment. There were no significant differences between treatments at any time point in the gender sub-groups.

Figure 6.4

Adjusted mean changes from baseline in ASEX total scores

Male patients (FAS, LOCF)

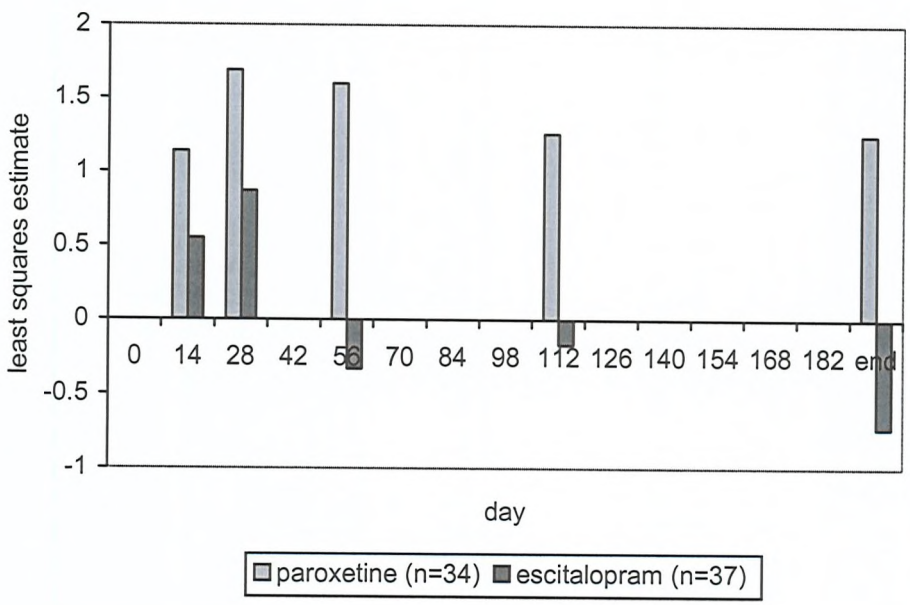


Figure 6.5

Adjusted mean changes from baseline in ASEX total scores

Female patients (FAS, LOCF)

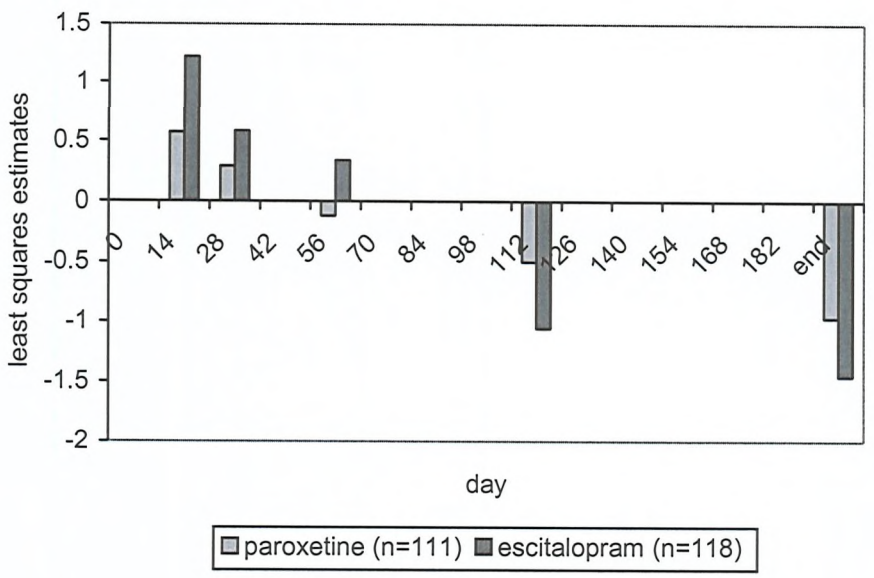


Table 6.8

Proportion of patients with sexual dysfunction according to ASEX scale

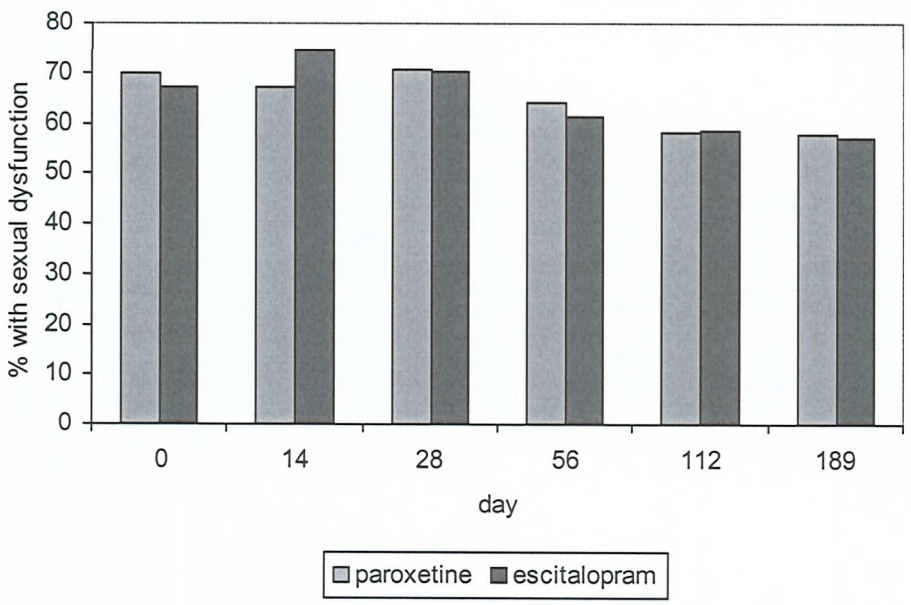
Analysis	Day	Paroxetine		Escitalopram		Estimated difference to escitalopram			
		N	%	N	%	%	95% CI lower (%)	95% CI upper (%)	p-value (Fisher)
LOCF	0	109	69.9	111	67.3	2.6	-7.6	12.8	0.632
	14	105	67.3	123	74.5	-7.2	-17.2	2.7	0.176
	28	110	70.5	116	70.3	0.2	-9.8	10.2	1.000
	56	100	64.1	101	61.2	2.9	-7.7	13.5	0.645
	112	91	58.3	97	58.8	-0.5	-11.2	10.3	1.000
	189	90	57.7	94	57.0	0.7	-10.1	11.5	0.911
OC	0	109	69.9	111	67.3	2.6	-7.6	12.8	0.632
	14	103	66.9	123	74.5	-7.7	-17.6	2.3	0.141
	28	106	70.2	111	69.4	0.8	-9.4	11.0	0.902
	56	93	62.8	92	60.1	2.7	-8.3	13.7	0.638
	112	70	53.0	85	57.8	-4.8	-16.5	6.9	0.470
	189	66	54.1	79	56.4	-2.3	-14.4	9.7	0.711

LOCF last observation carried forward

OC observed case

Figure 6.6

Proportion of patients with sexual dysfunction according to ASEX scale (FAS, LOCF)



FAS full analysis set

LOCF last observation carried forward

Table 6.9

Scores on ASEX single items during course of the study (FAS, OC) - all patients

Item	Day	Paroxetine			Escitalopram		
		N	Mean	SD	N	Mean	SD
1. Strength of sex drive	0	155	4.51	1.35	164	4.55	1.34
	14	150	4.46	1.28	160	4.68	1.21
	28	149	4.36	1.33	159	4.60	1.25
	56	144	4.11	1.42	150	4.37	1.29
	112	127	4.02	1.26	145	4.19	1.28
	189	121	4.01	1.39	136	4.17	1.35
2. Ease of sexual arousal	0	155	4.08	1.35	164	1.30	4.16
	14	150	4.10	1.34	158	4.31	1.26
	28	149	4.13	1.36	158	4.29	1.32
	56	142	3.76	1.30	151	4.21	1.31
	112	127	3.77	1.31	145	3.99	1.31
	189	120	3.66	1.36	136	3.95	1.34
3. Ease in achieving erection or lubrication	0	153	3.69	1.54	164	3.77	1.41
	14	150	3.88	1.41	161	4.05	1.33
	28	147	3.77	1.42	157	4.08	1.49
	56	141	3.62	1.35	149	3.91	1.44
	112	126	3.53	1.42	145	3.75	1.39
	189	120	3.41	1.40	137	3.76	1.40
4. Ease in reaching orgasm	0	147	3.99	1.46	155	4.08	1.30
	14	142	4.14	1.39	152	4.40	1.19
	28	139	4.23	1.32	147	4.29	1.30
	56	134	4.09	1.38	138	4.14	1.39
	112	122	3.95	1.32	139	3.99	1.37
	189	113	3.86	1.37	131	3.89	1.34
5. Satisfaction with orgasm	0	147	3.66	1.62	156	3.76	1.47
	14	142	3.99	1.55	152	4.14	1.39
	28	139	4.03	1.50	146	4.07	1.43
	56	134	4.01	1.50	138	4.00	1.45
	112	122	3.71	1.42	139	3.84	1.39
	189	113	3.66	1.53	131	3.69	1.43

Table 6.10

Recent Sexual Experience question scores - total sample (FAS, LOCF and OC)

Treatment group	Day	Last observation carried forward			Observed cases		
		N	Mean	SD	N	Mean	SD
Paroxetine	0	150	3.34	1.35	150	3.34	1.35
	14	150	3.51	1.30	150	3.50	1.30
	28	150	3.48	1.36	148	3.47	1.37
	56	150	3.44	1.34	145	3.39	1.34
	112	150	3.39	1.30	130	3.28	1.31
	189	150	3.25	1.32	121	3.13	1.32
Escitalopram	0	156	3.35	1.24	156	3.35	1.24
	14	156	3.62	1.23	159	3.62	1.23
	28	156	3.58	1.25	156	3.58	1.26
	56	156	3.43	1.32	149	3.41	1.32
	112	156	3.34	1.32	144	3.29	1.33
	189	156	3.23	1.31	138	3.17	1.30

LOCF last observation carried forward
OC observed cases
SD standard deviation

Figure 6.7

Recent Sexual Experience question scores over the course of the study (FAS, LOCF)

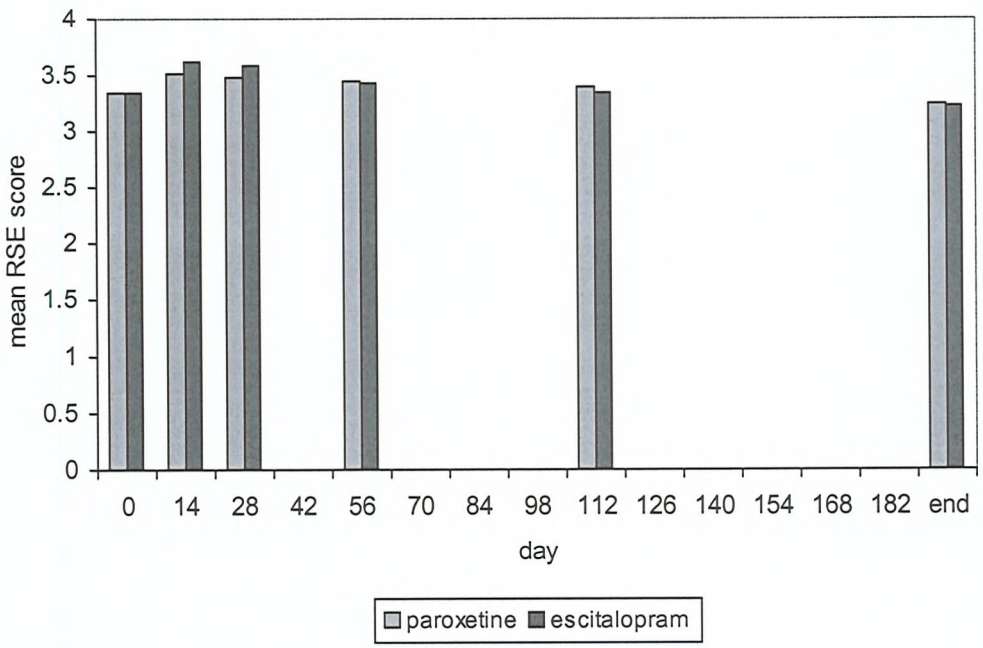


Table 6.11

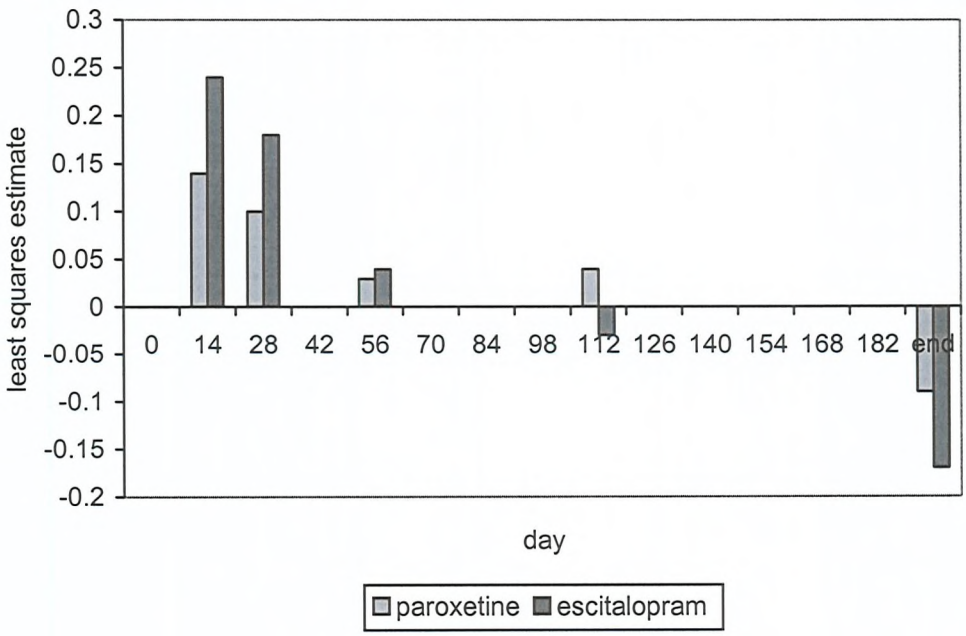
Treatment difference in adjusted mean changes in RSE score (FAS, LOCF and OC)

Analysis	Day	Paroxetine			Escitalopram			Difference to escitalopram				
		Least squares estimates			Least squares estimates							
		N	Mean	SE	N	Mean	SE	Mean	SE	95% CI lower	95% CI upper	p-value
LOCF	14	150	0.14	0.09	156	0.24	0.09	-0.09	0.11	-0.31	0.12	0.386
	28	150	0.10	0.09	156	0.18	0.09	-0.08	0.11	-0.31	0.14	0.469
	56	150	0.03	0.10	156	0.04	0.10	0.00	0.12	-0.24	0.23	0.977
	112	150	0.04	0.10	156	-0.03	0.10	0.08	0.12	-0.16	0.32	0.530
	189	150	-0.09	0.11	156	-0.17	0.11	0.08	0.13	-0.18	0.34	0.537
OC	14	148	0.14	-0.10	156	0.24	0.09	0.11	0.11	-0.31	0.12	0.378
	28	145	0.10	-0.09	151	0.20	0.10	0.12	0.12	-0.32	0.14	0.425
	56	142	0.00	-0.03	145	0.03	0.11	0.13	0.13	-0.27	0.22	0.839
	112	127	-0.09	0.02	139	-0.11	0.11	0.13	0.13	-0.24	0.28	0.879
	189	118	-0.30	0.03	132	-0.33	0.12	0.15	0.15	-0.26	0.32	0.856

LOCF last observation carried forward
OC observed case
SE standard error
CI confidence interval

Figure 6.8

Adjusted mean changes from baseline in RSE score (all patients - FAS, LOCF analysis)



Change in ASEX item 2 (sex arousal) in male and female patients

In the total sample, adjusted mean scores showed an increase over baseline values in the first eight weeks of treatment with paroxetine, and throughout the study with escitalopram. Higher values represent greater difficulty in achieving sexual arousal. Changes in the continuation phase of the study indicate a gradual resolution of problems in sexual arousal, to baseline levels with escitalopram, and beyond baseline values with paroxetine. There were no significant differences between treatments in the total sample, or gender sub-groups.

Change in ASEX item 3 (ease in achieving erection) in male patients

Adjusted mean changes in scores showed no significant differences between the treatment groups. In both the paroxetine and escitalopram groups, patients reported more difficulty in achieving and maintaining erection than at baseline, over the course of the study. There was some evidence of resolution of erectile difficulty in the continuation phase of treatment.

Change in ASEX item 3 (ease in achieving lubrication) in female patients

There were no significant differences between the treatment groups. In both groups, patients reported more difficulty in achieving vaginal moistening and lubrication, over the course of the study. There was some evidence of resolution during the continuation phase of treatment.

Change in ASEX item 4 (ease in reaching orgasm) in male and female patients

In the total sample, the adjusted mean scores showed an increase over baseline values throughout acute treatment, in both treatment groups. The score dropped below baseline value in the group receiving paroxetine at the end of the continuation phase of treatment; the endpoint and baseline values in the escitalopram group were essentially the same. There were no significant differences between groups, at any time point. In the sub-group of male patients, mean scores remained above baseline throughout the study in both groups. The sub-group of female patients showed a decline in score below baseline values at the end of the continuation phase, in both treatment groups. There were no significant differences between treatment groups in either the male or female patients.

Change in ASEX item 5 (satisfaction with orgasm) in male and female patients

In the total sample, adjusted mean scores on this item showed an increase in the first four weeks of double-blind treatment, followed by a decline in both the remainder of the acute phase, and in the continuation phase of treatment. There were no significant differences between treatment groups, in either the total sample or the gender sub-groups.

Recent sexual experience (RSE) scores - all patients

The 'Recent Sexual Experience' question (RSE) comprised a five-point scale, ranging from 'very unsatisfied' to 'very satisfied'. The question was posed at the same time as patients completed the ASEX, but presented on a separate form. There were no significant differences between treatment groups in baseline mean RSE score. In the total sample, mean RSE scores increased during the

acute phase of treatment, and declined during the continuation phase, in both the LOCF and OC analyses. Table 6.10 gives the RSE scores for the total sample, the LOCF analysis results being shown in Figure 6.7. The magnitude of the changes in mean RSE score was not great: the greatest increase being with escitalopram (0.24, day 14 in both LOCF and OC analyses), the greatest reduction -0.28 with paroxetine (OC analysis, day 189). These small changes are unlikely to be of clinical relevance.

Treatment difference in adjusted mean changes in RSE score

There were no differences between treatment groups in adjusted mean changes in RSE score, in either the acute or the continuation phase of treatment, in either the LOCF or OC analysis. Table 6.11 gives the adjusted mean values, standard errors of the mean, confidence intervals and p-values for both analyses; Figure 6.8 shows changes in the LOCF analysis. Finally, there were no significant differences between treatment groups in the sub-groups of male of female patients, in either the LOCF or OC analyses.

Sexual dysfunction as a reported adverse event

Very few patients complained of sexual problems as a treatment emergent adverse event, in either treatment group, in either acute or continuation treatment. In the APTS data set, adjusted for gender, only three patients (7.5%) treated with paroxetine, and no patients treated with escitalopram, complained of ejaculation failure.

DISCUSSION

Overall findings

This randomised, double-blind, flexible-dose, parallel-group, multi-national, multi-centre study did not reveal any significant differences in efficacy or tolerability between escitalopram or paroxetine in either the acute or continuation phase of the treatment of patients with major depression. Similar proportions of patients responded to double-blind treatment, and similar proportions showed symptomatic remission, at the end of both the acute and continuation phase of treatment. There were no significant differences between study treatments in change in sexual function as assessed by the total ASEX score, in either acute or continuation treatment, in either the overall sample of patients or in the sub-groups of male and female patients. The profile of change in individual ASEX items was essentially similar, as was the change in the patient ratings of satisfaction with recent sexual experiences.

Further data analysis may include the determination of the correlation between change in severity of depression (MADRS score) and change in sexual dysfunction (ASEX score); and an examination of whether patients who withdrew from the study differed in ASEX score from those patients who continued with double-blind treatment.

Study weaknesses

The study was designed and powered to show non-inferiority in antidepressant efficacy, as measured by change in the primary outcome measure, the MADRS. Randomised controlled trials in depressed patients need to be very large indeed to have the power to reveal significant differences between two active treatments, and such trials are usually not feasible in practice (Baldwin *et al*, 2003). The change in ASEX score was only a secondary outcome measure in this study, and although it was hoped that the study size (over 300 patients) would be sufficient to reveal significant differences between treatments, the sample size was calculated on the basis of non-inferiority in efficacy rather than superiority in tolerability.

Because of the need to recruit large numbers of patients, the investigation was a fairly classical multi-national, multi-centre study, with varying numbers of patients being recruited from 36 different primary or secondary care centres in six different countries, with differing health care systems. Whilst every effort was made to ensure satisfactory inter-reliability in diagnosis and rating, and rigid adherence to the study protocol, it is known that having many centres in a randomised controlled trial reduces the capacity of the study to detect true differences in treatment efficacy or tolerability (Baldwin *et al*, 2003).

Prevalence of sexual dysfunction at baseline

There was a high prevalence of sexual dysfunction at the time of baseline assessment. The mean ASEX score at baseline was 19.88 for paroxetine, and 20.28 for escitalopram, in both the LOCF and OC analyses. These mean scores are both higher than the cut-off point of 19 that is said to represent the point at which significant sexual dysfunction is thought to be present, indicating a substantial level of dysfunction even before the start of double-blind treatment. It is unclear whether this high baseline prevalence of sexual dysfunction is due to the effects of pre-morbid sexual problems, depression, comorbid physical illness or concomitant prescribed medication. However it is unlikely to be due to the effects of antidepressant drugs, as the washout period before starting double-blind treatment was sufficient to ensure adequate elimination of previously prescribed treatments.

Undoubtedly, the high prevalence of sexual dysfunction at baseline would make it difficult to reveal significant differences between the study treatments in the incidence of treatment- emergent sexual dysfunction, either as new cases of dysfunction or as worsening of existing sexual dysfunction. Furthermore, the decline in patient number over the course of the investigation (from 323 to 234 patients), further reduces the ability to differentiate between treatments, this being particularly so during the continuation phase of the study.

Change in ASEX score during the course of the study

There were few noticeable changes in mean total ASEX score over the course of the study, in either the acute or continuation phases of treatment, in either treatment group, in either the total study

sample or the sub-groups of male and female patients. The greatest increases over baseline in mean total ASEX score were 0.67 points with paroxetine (OC analysis) and 1.14 points with escitalopram (LOCF and OC analyses). The greatest reductions in mean total ASEX score were 1.20 points with paroxetine (OC analysis) and 1.14 points with escitalopram (OC analysis).

The absence of major change in the mean total ASEX scores might be thought to be due to poor sensitivity of the outcome measure, although previous studies had indicated that the ASEX has adequate sensitivity to change (Gelenberg *et al*, 2000; Masand *et al*, 2001). Furthermore, there was marked inter-individual change in ASEX score, with maximum increases in score of 22 points with paroxetine (OC analysis), and 18 points with escitalopram (LOCF and OC analyses). The greatest individual reductions in ASEX score were 18 points with paroxetine (LOCF and OC analyses) and 21 points with escitalopram (LOCF and OC analyses).

In general, mean total ASEX scores increased slightly above baseline values during the acute phase of treatment, but declined slightly below baseline values towards the end of the continuation phase of treatment. Mean total MADRS scores declined throughout the study, so the early increase in ASEX score is unlikely to be due to worsening depression. The slight decline in mean total ASEX score after day 56 might reflect some resolution of sexual problems, but it should be remembered that only those patients who had responded to and tolerated acute treatment were entered into the continuation phase of the study. The slight decline in ASEX score might result from the withdrawal from the study of patients who had more marked dysfunction during acute treatment. The study findings can neither confirm nor refute the suggestion that treatment-associated sexual dysfunction is more important to patients during the continuation phase of antidepressant treatment (Hirschfeld, 1999).

Treatment-emergent sexual adverse events

There was a very low incidence of patients reporting of sexual dysfunction as a treatment-emergent adverse event, even though participating patients were aware that sexual dysfunction was one of the concerns of the study. The majority of patients had sexual dysfunction at all study time-points, but the only complaint relating to sexual function that was reported by more than 5% of patients in either treatment limb was ejaculatory failure, reported by three (7.5) patients treated with paroxetine. This study finding emphasises the common finding that there is significant under-reporting of sexual difficulties by patients during randomised controlled trials with antidepressant drugs (Baldwin, 2001). The observation that very few patients spontaneously reported sexual adverse events, whilst most of the study sample fulfilled ASEX criteria for sexual dysfunction is intriguing. Possible explanations include the suppositions that patients did not regard any sexual problems as related to treatment, and did therefore not report them; or that patients knew that they would be asked to complete the ASEX scale, and used that as the mechanism for highlighting any problems; or that the ASEX does not take into account the degree to which patients might tolerate a symptom before reporting it as an adverse event.

Absence of significant differences between escitalopram and paroxetine

There were no significant differences between study treatments in the effects on sexual function, in either acute or continuation treatment, in either the total sample or in the subgroups of male and female patients. This study finding differs from the results of previous large-scale (more than 1000 patients) investigations, showing that the incidence rates of sexual dysfunction vary during the treatment of patients with differing SSRIs (Montejo *et al* 2001; Clayton *et al*, 2002). Escitalopram is the most selective SSRI available for use in clinical practice, and paroxetine is the one with the most anticholinergic effects. However, the absence of any significant differences between the study treatments in the effects on sexual function suggests that these differences in pharmacological properties are relatively unimportant, in determining their propensity to cause sexual dysfunction.

CHAPTER 7 : TREATMENT STUDY IN SSRI TREATMENT-EMERGENT SEXUAL DYSFUNCTION

AIM OF THE INVESTIGATION

The findings described in preceding chapters show that disturbances of sexual function and satisfaction are common among people treated with antidepressant drugs, and that antidepressants differ somewhat in their effects on sexual function, as measured by changes in score on item 14 of the HAM-D and on specific sexual function rating scales.

Given that depression is typically a recurring episodic illness, and that antidepressants have consistently been found effective in preventing early relapse and later recurrence of illness, current treatment guidelines recommend long term treatment with antidepressants, in patients at high risk of recurrence (Anderson *et al*, 2000). Antidepressant-treated patients may therefore be exposed to the risk of long term impairments in sexual function and satisfaction.

Since adequate sexual expression is considered an essential part of many human relationships, enhancing quality of life and providing a sense of physical, psychological and social well-being, it follows that efforts should be made to evaluate potential approaches to the management of sexual problems in patients taking antidepressants. The literature review in chapter one has shown that many approaches have been advocated (including dosage reduction, drug holidays, adjuvant treatments, switching to other antidepressants), but there is at present no consensus on which treatment approach is preferable in which patients.

The aim of this study was to evaluate the efficacy and tolerability of a potential new pharmacological approach to the management of previously depressed patients troubled by persistent sexual dysfunction associated with treatment with SSRI antidepressants. At first the patient sample was limited to those with sexual dysfunction associated with fluoxetine treatment, but the subsequent acquisition of further pharmacokinetic data allowed a protocol amendment, with the inclusion of patients with dysfunction associated with paroxetine.

As described in the first chapter of this thesis, a placebo-controlled augmentation study with the 5-HT_{1A} agonist buspirone found it to be helpful in the reduction of sexual dysfunction associated with SSRI treatment of depressed patients (Landen *et al*, 1998; 1999). More recently, a randomised placebo-controlled trial with the 5-HT_{1A} agonist gepirone found it to be associated with improved sexual function in patients with major depression (Davidson and Gilbertini, 2002). The investigational compound studied in this chapter (CEB-1555) has been shown to enhance sexual behaviour in pre-clinical models, and for this reason the compound was chosen, as a potential treatment for reducing sexual dysfunction associated with SSRI treatment.

Efficacy was assessed through evaluation of changes in score on the ASEX scale and on item 14 of the HAM-D during double-blind treatment with placebo or CEB-1555 (an agonist at $5HT_{1A}$ and $5HT_{1D}$ receptors). Tolerability was assessed by the profile of adverse events reported to an independent safety review committee. Other aims were to evaluate the effects of the compound on depressive symptoms. This chapter describes the design of the investigation; gives data on the feasibility of conducting such a study was feasible within United Kingdom primary care research settings; and reports the changes on the ASEX scale during placebo treatment. Other study findings will be reported separately.

The subjects included within this investigation took part in a phase IIa multi-centre double-blind placebo-controlled parallel-group fixed-dose randomised controlled trial, comparing CEB-1555 with placebo, in the treatment of patients with SSRI treatment-emergent sexual dysfunction. The overall treatment study was supported by a pharmaceutical company.

As overall principal investigator for the study, my roles include -

- demonstrating the need for the study
- developing the overall study protocol in collaboration with the pharmaceutical company
- corresponding with the United Kingdom Medicines Control Agency
- submitting the protocol to a United Kingdom Multicentre Research Ethics Committee
- producing the rating scale training videos
- training investigators in use of the assessment interview and rating scales
- communicating with study investigators via the company through a study newsletter
- analysing the data in association with employees of the pharmaceutical company
- presenting the results to the study investigators
- preparing the final study report
- preparing the results for publication

METHOD

As research into treatment approaches for sexual dysfunction associated with SSRI treatment is a new area, the study methodology is described in more detail than in previous chapters.

Study objectives

The primary objective of the study was to compare the effects of CEB-1555 and placebo on sexual dysfunction, as measured by the proportion of patients with a change in ASEX scores from a value indicating sexual dysfunction to one indicating no sexual dysfunction, from Day 15 (beginning of treatment) to Day 43 (end of treatment).

The secondary objectives were

- to compare the change in total ASEX score from Day 15 to Day 43
- to compare the proportion of patients with a 50% reduction of the total ASEX score
- to compare the change in individual item scores on the ASEX
- to compare the proportion of responding patients as assessed by the CGI-I
- to evaluate the safety and tolerability of repeated oral dosing with CEB-1555.

Study design

The overall study was a phase IIa multi-centre double-blind placebo-controlled parallel-group fixed-dose randomised controlled trial of the efficacy, safety and tolerability of CEB-1555 in the short-term treatment of previously depressed patients with SSRI treatment-emergent sexual dysfunction. The participating patients underwent a two-week screening period, followed by four weeks of double-blind treatment, and a subsequent two-week follow-up. Assessment visits occurred at day 1 (screen) and day 8 (run-in), then at weekly intervals from day 15 to day 43, with a post-treatment visit at day 50 and follow-up at day 57.

Patients were required to be sexually active. Sexual activity was defined as any sexual activity, either with a partner or through masturbation, which had the potential to lead to orgasm. The diagnosis of previous depression was confirmed by use of the MINI, described in earlier chapters. As depression affects sexual function, patients with significant current depressive symptoms (a score on the 17-item HAM-D greater than 12) were excluded.

Approximately 240 patients with SSRI treatment-emergent sexual dysfunction were required. To achieve this, it was anticipated that approximately 270 patients would need to be randomised into the study. To ensure that there were sufficient numbers of men and women to have enough power to detect drug-placebo differences, an overall maximum ratio of 2:1 to either gender was imposed.

Inclusion criteria

- male or female patients aged 18 to 65 years inclusive
- sexual dysfunction categorised according to DSM-IV as rated by the ASEX. Sexual dysfunction was defined as either a total ASEX score of 19 or more, or any one item with an individual score of 5 or more, or any 3 items with individual scores of 4 or more. ASEX scores of sexual dysfunction had to be present at screening and Day 8 and Day 15.
- previous diagnosis of depression, on the basis of clinical impression, confirmed by completion of the MINI
- a score on the 21-item version of the HAM-D of no more than 12 at screening, Day 8 and Day 15
- receiving a stable dose of fluoxetine or paroxetine for a minimum of 8 weeks, prior to screening. For the 4 weeks prior to screening, the prescribed SSRI dose had to be the same

- expected to remain on current fluoxetine or paroxetine dose for next 3 months
- sexual dysfunction onset since starting SSRI treatment, defined as either sexual dysfunction new with treatment, or sexual dysfunction worsened with treatment
- satisfactory sexual relationship prior to onset of depression
- willing to discuss sexual functioning with study personnel and complete the ASEX rating scale
- willing to be involved in sexual activity (in a stable relationship or through masturbation) that had the potential to lead to orgasm on at least one occasion each week for the duration of the study. Sexual activity should be restricted to early evening/ late evening
- female patients of childbearing potential had to have a negative urinary pregnancy test at screening. Females considered not to be of child-bearing potential were those who were at least 2 years post-menopausal and had demonstrated appropriate hormonal status or who had been surgically sterilised
- males and females of child-bearing potential must be using a reliable form of contraception (oral contraceptive pill, intrauterine contraceptive device (IUCD), depot progesterone or implant, barrier methods with spermicide) throughout the study without change
- able and willing to sign informed consent and to comply with the requirements of the entire study, including completion of the diary cards.

Exclusion criteria

- significant genital abnormalities or non-substance induced sexual arousal disorders as assessed by DSM-IV criteria for sexual dysfunction disorders
- any other condition or use of other drugs associated with sexual dysfunction
- use of drugs or devices for the treatment of sexual dysfunction e.g., sildenafil, herbal preparations, or alprostadil
- patients considered to be suicidal, as assessed by the investigator
- patients with a history of alcohol or substance abuse within the previous year
- female patients who were pregnant, or the female partners of male patients who were intending to try to become pregnant within 3 months after the last dose of study medication
- female patients who were breast-feeding
- patients who had any change in their contraceptive method (if applicable) in the 3 months prior to screening, or who anticipated any changes in the next 3 months
- a clinically significant medical condition or a history of such a condition that the Investigator considered should exclude the subject from the study
- patients with multiple drug allergies or an allergy to any of the components of VML 670 or its matching placebo
- significant acute infection, in the opinion of the investigator, within 4 weeks of screening
- any illness or drug treatment that might affect the absorption, metabolism or elimination of study medication

- treatment with any investigational drug within 4 months prior to screening
- significant abnormalities on laboratory screening tests, particularly liver and renal function tests
- patients whose general practitioner raised any medical or social reasons for not participating in the study
- use of non-permitted medications for 1 month prior to screening or expected use in subsequent 3 months
- any clinically significant abnormal physical findings on examination; any abnormal 12-lead ECGs at screening, Day 8 and Day 15; or any clinically significant abnormal laboratory safety tests at screening and Day 8.

Randomisation and blinding procedures

At screening (Day 1), patients who fulfilled all the entry criteria were assigned a patient number. Patients who returned on Day 8 and Day 15 but did not meet the inclusion/exclusion criteria were classed as 'screening failures'. On Day 15, patients who fulfilled all the entry criteria were assigned the next available randomisation number, according to gender. Numbers were used in sequence within gender group and no number was missed or substituted. The randomisation number determined assignment to treatment via a computer generated schedule, stratified by gender. Unique randomisation numbers were pre-printed on the study medication packs.

Schedule of assessments

Table 7.1 gives the study assessment schedule. All patient visits had a time window of plus or minus one day. Patients who met the inclusion/exclusion criteria were asked to complete daily diary cards between clinic visits from Day 1 (after the screening visit) to Day 57 (follow-up visit). The template for the diary card is shown in Appendix 7.1. Patients were trained how to complete the diary card, which recorded the date and time that study medication was taken (Day 15 to Day 42), any sexual activity, time of food intake around dosing times, concomitant medications including fluoxetine or paroxetine, and any adverse events.

Double-blind treatment

During the treatment phase (Day 15 to 42) patients received a single 300 μg dose of double-blind medication daily between 5.00 p.m. and 7.00 p.m. for 4 weeks, without food from 1 hour before to 1 hour after dosing. Only water could be consumed freely during this time. This dose was chosen following the single, ascending dose safety and tolerability study of CEB-1555 where doses of 100 μg to 500 μg were administered, described in the first chapter of the thesis.

Table 7.1 Schedule of study assessments

Parameter	Screen	Run-in Phase	Treatment Phase					Post Treatment Phase	Follow up
	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36	Day 43	Day 50	Day 57
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
Informed Consent	✓								
Medication history	✓								
Medical/surgical history	✓								
Vital signs	✓	✓	✓*	✓	✓	✓	✓	✓	✓
Physical examination, height, weight, oral temperature	✓								✓***
12-Lead ECG	✓		✓*	✓	✓		✓		✓
Laboratory safety (haematology, biochemistry, urinalysis)	✓	✓		✓	✓		✓		✓
PSA (males only)	✓	✓					✓		✓
Alcohol/drugs test	✓								
Pregnancy test	✓	✓	✓*+	✓	✓	✓	✓	✓	✓
Inclusion/exclusion criteria review	✓	✓	✓*						
Mini-Mental State assessment	✓								
$HAMD_{21}$	✓	✓	✓*	✓	✓	✓	✓	✓	✓
ASEX	✓	✓	✓*	✓	✓	✓	✓	✓	✓
CGI			✓*				✓		
Randomisation number assignment			✓*						
VML 670/placebo dosing regimen			✓	✓	✓	✓**			
AE review		✓	✓*	✓	✓	✓	✓	✓	✓
Concomitant medication review	✓	✓	✓*	✓	✓	✓	✓	✓	✓
Issue of weekly diary card	✓	✓	✓	✓	✓	✓	✓	✓	
Patient diary card completion/review	✓	✓	✓*	✓	✓	✓	✓	✓	✓
Weekly medication dispensed			✓	✓	✓	✓			
Medication compliance review				✓	✓	✓	✓		

✓* prior to dosing; ** last dose received Day 42; *** excluding measurement of height ; + Pregnancy test on Day 15 performed at study centres

Patient compliance with the requirements of the protocol was checked at each visit. During double-blind treatment, the returned study medication packs and diary cards were checked for compliance in the presence of the patient, and any discrepancies were discussed. Compliance was measured in terms of the number of capsules taken each week, the minimum requirement being 80% (i.e. 23 out of 28) of the total number of capsules during double-blind treatment.

Assessments of efficacy

Efficacy in relieving sexual dysfunction was evaluated by completion of the ASEX scale at all study assessments. The CGI-S was completed at day 15 and 43, and the CGI-I at day 43. Depressive symptoms were rated by the first 17 items of the 21-item version of the HAM-D at all study assessments. Patients were considered to have responded to double-blind treatment if the ASEX score dropped from a value indicating sexual dysfunction to one indicating no sexual dysfunction.

Assessments of tolerability

The investigator conducted a physical examination at the screening and follow up visits. Vital signs (pulse rate, blood pressure) were measured at each visit. Laboratory analysis samples were collected on study Day 1, 8, 22, 29, 43 and 57, for routine haematology and biochemistry testing. Twelve-lead ECGs were recorded on Days 1, 15, 22, 29, 43 and 57; they were evaluated centrally, each report being reviewed for clinically significant findings by an independent cardiologist. Subjects with any abnormalities found at screening that were considered clinically significant were not enrolled into the study.

Adverse events were reviewed at weekly intervals from study Day 8. Patients were asked to record any adverse events that occurred in the relevant diary card. The study investigators also questioned each patient about the occurrence of any other adverse events that might have occurred. All adverse events were then transcribed into the patient case record folder.

In addition to these precautions, an Independent Safety Monitoring Committee was specifically convened for the purposes of reviewing safety data and providing recommendations about continuing, modifying or stopping the study. The Committee consisted of one facilitator/chairperson, one statistician, and two medically qualified personnel (one psychiatrist and one clinical pharmacologist) with expertise in conducting clinical trials.

Concomitant and prohibited medication

All medication taken by patients in the four weeks prior to screening and during the study was recorded, giving details of the dosage, duration and reason for administration. In addition, patients were asked to record any medication taken during the study in the relevant diary, which was checked by the investigator each week. For one month prior to screening and up to the post-study follow-up visit, patients were prohibited from taking medication that might increase the risk to the individual, or decrease the chance of obtaining satisfactory data. This included other

antidepressants, medication used to treat sexual dysfunction, and significant inducers or inhibitors of drug absorption, metabolism or elimination. Widely used drugs that can impair sexual function (e.g. β-adrenoceptor antagonists and thiazide diuretics) could be continued during the study, provided the treatment had been unchanged for at least 3 months prior to screening, and that starting treatment was clearly not associated with the onset or exacerbation of sexual dysfunction.

STATISTICAL METHODS

Sample size estimation

It was calculated that 120 patients per treatment group with baseline and end of treatment ASEX scores would be needed to detect a difference between placebo and CEB-1555 of 20% in the percentage of responders (defined as a reduction in ASEX score from a score of sexual dysfunction to a score of no sexual dysfunction), with 90% power, at the 2-sided 5% significance level. The placebo response rate was anticipated to be 20%. 'No sexual dysfunction' is defined as a total ASEX score of less than 19, and no item with an individual score of more than 4, and fewer than three items with individual scores of more than 3. It was anticipated that approximately 270 patients would need to be randomised to provide 240 evaluable patients.

Criteria for evaluation of efficacy

The primary parameter was the proportion of patients with a change in ASEX score from a score of sexual dysfunction at Day 15 to a score of no sexual dysfunction at Day 43. The secondary parameters were the change in ASEX total score at assessments between Day 15 and Day 43; the proportion of patients with a reduction of at least 50% in ASEX total score from Day 15 to Day 43; the change in individual ASEX item scores from Day 15 to Day 43; and as a supporting measure, the proportion of patients who were "very much" or "much improved" on the CGI-I scale at Day 43.

Criteria for evaluation of safety and tolerability

The safety and tolerability were assessed by review of adverse events, HAM-D total scores, the findings on physical examination (including weight and oral temperature), vital signs, 12-lead ECGs, and haematology, biochemistry and urinalysis data.

Population data sets

The *safety population* included all randomised patients who took at least one dose of study medication, and was used for all safety analyses. The *intention to treat population* (ITT) included all randomised patients who took at least one dose of study medication and who provided at least one ASEX rating scale after randomisation, and was used for all efficacy analyses.

Two ITT datasets were defined for the primary analysis. The first was the *last observation carried forward* (ITT LOCF) set, in which missing Day 43 data were replaced by the last non-missing data (from Day 36, Day 29 or Day 22). Missing Day 15 data are replaced by Day 8 data for the ASEX

rating scale in the event of menstrual period. The second was the *observed data* (ITT OC) set, in which data were analysed as recorded.

Descriptive analyses

All summaries of efficacy parameters were presented by treatment group, in the overall sample and by gender. The ASEX scores (individual and total scores) are listed and descriptive statistics of absolute values and change from baseline summaries are presented by visit. The proportion of patients showing a reduction of at least 50% in ASEX total score, and the CGI-I data, are summarised by visit.

Treatment-emergent adverse events were summarised by treatment group, system organ class and preferred term. The findings of physical examination (including weight and oral temperature), 12-lead ECG results, vital signs, urinalysis data, haematology and biochemistry data, and concomitant medications are listed and summarised by treatment group and visit. Where relevant, descriptive statistics of absolute values and change from baseline (last pre-dose values) summaries were presented by treatment group and visit.

The total scores on the first 17 items of the HAM-D were listed and descriptive statistics of absolute values and change from baseline (last pre-dose values) summaries were presented by treatment group and visit, overall and by gender. The diary data were listed and summarised to evaluate study compliance, but no formal statistical analysis was performed.

Comparison between treatment groups - primary analysis

The primary analysis was based on the ITT-LOCF dataset, with support from analysis of the ITT-OC dataset. The proportion of patients showing a reduction in ASEX score from a score of sexual dysfunction at Day 15 to no sexual dysfunction at Day 43 was calculated, treatment groups being compared using the Cochran-Mantel-Haenszel test, taking account of gender. Summaries by centre were reviewed to see detect any treatment-by-centre effects.

Comparison between treatment groups - secondary analyses

All summaries and analyses of secondary efficacy parameters were based on the ITT-LOCF dataset. The change in ASEX total score between Day 15 and Day 43 was calculated, and change in the treatment groups compared using the t-test. If assumptions of normality are not met, the treatment group comparison was made using the Wilcoxon 2-sample test. A similar approach was used to compare the change in individual ASEX item scores.

The proportion of patients showing a reduction of at least 50% in ASEX total score from Day 15 to Day 43 was calculated, and the treatment groups compared using the chi-squared test. A similar approach was used to examine the proportion of patients with a score of "very much" or "much improved" at Day 43 on the CGI-I scale.

ETHICAL CONSIDERATIONS

The overall treatment study was conducted in accordance with the Declaration of Helsinki and its subsequent revisions, the Principles for the Clinical Evaluation of Drugs and Guidelines for Evaluation of Drugs for Use in Man, and the Note for guidance on Good Clinical Practice. The study was approved by a multi-centre research ethics committee, and by local research ethics committees when needed.

No ethical problems were foreseen for the participation of patients in the study. There is at present no generally accepted treatment for sexual dysfunction associated with SSRI antidepressants. The dosage of CEB-1555 was chosen following the results of dose-finding and safety and tolerability studies in healthy volunteers. Participation could only occur after the provision of written informed consent; patients attended appointments frequently and regularly; and assessments of efficacy and tolerability were comprehensive and relevant to clinical practice and patient concerns. An Independent Safety Committee monitored the reports of adverse events during the study.

RESULTS

General practitioner recruitment

Patient recruitment occurred between May 2002 and May 2003. A total of 3134 primary care patients, currently prescribed either fluoxetine or paroxetine, and with a record of possible sexual dysfunction, were considered for potential participation in the study. Following approach by their doctors, a total of 2198 patients were potentially interested in participating in research in the study area. The stated reasons for not taking part in the study included absence of sexual dysfunction (354 patients), having stopped SSRI treatment (461 patients) current depression (62 patients) and use of restricted concomitant medication (57 patients). The number of patients screened at study centres ranged from 1 to 46.

Patient disposition

A total of 289 patients were randomized to receive double-blind medication, 149 being allocated to receive CEB-1555 and 140 to receive placebo. One patient did not take double-blind medication. The intention-to-treat (ITT) population includes 282 patients (147 treated with CEB-1555, 135 with placebo), the per protocol (PP) population comprises 199 patients. A total of 43 patients were withdrawn during double-blind treatment (22 with CEB-1555, 21 with placebo), the primary reason for withdrawal being adverse events (10 with CEB-1555, 4 with placebo). Table 7.2 gives details of patient disposition during the study.

Patient demographics in the safety population

The safety population comprised 288 patients (84 men, 204 women; mean age 44.2 years, age range 22-67 years). Nearly all patients were of white Caucasian origin. There were 149 patients (42 men, 107 women) allocated to CEB-1555, and 139 (42 men, 97 women) to placebo. Most patients (221, 76.7%) were undergoing current treatment with fluoxetine. The mean total score on the first 17 items of the HAM-D was 6.1. There were no significant differences between treatment groups in demographic characteristics. Table 7.3 gives demographic characteristics in the two treatment groups, in the safety population; Table 7.4 gives these characteristics when the population is sub-divided, according to prescribed antidepressant.

Categories of sexual dysfunction in the safety population

There were no significant differences between treatment groups in the proportions with impairments in sexual desire, arousal and orgasm, described according to DSM-IV criteria. Few patients were described as having dysfunction with sexual pain. As required by the study protocol, all patients had an acquired sexual dysfunction. Most patients in the safety population (273, 94.8%) fulfilled criteria for the generalised form of sexual dysfunction. In only a minority of patients (5, 1.7%) was sexual dysfunction ascribed purely to psychological factors; most patients were described as having sexual dysfunction due to combined psychological and physical factors (113, 39.2%). In most patients (173, 60.1%), sexual dysfunction was recorded as being 'substance-induced' (in this case, directly related to antidepressant treatment). There were no significant differences between treatment groups, in the proportion of patients with differing forms of sexual dysfunction. Table 7.5 gives details of the DSM-IV specifiers for sexual dysfunction; Table 7.6 provides this information, sub-divided according to prescribed antidepressant.

ASEX scores in the safety population

One patient did not return a completed ASEX scale at the start of the study. The mean ASEX scores at baseline did not differ significantly between treatment groups (compound, 21.8; placebo, 22.2); either when the genders were combined, or when sub-grouped according to gender. Most patients described impairment in all items of the ASEX scale, there being no significant difference between treatment groups in individual item scores, either when the genders could be combined (ASEX items 1, 2, 4 and 5), or grouped according to gender (all items). Table 7.7 gives the ASEX scores at baseline in the safety population, by gender. Table 7.8 gives the ASEX scores at baseline in the safety population, by antidepressant.

Table 7.2

Summary of patient disposition

	CEB-1555 N (%)	Placebo N (%)	Total N (%)
All randomised patients	149	140	289
Safety population	149 (100.0)	139 (99.3)	288 (99.7)
Intention to treat population	147 (98.7)	135 (96.4)	282 (97.6)
Per protocol population	103 (69.1)	96 (68.6)	199 (68.9)
Withdrawn patients	22 (14.8)	21 (15.0)	43 (14.9)

Table 7.3

Summary of patient demographics in safety population

	CEB-1555	Placebo	Total
Number of patients	149	139	288
Gender			
Male N (%)	42 (28.2)	42 (30.2)	84 (29.2)
Female N (%)	107 (71.8)	97 (69.8)	204 (70.8)
Age			
Mean age (years)	43.5	44.9	44.2
Median age (years)	43	45	Missing
SD (years)	9.8	10.2	Missing
Minimum age (years)	23	22	22
Maximum age (years)	65	67	67
Ethnicity			
Caucasian N (%)	147 (98.7)	136 (97.8)	283 (98.3)
Black N (%)	2 (1.3)	1 (0.7)	3 (1.0)
Other N (%)	0 (0.0)	2 (1.4)	2 (0.7)
HAM-D score			
Mean	6.1	6.2	6.1
SD	2.93	2.88	Missing

SD standard deviation

HAM-D total score on first 17 items of HAM-D

Table 7.4

Demographic characteristics, according to prescribed antidepressant (safety population)

	CEB-1555		Placebo	
	Fluoxetine	**Paroxetine**	**Fluoxetine**	**Paroxetine**
Number of patients	115	34	106	33
Gender				
Male, N (%)	31 (27.0)	11 (32.4)	34 (32.1)	8 (24.2)
Female, N (%)	84 (73.0)	23 (67.6)	72 (67.9)	25 (75.8)
Age				
Mean (yrs)	43.5	43.4	43.8	48.4
Standard deviation (yrs)	9.9	9.7	10.5	8.5
Age range (yrs)	23-65	26-62	22-67	29-63

Table 7.5

DSM-IV criteria for sexual dysfunction at screening, by gender (safety population)

	CEB-1555			Placebo		
	Male	**Female**	**Total**	**Male**	**Female**	**Total**
Number of patients	42	107	149	42	97	139
Specifiers *						
With impaired desire, N (%)	37 (88.1)	103 (96.3)	140 (94.0)	35 (83.3)	93 (95.9)	128 (92.1)
With impaired arousal, N (%)	37 (88.1)	87 (81.3)	124 (83.3)	34 (81.0)	84 (86.6)	118 (84.9)
With impaired orgasm, N (%)	31 (73.8)	79 (73.8)	110 (73.8)	35 (83.3)	82 (84.5)	117 (84.2)
With sexual pain, N (%)	0	2 (1.9)	2 (1.3)	0	3 (3.1)	3 (2.2)
Sub-type of sexual dysfunction *						
Lifelong, N (%)	0	0	0	0	0	0
Acquired, N (%)	42 (100.0)	107 (100.0)	149 (100.0)	42 (100.0)	97 (100.0)	139 (100.0)
Generalized, N (%)	39 (92.9)	100 (93.5)	139 (93.3)	41 (97.6)	93 (95.9)	134 (96.4)
Situational, N (%)	2 (4.8)	6 (5.6))	8 (5.4)	1 (2.4)	2 (2.1)	3 (2.2)
Due to psychological factors, N (%)	3 (7.1)	1 (0.9)	4 (2.7)	1 (2.4)	0	1 (0.7)
Due to combined factors, N (%)	17 (40.5)	41(38.3)	58 (38.9)	16 (38.1)	39 (40.2)	55 (39.6)
Substance induced, N (%)	25 (59.5)	64(59.8)	89 (59.7)	26 (61.9)	58 (59.8)	84 (60.4)

* categories not mutually exclusive

Table 7.6

DSM-IV criteria for sexual dysfunction at screening, by prescribed antidepressant (safety population)

	CEB-1555		Placebo	
	Fluoxetine	**Paroxetine**	**Fluoxetine**	**Paroxetine**
Number of patients	115	34	106	33
Specifiers *				
With impaired desire, N (%)	110(95.7)	30 (88.2)	96 (90.6)	32 (97.0)
With impaired arousal, N (%)	96 (83.5)	28 (82.4)	92 (86.8)	26 (78.8)
With impaired orgasm, N (%)	86 (74.8)	24 (70.6)	88 (83.0)	29 (87.9)
With sexual pain, N (%)	1 (0.9)	1 (2.9)	2 (1.9)	1 (3.0)
Sub-type of sexual dysfunction *				
Lifelong, N (%)	0	0	0	0
Acquired, N (%)	115 (100.0)	34 (100.0)	106 (100.0)	33 (100.0)
Generalized, N (%)	105 (91.3)	34 (100.0)	101 (95.3)	33 (100.0)
Situational, N (%)	8 (7.0)	0	3 (2.8)	0
Due to psychological factors, N (%)	4 (3.5)	0	1 (0.9)	0
Due to combined factors, N (%)	38 (33.0)	20 (58.8)	41 (38.7)	14 (42.4)
Substance induced, N (%)	75 (65.2)	14 (41.2)	65 (61.3)	19 (57.6)

* categories not mutually exclusive

Primary outcome measures

The primary objective of the study was to compare the effects of CEB-1555 and placebo on sexual dysfunction, as measured by the proportion of patients with a change in ASEX scores from a value indicating sexual dysfunction to one indicating no sexual dysfunction, from Day 15 (beginning of treatment) to Day 43 (end of treatment). In the ITT, LOCF analysis, proportionately more patients became free of sexual dysfunction with CEB-1555 than with placebo (32.7% and 26.7%, respectively), but this difference was not significant. Similar findings were seen in the per protocol population (34.0% with CEB-1555, 30.2% with placebo). Table 7.9 gives the proportions of patients with and without sexual dysfunction at baseline and at the end of double-blind treatment, in both treatment groups, in the ITT population.

Secondary outcome measures

Change in ASEX score

In the ITT population, mean total ASEX scores declined only slightly during double-blind treatment in either group, both in the overall patient sample and in the gender sub-groups. Figure 7.1 shows the decline in mean score over time. With CEB-1555, the mean total ASEX score declined from 22.0 at baseline to 19.3 at the end of the double-blind treatment phase; with placebo, scores declined from 22.1 to 19.6 (LOCF analysis). Figure 7.2 shows there was a similar decline in mean total ASEX score in the sub-groups of male and female patients. Table 7.10 gives mean total ASEX scores at all assessments in the overall sample and in the gender sub-groups.

The decline in mean total ASEX score was numerically greater in patients receiving fluoxetine than in those receiving paroxetine, in both treatment groups (LOCF analysis). In the sub-group of patients receiving fluoxetine, mean total ASEX scores declined by 3.2 with CEB-1555, and by 2.8 with placebo. In patients receiving paroxetine, the reduction in score was only 0.9 with CEB-1555, and 1.4 with placebo. Table 7.11 gives mean total ASEX scores at all assessments in the overall sample and in the sub-groups of patients receiving fluoxetine or paroxetine. Figure 7.3 shows the decline in mean total ASEX score, by prescribed antidepressant.

Proportion of patients with a reduction of 50% or more in ASEX score

Very few patients showed a substantial reduction in total ASEX score during double-blind treatment. In the ITT LOCF population, the proportion of patients with a 50% or more reduction in ASEX score was 7.2% with CEB-1555, and 4.7% with placebo. Numerically more female patients than male patients achieved this criterion, in both treatment groups. No patient receiving paroxetine met this criterion, in either treatment group; in those receiving fluoxetine, 9.3% met the criterion with CEB-1555, and 6.1% with placebo. Tables 7.12 and 7.13 give the proportions of patients according to gender and antidepressant, respectively.

Table 7.7 ASEX scores at screening, by gender (safety population)

	CEB-1555			Placebo		
	Male	**Female**	**Total**	**Male**	**Female**	**Total**
Number of patients	42	107	149	42	97	139
ASEX scale completed	42	107	149	42	96	138
ASEX total score						
Mean	20.70	22.30	21.80	21.20	22.70	22.20
SD	3.43	3.30	3.40	3.25	3.11	3.22
Minimum	14	11	11	15	16	15
Maximum	30	30	30	30	29	30
Mean ASEX item scores						
1. how strong is your sex drive?	4.59	4.97	4.88	4.64	5.10	4.96
2. how easily are you sexually aroused?	4.21	4.56	4.45	4.28	4.76	4.54
3. can you easily get and keep an erection?	4.19	N/A	N/A	4.00	N/A	N/A
3. how easily does your vagina become moist or wet?	N/A	3.93	N/A	N/A	3.94	N/A
4. how easily can you reach an orgasm?	4.17	4.72	4.56	4.21	4.73	4.57
5. are your orgasms satisfying?	3.50	4.18	3.99	4.05	4.29	4.22

Table 7.8 ASEX scores at screening, by prescribed antidepressant (safety population)

	CEB-1555			Placebo		
	Fluoxetine	**Paroxetine**	**Total**	**Fluoxetine**	**Paroxetine**	**Total**
Number of patients (male and female)	115	34	149	106	33	139
ASEX scale completed	115	34	149	105	33	138
ASEX total score						
Mean	21.7	22.5	21.8	21.9	23.3	22.2
SD	3.31	3.68	3.40	3.24	2.97	3.22
Minimum	11	14	11	15	17	15
Maximum	30	30	30	30	29	30
Mean ASEX item scores						
1. how strong is your sex drive?	4.86	4.94	4.88	4.91	5.12	4.96
2. how easily are you sexually aroused?	4.39	4.65	4.45	4.48	4.76	4.54
3. can you easily get and keep an erection?	4.16 (n=31)	4.27 (n=11)	4.19	3.97 (n=34)	4.13 (n=8)	4.00
3. how easily does your vagina become moist or wet?	3.96 (n=84)	3.83 (n=23)	3.93	3.93 (n=72)	3.96 (n=25)	3.94
4. how easily can you reach an orgasm?	4.45	4.64	4.56	4.49	4.82	4.57
5. are your orgasms satisfying?	3.87	4.26	3.99	4.03	4.58	4.22

Table 7.9

Change in proportion of subjects with sexual dysfunction during double-blind treatment
(Intention to treat population)

From day 15 to day 43	CEB-1555 (N = 147)		Placebo (N = 135)		p-value*
	No sex dys n (%)	Sex dys n (%)	No sex dys n (%)	Sex dys n (%)	
Observed case analysis					
No sexual dysfunction	2 (1.4)	0	0	1 (<1.0)	
Sexual dysfunction	39 (26.5)	71 (48.3)	31 (23.0)	73 (54.1)	0.44
LOCF analysis					
No sexual dysfunction	2 (1.4)	0	0	1	
Sexual dysfunction	48 (32.7)	90 (61.2)	36 (26.7)	92 (68.1)	0.27

Sex dys, sexual dysfunction; LOCF, last observation carried forward

* Cochran-Mantel-Haenszel test, stratified by gender and antidepressant, testing change in ASEX score from a score indicating sexual dysfunction at day 15 to a score indicating no sexual dysfunction at day 43

Only those patients with an ASEX score at both day 15 and day 43 are included

Table 7.10

Mean ASEX total score, by assessment (intention to treat population), by gender

Day	CEB-1555 (N = 147)									Placebo (N = 135)								
	Male (N = 41)			Female (N = 106)			Both			Male (N = 41)			Female (N = 94)			Both		
	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD
Screening																		
1	41	20.7	3.47	104	22.3	3.30	145	21.9	3.41	41	21.0	2.97	92	22.7	3.09	133	22.2	3.15
8	35	20.6	3.57	94	22.4	3.19	129	21.9	3.38	39	21.3	2.86	80	22.2	3.23	119	21.9	3.13
15	39	20.9	3.18	99	22.6	3.18	138	22.1	3.23	36	21.0	3.15	89	22.6	3.40	125	22.1	3.40
Double-blind																		
Baseline	41	21.0	3.43	106	22.4	3.15	147	22.0	3.28	41	21.1	3.07	93	22.6	3.41	134	22.1	3.37
22	39	20.1	3.82	92	20.7	4.22	131	20.5	4.10	36	19.9	3.48	81	20.4	3.86	117	20.3	3.74
29	39	19.5	4.15	93	20.2	4.37	132	20.0	4.31	32	19.8	4.70	80	19.8	4.05	112	19.8	4.23
36	38	18.8	4.86	86	19.5	4.92	124	19.3	4.89	37	19.4	4.62	80	20.1	4.57	117	19.9	4.57
43 (OC)	34	18.8	5.22	84	19.6	5.53	118	19.3	5.43	32	19.1	4.32	79	19.3	4.48	111	19.3	4.42
43 (LOCF)	39	18.6	5.08	100	19.6	5.27	139	19.3	5.22	40	19.6	4.37	91	19.6	4.49	131	19.6	4.44
Follow-up																		
50	35	19.5	5.12	81	19.2	5.26	116	19.3	5.20	28	18.8	3.12	68	19.8	4.29	96	19.5	3.99
57	38	18.7	4.67	91	19.7	5.18	129	19.4	5.03	34	19.5	4.76	79	20.0	4.58	113	19.9	4.62

n, number of observations at that assessment; OC, observed case analysis; LOCF, last observation carried forward analysis

Table 7.11

Mean ASEX total score, by assessment (intention to treat population), by antidepressant

Day	CEB-1555 (N = 147)									Placebo (N = 135)								
	Fluoxetine (N=114)			Paroxetine (N=33)			Total			Fluoxetine (N=103)			Paroxetine (N=32)			Total		
	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD
Screening																		
1	112	21.7	3.31	33	22.5	3.71	145	21.9	3.41	101	21.9	3.15	32	23.2	2.98	133	22.2	3.15
8	104	22.0	3.42	25	21.9	3.30	129	21.9	3.38	93	21.7	3.14	26	22.7	3.01	119	21.9	3.13
15	107	22.0	3.14	31	22.5	3.55	138	22.1	3.23	95	21.9	3.42	30	22.9	3.26	125	22.1	3.40
Double-blind																		
Baseline	114	21.9	3.22	33	22.4	3.49	147	22.0	3.28	102	21.9	3.41	32	22.8	3.16	134	22.1	3.37
22	100	20.4	4.13	31	21.0	4.06	131	20.5	4.10	93	19.9	3.70	24	21.8	3.60	117	20.3	3.74
29	104	19.7	4.40	28	21.3	3.72	132	20.0	4.31	87	19.4	4.31	25	21.1	3.69	112	19.8	4.23
36	99	18.8	4.95	25	21.4	4.17	124	19.3	4.89	89	19.4	4.69	28	21.4	3.84	117	19.9	4.57
43 (OC)	90	18.7	5.56	28	21.4	4.50	118	19.3	5.43	85	18.5	4.34	26	21.6	3.90	111	19.3	4.42
43 (LOCF)	109	18.7	5.25	30	21.5	4.53	139	19.3	5.22	101	19.1	4.53	30	21.4	3.66	131	19.6	4.44
Follow-up																		
50	93	18.8	5.32	23	21.0	4.37	116	19.3	5.20	72	18.9	3.92	24	21.3	3.70	96	19.5	3.99
57	101	19.2	5.22	28	20.3	4.27	129	19.4	5.03	85	19.4	4.82	28	21.3	3.70	113	19.9	4.62

n, number of observations at that assessment; OC, observed case analysis; LOCF, last observation carried forward analysis

Change in individual ASEX item scores

There was a slight reduction in mean score (indicating improved sexual function) on each of the ASEX items, in both treatment groups, both in the overall patient sample, and in the sub-groups of male and female patients. The difference between treatment groups in change in mean score on any ASEX item was slight, there being only one item showing a significant difference (item 3 in men, $p<0.05$), with an advantage for CEB-1555 over placebo. Tables 7.14 and 7.15 give the changes in individual ASEX item scores during double-blind treatment, according to gender and antidepressant, respectively.

Change in scores on Clinical Global Impression scales

The proportion of patients in the ITT population who were rated as 'much improved' or 'very much improved' on the Clinical Global Impression of Improvement scale was 17.7% with CEB-1555 and 14.1% with placebo ($p=0.51$, chi-squared test). A greater proportion of female than male patients responded, in both treatment groups (CEB-1555, 19.8% vs. 12.2%; placebo, 16.0% vs. 9.8%). Proportionately more patients who were receiving fluoxetine responded to double-blind treatment than did patients who were receiving paroxetine, in both treatment groups (CEB-1555, 21.9% vs. 3.0%; placebo, 16.5% vs. 6.3%).

Change in mean total score on 17-item HAM-D, and item 14 (genital symptoms)

There was no evidence that double-blind treatment improved or worsened depressive symptoms. In the safety population, the mean total score on first 17 items of the HAM-D declined slightly over the course of the study, in both treatment groups. During double-blind treatment, the mean score declined from 5.3 to 5.1 with CEB-1555, and from 5.4 to 5.0 with placebo. The proportion of patients with 'severe' symptoms on item 14 of the HAM-D (genital symptoms) declined over the course of the study, in both treatment groups. In the safety population during double-blind treatment, this proportion changed from 76.5% to 43.0% with CEB-1555, and from 74.1% to 47.5% with placebo.

Adverse events relating to sexual function

Most patients reported at least one adverse event. With CEB-1555, a total of 708 events were reported by 124 (83%) patients; with placebo, a total of 491 events were reported by 108 (78%) patients. No patient reported an adverse event related to sexual dysfunction whilst receiving CEB-1555; one patient, receiving fluoxetine, was classed as having an adverse related to sexual function, whilst undergoing double-blind treatment with placebo.

Table 7.12

Change in total ASEX score during double-blind treatment, by gender (intention to treat population)

	CEB-1555 (N = 147)			Placebo (N =135)		
	Male (N = 41)	**Female (n = 106)**	**Both**	**Male (N = 41)**	**Female (N = 94)**	**Both**
OC population						
N	34	84	118	32	78	110
Reduction of 50% or more, N (%)	2 (5.9)	8 (9.5)	10 (8.5)	1 (3.1)	5 (6.4)	6 (5.5)
LOCF population						
N	39	99	138	40	89	129
Reduction of 50% or more, N (%)	2 (5.1)	8 (8.1)	10 (7.2)	1 (2.5)	5 (5.6)	6 (4.7)

OC observed case
LOCF last observation carried forward

p-value (chi-square test): OC analysis, 0.53; LOCF analysis, 0.53 (combining genders)

Table 7.13

Change in total ASEX score during double-blind treatment, by antidepressant (intention to treat population)

	CEB-1555 (N = 147)			Placebo (N =135)		
	FLX (N = 114)	PAR (n = 33)	Both	FLX (N = 103)	PAR (N = 32)	Both
OC population						
N	90	28	118	84	26	110
Reduction of 50% or more, N (%)	10 (11.1)	0	10 (8.5)	6 (7.1)	0	6 (5.5)
LOCF population						
N	108	30	138	99	30	129
Reduction of 50% or more, N (%)	10 (9.3)	0	10 (7.2)	6 (6.1)	0	6 (4.7)

FLX fluoxetine
PAR paroxetine
OC observed case
LOCF last observation carried forward

Table 7.14 Change in individual ASEX item scores during double-blind treatment (ITT LOCF population), by gender

ASEX item	CEB-1555(N = 147)			Placebo (N = 135)			p-value*
	n	mean	SD	N	mean	SD	
1. How strong is your sex drive?							
Men	38	-0.8	1.15	35	-0.3	0.64	
Women	95	-0.7	1.14	87	-0.7	1.07	
Combined	133	-0.7	1.14	122	-0.6	0.98	0.43
2. How easily are you sexually aroused?							
Men	37	-0.6	1.01	35	-0.3	0.99	
Women	94	-0.7	1.19	87	-0.6	1.06	
Combined	131	-0.7	1.14	122	-0.5	1.05	0.54
3. How easily does your vagina become moist or wet?	94	-0.3	1.08	87	-0.4	1.09	0.14
3. Can you easily get and keep an erection?	37	-0.5	0.87	35	-0.1	0.87	0.01**
4. How easily can you reach orgasm?							
Men	37	-0.3	1.07	35	-0.4	0.81	
Women	93	-0.5	1.14	87	-0.5	1.22	
Combined	130	-0.5	1.12	122	-0.5	1.12	0.52
5. Are your orgasms satisfying?							
Men	37	-0.2	1.16	35	-0.4	0.91	
Women	93	-0.5	1.46	87	-0.6	1.35	
Combined	130	-0.4	1.39	122	-0.5	1.24	0.22

n, number of observations; * p-value from Wilcoxon 2-sample test of difference in mean values; ** p=0.0127

Table 7.15 Change in individual ASEX item scores during double-blind treatment (ITT LOCF population), by antidepressant

ASEX item	CEB-1555 (N = 147)			Placebo (N = 135)		
	n	mean	SD	n	mean	SD
1. How strong is your sex drive?						
Fluoxetine	104	-0.8	1.13	93	-0.6	1.02
Paroxetine	29	-0.3	1.08	29	-0.4	0.82
2. How easily are you sexually aroused?						
Fluoxetine	103	-0.7	1.19	93	-0.6	1.10
Paroxetine	28	-0.5	0.92	29	-0.5	0.87
3. How easily does your vagina become moist or wet?						
Fluoxetine	74	-0.4	1.11	65	-0.6	1.19
Paroxetine	20	0.2	0.88	22	-0.1	0.64
3. Can you easily get and keep an erection?						
Fluoxetine	29	-0.5	0.95	28	-0.1	0.85
Paroxetine	8	-0.6	0.52	7	0.0	1.00
4. How easily can you reach orgasm?						
Fluoxetine	102	-0.5	1.12	93	-0.6	1.19
Paroxetine	28	-0.2	1.09	29	-0.3	0.80
5. Are your orgasms satisfying?						
Fluoxetine	102	-0.5	1.41	93	-0.6	1.32
Paroxetine	28	0.0	1.20	29	-0.3	0.93

n, number of observations; * p-value from Wilcoxon 2-sample test of difference in mean values; ** p=0.0127

DISCUSSION

Overall findings

The findings of this multi-centre, randomised, placebo-controlled, parallel-group, fixed-dose treatment study indicate that the investigational compound CEB-1555 (a 5-HT_{1A} and 5-HT_{1D} receptor agonist) is not efficacious in the reduction of sexual dysfunction associated with the SSRI antidepressants fluoxetine or paroxetine. Although there was a numerical advantage for CEB-1555 over placebo on the primary outcome measure (i.e. change in proportion of patients with a total ASEX score from a value indicating sexual dysfunction to a value indicating no sexual dysfunction), this difference was small and not statistically significant. There were numerical advantages for CEB-1555 over placebo on most of the secondary outcome measures (reduction in mean total ASEX score; proportion of patients with a 50% or more reduction in ASEX score; proportion of patients rated as 'very much' or 'much' improved on the CGI-I) but again these were not statistically significant.

In male patients, CEB-1555 was significantly more efficacious than placebo on one secondary outcome measure, that is in reducing difficulty in achieving and maintaining erection (ASEX item 3). However, the magnitude of the difference in mean score on this item at the end of double-blind treatment was only small (0.4), and is unlikely to be of clinical significance. Furthermore, the relatively small numbers of male patients (n=72) who provided data at both the beginning and end of double-blind treatment in the ITT population reduces the confidence which could be placed in this finding.

The results of this study therefore contrast with other findings, indicating that treatment with drugs with 5-HT_{1A} agonist properties can be efficacious in improving sexual dysfunction, associated with major depression (Davidson and Gilbertini, 2002) or with SSRI treatment (Landen *et al*, 1999).

Study strengths and weaknesses

The study was designed to test the hypothesis that treatment with CEB-1555 would prove efficacious in relieving sexual dysfunction associated with fluoxetine or paroxetine. The study had a number of strengths, including the exclusion of patients with significant current depressive symptoms; the requirement that sexual dysfunction was 'treatment-emergent' rather than long-standing; the placebo-control, parallel-group design; the use of a screening period, to ensure that sexual dysfunction was not transient; and the large sample size. The numerical advantages for CEB-1555 over placebo on most of the outcome measures, reflecting the observations of pre-clinical investigations suggests that the study design was robust enough to have revealed any major differences, if they had existed.

The failure to find a significant difference between CEB-1555 and placebo on the primary outcome measure and nearly all the secondary outcome measures may of course result from potential

deficiencies in study design. These include the use of multiple study centres; the reliance on patient diary cards; and the use of possibly insensitive outcome measures. However, adequate study centre inter-rater reliability was established prior to starting the investigation, and data analysis did not reveal a treatment-by-centre effect. In addition, patient compliance with diary cards was high (add details here). Furthermore, although some other studies in this area that have employed the ASEX scale were not able to detect a difference between and 'active treatment' and placebo, other randomised controlled studies have been able to reveal significant differences in efficacy.

Implications for research

Given the balance of study strengths and weaknesses, it seems likely that CEB-1555 was not efficacious in relieving sexual dysfunction associated with fluoxetine or paroxetine, at least with the daily dosage, treatment adherence and treatment duration used in this study. The dosage of CEB-1555 was chosen after consideration of its effects in pre-clinical studies and from the results of tolerability studies in healthy volunteers, and was considered optimal on the basis of existing information. Patient adherence to study medication was high, as all patients treated with CEB-1555 and 97.8% of patients treated with placebo were recorded as having compliance rates of 80% or greater. The duration of double-blind treatment (four weeks) was considered sufficient to reveal any potential differences in efficacy, and there was no evidence that longer treatment might have resulted in a further reduction in total ASEX score, as most of the reduction occurred in the first two weeks of double-blind treatment.

The finding that double-blind treatment with CEB-1555 was associated with a numerically greater reduction in mean total ASEX score in fluoxetine-treated patients than in those who received placebo (3.2 compared to 0.9) is intriguing. This is reflected in the observation that the proportion of patients who achieved a reduction of 50% or more in total ASEX score was notably greater with fluoxetine (9.3%) than with paroxetine, where no patients met this criterion. Caution is need in considering this finding further, as double-blind treatment with placebo was also associated with a greater reduction in total ASEX score in patients who were receiving fluoxetine compared to those receiving paroxetine (2.8 and 1.4 respectively). Furthermore, the number of patients receiving paroxetine (n=77) was small (only 23.3% of the safety population).

Implications for clinical practice

Whilst CEB-1555 was significantly more beneficial than placebo on item 3 of the ASEX scale in male patients (i.e. on ability to achieve and maintain erection), the magnitude of the difference was small, and is probably not of clinical significance. The findings of this study suggest that a drug which relied solely on 5-HT_{1A} and 5-HT_{1D} agonist properties would be unlikely to be widely adopted in the management of men with erectile failure, given the proven efficacy of phosphodiesterase inhibitors in that indication.

CHAPTER 8 : STABILITY OF SEXUAL DYSFUNCTION AND PSYCHIATRIC DIAGNOSIS

AIM OF THE INVESTIGATION

The previous studies described within this thesis have shown that sexual problems are common among secondary care patients treated with antidepressant drugs, and that antidepressants differ in their effects on sexual function and satisfaction. The study described in the preceding chapter shows that it is possible to conduct placebo-controlled augmentation studies in primary care depressed patients with sexual dysfunction associated with treatment with SSRI antidepressants. The randomised controlled trials described in chapters two, four, five and six all include both an acute and a continuation phase treatment study. However, longer-term double-blind data was only available for the studies reported in chapter two (nefazodone versus paroxetine, up to 16 weeks) and chapter six (escitalopram versus paroxetine, up to 19 weeks). The previous studies have not been designed to examine the longer-term course of sexual dysfunction among antidepressant-treated patients. As described in the literature review (chapter one), there is little data on the course and outcome of sexual dysfunction in depressed patients. For these, reasons the study reported within this chapter involved the long-term follow up of the patient sample that was first described in chapter three.

This study had three aims. The first was to re-interview the group of patients who were undergoing antidepressant treatment at the time of the first study (1997-98), using the same instruments, i.e. the MINI and DASEX scales, to examine the stability of psychiatric diagnosis and self-reported sexual problems. The second was to examine how the distribution of scores on the sexual function and enjoyment questionnaire compared to that on the ASEX scale, by using both scales in the second assessment. The third was to identify any features that were associated with the presence of sexual problems at both interviews.

METHOD

The method for this study is simple. The names and hospital number of each of the 83 patients who comprised the original study sample had been kept in a locked file; the consent forms and completed data collection sheets had been kept separately. These were all examined and efforts were made to ascertain whether the patients were still under my consultant care. For those patients who were still under my care, the rationale for the follow-up study was discussed during the next routine outpatient appointment. If a patient indicated that he or she was in principle disposed to take part, they were introduced to a research assistant who described the study in more detail, provided a patient information sheet and obtained written consent.

Those patients who were no longer under my consultant care were contacted by letter on up to two occasions, inviting them to contact the research assistant to discuss the study if they were potentially

interested in taking part. Once they had made contact with the assistant, appointments were made for the participants to attend the outpatient clinic. Hospital records indicated that some patients were now under the care of other consultant teams: in this situation, the consultant was contacted and the study was described, in the hope of gaining permission to contact the patient. If permission was obtained from that consultant, the patient was then contacted by letter.

Assessments

The presence of current and lifetime psychiatric morbidity was determined by completion of the MINI in each patient. Changes in sexual function and satisfaction were elicited by self-completion of the gender-specific versions of the sexual function and enjoyment questionnaire. Sexual dysfunction was assessed by completion of the gender-specific versions of the ASEX scales. The MINI and sexual function and enjoyment questionnaire are shown at the end of chapter three, and the ASEX scales at the end of chapter six. In addition, each patient was questioned about their current treatment with psychotropic and other drugs, and asked about their current physical health.

Statistical analysis

The data for each patient were anonymised and entered into spreadsheets. The computerised statistical package STATA 7.0 was used to perform descriptive analyses. The dataset was then examined to calculate the mean score on each item on the sexual function and enjoyment questionnaire, and to compare that score to the mean score at the original assessment. The relationship between individual questionnaire item scores at the two assessments was then examined using the Wilcoxon matched-pairs signed ranks test. The ASEX scores were examined to identify the proportion of patients with probable sexual dysfunction, according to the proposed criteria described previously in chapter 6 and 7. Finally the sexual function and enjoyment questionnaire and ASEX scores were compared, in an attempt to define the threshold for probable sexual dysfunction, according to score on the sexual function and enjoyment questionnaire.

ETHICAL CONSIDERATIONS

No ethical problems were foreseen for the participation of patients in the study. Patients were asked to report any current or previous symptoms of mental health problems, as they would do within routine psychiatric interviews. The patients were also asked to report any current sexual problems or changes form normal levels of sexual functioning, but each patient had previously freely consented to complete such assessments.

The study protocol was approved by the Southampton and South West Local Research Ethics Committee in August 2002. As it was felt that there might be subconscious pressure on patients under

my consultant care to consent to participate in the study, the protocol required that the information sheet and consent form were presented by research colleagues.

RESULTS

Study sample

The original patient sample consisted of 83 patients. Of these, three had died of natural causes, one had emigrated to Australia, and another to the United States. One patient had been involved in a dispute with the Trust and it was considered inadvisable to contact him. A total of 77 individuals were potentially available for interview; 36 were current outpatients and were approached at the time of an appointment, the other 41 were contacted by post or telephone. From this group of 77 individuals, 48 subjects (20 men, 28 women) participated in the follow-study, representing 57.8% of the original sample.

The interval between the original and follow-up assessment ranged between 4.63 and 5.23 years (mean interval 5.08 years, standard deviation 0.14 years). The data for each study subject are given in Table 8.1. The demographic and diagnostic characteristics of the study sample are summarised in Table 8.2.

Psychiatric diagnosis

The most common diagnoses generated by the MINI were major depressive episode, bipolar disorders and agoraphobia; current and previous bipolar disorders were more prevalent in men than women (60% compared to 36%), whereas agoraphobia was more prevalent in women (50% versus 40%). There was substantial psychiatric co-morbidity: the mean number of current MINI diagnoses was 2.48, compared to a sample mean of 3.33 at the original assessment. The mean number of combined current and lifetime diagnoses in the follow-up sample was 3.43.

There was much fluidity of psychiatric diagnosis over the follow-up period. The greatest stability of MINI diagnosis was in the group of depressive disorders (major depressive episode, dysthymia) where 19% of patients had the same diagnosis over five years. Anxiety disorders showed the highest resolution, such that 18.2% of patients no longer fulfilled diagnostic criteria. However, the group of anxiety disorders also showed the greatest incidence, with 15.8% of patients gaining a new anxiety disorder diagnosis. There was a greater five-year incidence than resolution for bipolar disorders and psychotic disorders, so the overall prevalence of these conditions increased.

Figure 8.1 shows the proportion of male and female patients with unchanged, increasing or decreasing psychiatric morbidity, defined according to the number of current MINI diagnoses. Both male and

Table 8.1 Demographic and clinical details of patients

Patient	Gender	Age	Current MINI diagnoses	Lifetime MINI diagnoses	Current physical illness	Anti-depressant	Other psychotropics	Other drugs	Sexual abuse	Sexual partner	Current sexual dysfunction
003	M	67	-	Past manic episode	Hypertension	SNRI	Lithium	Aspirin	N	-	Y
004	F	60	-	-	Irritable bowel syndrome, vulvitis[a]	SSRI, TCA	-	Steroid[b]	N	-	Y
005	M	51	Agoraphobia	Past hypomanic episode	Back problems[a]	-	-	-	N	Y	Y
007	M	39	Panic disorder, agoraphobia, social phobia	-	-	SSRI	Diazepam[b]	-	N	-	N
009	F	53	OCD, alcohol dependence, generalised anxiety disorder	Panic disorder	Hypothyroid	SSRI	Olanzapine[b]	Thyroxine	Y	N	Y
010	M	51	Major depressive episode, panic disorder, agoraphobia, social phobia, OCD, psychotic disorder	Past hypomanic episode, panic disorder, psychotic disorder	Sensorineuronal deafness	MAOI	Risperidone[b], Diazepam[b]	'Coproxamol'	N	-	Y
011	F	45	Major depressive episode, PTSD	Panic disorder	Hypercholesterolemia, hiatus hernia	5-HT_2 antagonist	-	Bezafibrate[b], lansoprazole[b], Hormone replacement therapy [b]	Y	Y	Y
012	F	45	Major depressive disorder, generalised anxiety disorder	-	-	TCA	Lithium, sulpiride[b]	-	Y	-	-
013	M	42	Major depressive episode, OCD, generalised anxiety disorder	-	-	-	-	-	N	-	N
017	F	40	-	Panic disorder	-	SSRI	-	-	N	-	N
018	M	39	-	Panic disorder	Hyperbilirubinaemia	SSRI	-	-	N	N	N
021	F	40	Major depressive episode, panic disorder, agoraphobia, generalised anxiety disorder, PTSD	Panic disorder	Sinusitis	SNRI	-	Oral contraceptive pill[b]	Y	Y	Y

Patient	Gender	Age	Current MINI diagnoses	Lifetime MINI diagnoses	Current physical illness	Anti-depressant	Other psychotropics	Other drugs	Sexual abuse	Sexual partner	Current sexual dysfunction
023	F	43	-	Psychotic disorder	Asthma[a], hypothalamic disease[a]	-	-	-	N	-	N
026	M	47	Major depressive disorder, social phobia, PTSD, alcohol dependence, generalised anxiety disorder	Panic disorder	Hypertension, osteoarthritis[a]	SSRI	-	Tramadol[b], nifedipine[b], ramipril[b], bisoprolol fumarate[b]	N	N	Y
028	M	55	Hypomanic episode, agoraphobia, OCD	Past manic episode, limited panic disorder, psychotic disorder	Migraine, ileostomy[a]	TCA	Lithium	'Paracodol'	N		
029	F	55	Major depressive episode, panic disorder, agoraphobia, social phobia, psychotic disorder, generalised anxiety disorder	Past hypomanic episode, panic disorder, psychotic disorder	Hypothyroidism	SSRI	Quetiapine	Thyroxine	N	Y	Y
031	F	34	Panic disorder, agoraphobia	Panic disorder	Pregnancy[a]	TCA	-	-	N	-	N
034	F	67	Agoraphobia, social phobia	-	Hypertension, hyper-cholesterolaemia	SNRI	-	Aspirin, simvastatin, tramadol[b], atenolol, dipyrimadole	N	-	Y
036	M	61	Major depressive disorder, OCD, generalised anxiety disorder	-	Heart disease[a], asthma[a]	-	Diazepam[b]	Ramipril[b], aspirin, bendrofluazide[b]	N	N	Y
039	F	48	Alcohol dependence, generalised anxiety disorder	Psychotic disorder	Minor prolapsed uterus[a]	SNRI, TCA	-	Nizatadine[b]	N	Y	N
040	M	35	Hypomanic episode, agoraphobia, OCD	Past hypomanic episode	Epilepsy[a], hypertension, hyper-cholesterolaemia	SNRI	Diazepam[b]	Sodium valproate, simvastatin, atenolol[b]	N	Y	Y

Patient	Gender	Age	Current MINI diagnoses	Lifetime MINI diagnoses	Current physical illness	Anti-depressant	Other psychotropics	Other drugs	Sexual abuse	Sexual partner	Current sexual dysfunction
041	F	47	Major depressive episode	Past hypomanic episode	Hypothyroidism, hypertension	SNRI	Olanzapine[b]	Thyroxine, thiazide[b]	Y	-	Y
044	F	44	Agoraphobia	Panic disorder	-	SSRI	-	Quinine	N	-	Y
045	F	55	OCD	-	Arthritis[a]	TCA	-	'Coproxamol'	N	-	Y
046	F	30	Agoraphobia	Panic disorder	-	SSRI	-	-	N	Y	Y
049	M	56	Major depressive episode, agoraphobia, social phobia, alcohol dependence, generalised anxiety disorder	-	Back pain[a], psoriasis	MAOI	Chlorpromazine[b]	-	N	-	Y
050	F	43	Major depressive disorder, panic disorder, agoraphobia, social phobia, PTSD	Past hypomanic episode, panic disorder	-	SNRI	Chlorpromazine[b], cyclopyrrolone	-	N	N	Y
051	F	24	-	-	-	-	-	Oral contraceptive [b]	N	-	N
053	F	35	Manic episode, panic disorder, agoraphobia, social phobia, OCD, psychotic disorder, generalised anxiety disorder	Past manic episode, panic disorder, psychotic disorder	Hypothyroidism	TCA	Olanzapine	Procyclidine, promethazine hydrochloride, thyroxine	Y	Y	Y
054	F	49	Major depressive episode, agoraphobia, social phobia, generalised anxiety disorder	-	Non-insulin-dependent diabetes mellitus[a]	5-HT_2 antagonist	-	-	N	-	Y
055	F	40	Major depressive episode, agoraphobia, social phobia, OCD, psychotic disorder	Psychotic disorder	Hyperthyroidism, back problems[a]	SSRI	-	-	N	N	Y
056	F	46	Major depressive episode, OCD	Panic disorder	Irritable bowel syndrome	5-HT_2 antagonist	Lithium, temazepam[b], trifluoperazine[b], chlorpromazine[b]	Pindolol[b], mebeverine, 'Fybogel'	Y	-	Y
057	F	61	Major depressive episode, agoraphobia, social phobia	Past hypomanic episode, panic disorder	-	5-HT_2 antagonist	-	Hormone replacement therapy [b]	N	Y	Y

Patient	Gender	Age	Current MINI diagnoses	Lifetime MINI diagnoses	Current physical illness	Anti-depressant	Other psychotropics	Other drugs	Sexual abuse	Sexual partner	Current sexual dysfunction
058	F	40	-	Past hypomanic episode, panic disorder	-	SSRI	-	Oral contraceptive pill[b]	N	-	N
059	F	35	OCD	-	-	SSRI	Quetiapine	-	N	-	Y
060	M	36	Alcohol dependence	-	Migraine, non-epileptic seizures[a]	-	-	Naproxen, 'Migraleve'	N	Y	N
062	M	43	Major depressive disorder, alcohol dependence, generalised anxiety disorder	Past manic episode, psychotic disorder	-	5-HT_2 antagonist	-	-	N	N	Y
064	F	26	Agoraphobia, generalised anxiety disorder	Panic disorder	-	-	-	-	N	Y	Y
065	M	54	Major depressive episode, social phobia, generalised anxiety disorder	Panic disorder, psychotic disorder	Angina[a], back problems[a]	SSRI	Lithium	-	N	-	Y
066	M	28	Social phobia, OCD	Past hypomanic episode, panic disorder	-	SSRI	Lamotrigine	-	N	-	N
067	M	54	Major depressive episode	Past manic episode	Non-insulin dependent diabetes mellitus[a], hypertension	5-HT_2 antagonist, reboxetine	-	Tolbutamide, doxazosin[b], loratadine, bendrofluazide[b]	N	-	Y
069	M	60	-	Past manic episode	Non-insulin dependent diabetes mellitus[a], cardiomegaly, hypotension, arthritis[a], ileostomy[a]	RIMA	Quetiapine, clonazepam[b], sodium valproate	Aspirin, frusemide, spironalactone[b], mesalazine, telmisartan, lansoprazole[b], ranitidine[b], gliclazide,	N	Y	Y
074	M	54	Major depressive episode, agoraphobia, generalised anxiety disorder	-	-	TCA	Risperidone[b], diazepam[b]	"Beta blocker"[b]	N	-	Y

Patient	Gender	Age	Current MINI diagnoses	Lifetime MINI diagnoses	Current physical illness	Anti-depressant	Other psychotropics	Other drugs	Sexual abuse	Sexual partner	Current sexual dysfunction
076	M	55	Major depressive episode, panic disorder, agoraphobia, social phobia, OCD, psychotic disorder, generalised anxiety disorder	Panic disorder, psychotic disorder	-	TCA	Risperidone[b], clonazepam[b]	-	N	-	Y
079	M	55	-	Past manic episode, panic disorder	Gallstones	SSRI	-	Mebeverine	N	Y	N
080	F	47	Major depressive episode, manic episode, agoraphobia, social phobia, OCD, psychotic disorder	Past manic episode, panic disorder, psychotic disorder	Asthma[a], hypertension	SNRI	Olanzapine[b]	Lansoprazole[b], orlistat, salbutamol, beclomethasone[b]	N	Y	Y
082	F	49	-	Panic disorder	-	SSRI	-	-	N	-	Y
083	F	36	Major depressive episode, panic disorder, agoraphobia, social phobia, generalised anxiety disorder	Past hypomanic episode, panic disorder	Headache	SSRI	-	-	Y	-	Y

[a] - medical condition associated with sexual dysfunction.
[b] - medication (other than antidepressants) associated with sexual dysfunction.

Sexual dysfunction determined by the Arizona sexual function questionnaire (ASEX)

Table 8.2

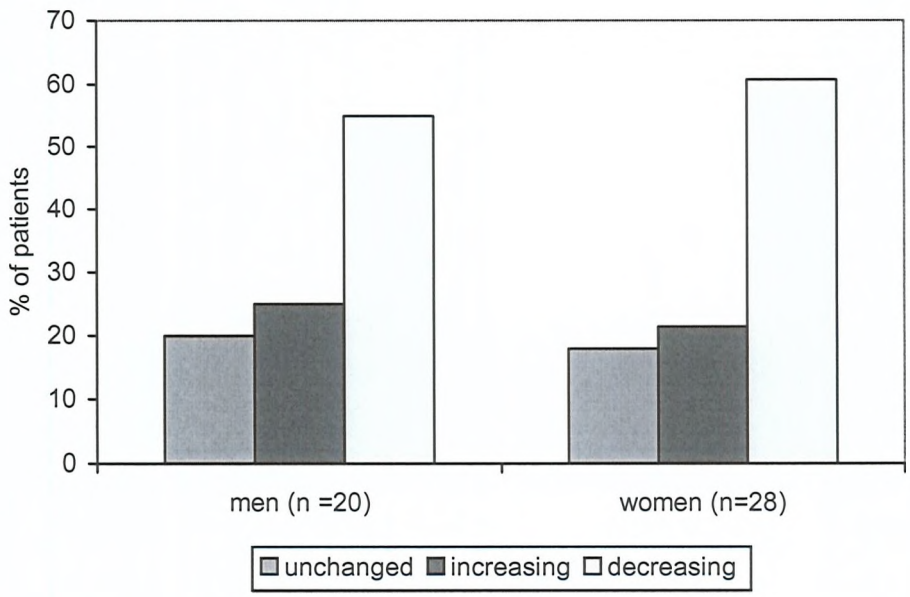
Demographic and clinical characteristics of the study sample

	Men	Women	Total
N	20	28	48
Mean age (years)	49.1	44.2	46.2
Age range (years)	28-67	24-67	24-67
MINI diagnoses			
Major depressive episode	10	12	22
Dysthymia	0	0	0
Manic episode (current)	0	2	2
Manic episode (previous)	6	2	8
Hypomanic episode (current)	2	0	2
Hypomanic episode (previous)	4	6	10
Panic disorder (current)	3	6	9
Panic disorder (lifetime)	7	12	19
Agoraphobia	8	14	22
Social phobia	7	9	16
Obsessive-compulsive disorder	7	7	14
Post-traumatic stress disorder	1	3	4
Alcohol dependence *	4	2	6
Psychotic disorder (current)	2	4	6
Psychotic disorder (lifetime)	5	6	11
Generalised anxiety disorder	8	9	17
Mean number of MINI diagnoses			
Current only	2.60	2.43	2.48
Current and lifetime	3.55	3.36	3.43

* 2 patients (1 male, 1 female) fulfilled criteria for alcohol abuse and alcohol dependence and are recorded here with the more significant diagnosis.

Figure 8.1

Proportion of patients with unchanged, increasing or decreasing psychiatric morbidity



Psychiatric morbidity defined according to the number of current MINI diagnoses

female subjects showed a reduction in the number of MINI diagnoses, this change being more marked in the female patients (60.7%, as compared to 55.0% in men): in addition the proportion of patients with increased co-morbidity was greater in men (25.0%) than in women (21.4%).

Co-morbid physical illness and prescribed medication

As in the overall sample described in chapter three, there was substantial current physical co-morbidity. The follow-up sample of 48 patients had a total of 51 medical conditions (including one case of pregnancy); in 17 (35.4%) patients there was a current physical illness that could affect sexual function adversely.

Most patients (29, 60.4%) were either taking a different antidepressant drug to that at the original assessment, or were no longer being prescribed an antidepressant. The mean number of prescribed medicines per patient was 2.77, compared to a mean number of 2.40 in this sample at their original assessment. As in chapter three, the British National Formulary (March 2003 edition) was examined to establish whether each medication has been associated with sexual problems, and a total of 24 (50.0%) patients were taking at least one medicine that could have untoward effects on sexual function. The mean number of medicines per patient that could affect sexual function adversely had increased from 1.56 at the original assessment to 1.79 at the final assessment.

Scores on the sexual function and enjoyment questionnaire at follow-up assessment

As in the original patient sample, few patients described improvements in any aspect of their sexual function, over 'normal' levels. Only 17 of the completed items, from a possible total of 240 items, indicated an improvement over normal levels in an area of sexual functioning. No male patient reported an improvement over normal levels of sexual functioning, this probably being due to continuing physical or mental health problems. As before, most patients described considerable impairments in sexual function: 149 responses to individual items showed either minor or major impairment in an area of sexual functioning. The questionnaire item scores are given in Table 8.3.

The findings from the sub-group of 20 male patients indicate that aspects of function were affected adversely more often than in women. In men, out of a total of 99 completed items, 31 (31.3%) were rated as showing no change, and the score on 56 items (56.6%) indicated substantial impairment. In the sample of 28 women, out of 128 completed items, 30 (23.4%) indicated no change compared to normal in that area of sexual functioning, and 59 items (46.1%) indicated substantial impairment. Because of the small numbers, no gender comparisons were made.

Table 8.3

Sexual function and enjoyment questionnaire scores at follow-up interview, grouped by gender

		-2	-1	0	+1	+2	9
		← Increasing impairment			Increasing improvement →		Missing
Male patients (n=20)							
Item 1	Desire	12	2	6	0	0	0
Item 2	Achieve erection	10	4	6	0	0	0
Item 3	Maintain erection	11	3	6	0	0	0
Item 4	Ejaculate	12	2	6	0	0	0
Item 5	Enjoyment	11	1	7	0	0	1
Female patients (n=28)							
Item 1	Desire	13	4	7	1	2	1
Item 2	Arousal	15	2	5	3	1	2
Item 3	Achieve orgasm	10	6	6	2	1	3
Item 4	Intensity of orgasm	7	7	8	2	1	3
Item 5	Enjoyment	14	3	4	2	2	3

Relationship between questionnaire scores in original and follow-up assessments

In most patients, there was a striking similarity between the individual questionnaire item scores at the original and follow-up assessments. As an example, the relationship between scores on item 1 (desire for sex) in male patients at the two assessments is shown as a scatter plot in Figure 8.2. The mean scores on the five questionnaire items at the original and follow-up assessments are shown in Table 8.4, together with the mean scores from the original sample of 83 patients. The sub-group of 20 male patients in the follow-up sample had numerically lower mean scores at baseline assessment (indicating a greater degree of sexual difficulties) on each of the items, compared to the 41 male patients in the original sample. The converse is seen in the sub-group of 28 female patients in the follow-up sample, in which there were numerically greater mean scores at baseline, than in the 42 female patients in the overall sample. The maximum difference between the overall sample and the follow-up sample in the mean score on any questionnaire item in men was 0.47 (item 3, ability to maintain erection), and in women was 0.14 (item1, desire for sex).

In the sub-group of female patients, the mean score on each of the five items of the sexual function and enjoyment questionnaire increased, indicating an improvement in that aspect of sexual function, compared to baseline assessment. The greatest positive change in mean score (an increase of 0.6) was for item 5 (enjoyment of sex). In the male patients, the picture was more complex: there were improvements in three items (ease of achieving erection, ease of maintaining erection, enjoyment of sex), but worsening on two items (desire for sex, ability to ejaculate). The greatest change in men (a decrease of 0.35) was on item 4 (ability to ejaculate).

The results of the Wilcoxon matched-pairs signed ranks test are shown in Table 8.5. In this comparison, the null hypothesis is that the score on an item at original assessment is equivalent to that at the follow-up assessment. Scores at follow-up are categorised as positive (i.e. increased), negative (decreased) or the same. By taking into account the ways in which scores could theoretically change an expected score is calculated and compared to the observed sum of the ranks. P-values greater than 0.05 indicate that the null hypothesis cannot be rejected. The probability values are consistently greater than 0.05 indicating that the scores at the original and follow-up assessments are not significantly different.

ASEX scores

The distribution of ASEX scores in male and female patients is given in table 8.6. Impairments in sexual drive, sexual arousal and ease of achieving and erection were each reported by 70.0% of male patients. Difficulty in achieving orgasm and dissatisfaction with orgasm were reported by 70% and 50% of men, respectively. In female patients, impairments in sexual drive and arousal were each reported by 75%; difficulty in achieving vaginal lubrication, achieving orgasm and dissatisfaction with orgasm were reported by 53.6%, 64.3% and 32.1%, respectively.

Figure 8.2

Sexual function and enjoyment questionnaire item 1 (desire for sex) in sub-group of 20 male patients

Scatter plot of score at original and follow-up assessment

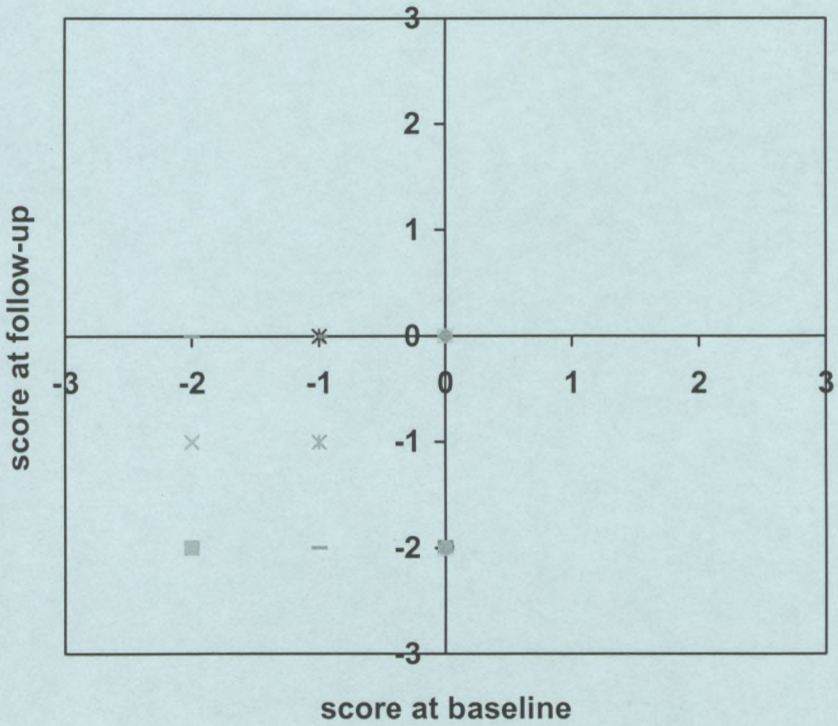


Table 8.4

Mean scores on sexual function and enjoyment questionnaire items in male and female patients at original and follow-up assessments

Gender	Original overall sample			Follow-up sample (48 patients)					
Questionnaire item	(83 patients)			Original assessment			Follow-up assessment		
Male patients	N	Mean	SD	N	Mean	SD	N	Mean	SD
Desire for sex	40	-0.73	1.15	20	-1.15	0.88	20	-1.30	0.92
Ease of achieving erection	40	-1.03	1.00	20	-1.40	0.88	20	-1.20	0.89
Ability to maintain erection	40	-0.88	1.10	20	-1.35	0.93	20	-1.25	0.91
Ability to ejaculate	40	-0.88	0.88	20	-0.95	0.88	20	-1.30	0.92
Enjoyment of sex	38	-0.93	0.94	20	-1.35	0.81	19	-1.21	0.98
Female patients									
Desire for sex	39	-1.26	1.18	26	-1.12	1.18	27	-0.93	1.27
Sexual arousal	39	-1.49	0.88	25	-1.40	0.91	26	-1.04	1.28
Ability to achieve orgasm	38	-1.16	1.00	25	-1.04	1.10	25	-0.88	1.17
Satisfaction with orgasm	37	-1.32	0.85	24	-1.25	0.90	25	-0.68	1.11
Enjoyment of sex	38	-1.34	0.85	25	-1.28	0.84	25	-0.68	1.35

N, number of observations; SD, standard deviation

All calculations given to two decimal places

Table 8.5

Relationship between sexual function and enjoyment questionnaire scores at original and follow-up assessment

	Sign									z score	Prob> z
	Positive			Stayed the same			Negative				
Variable	n	sum rank	expected	n	Sum rank	expected	n	sum rank	expected		
Men (n=20)											
Desire for sex	5	70.00	77.50	10	55	55.00	5	85.00	77.50	-0.30	0.76
Ease of achieving erection	6	96.00	72.00	11	66	66.00	3	48.00	72.00	0.99	0.32
Ability to maintain erection	5	81.00	59.50	13	91	91.00	2	38.00	59.50	0.95	0.34
Ability to ejaculate	3	48.00	87.00	8	36	36.00	9	126.00	87.00	-1.52	0.13
Enjoyment of sex	6	96.50	72.00	11	66	66.00	3	47.50	72.00	1.01	0.31
Women (n=28)											
Desire for sex	7	152.00	157.50	13	91	91.00	8	163.0	157.5	-0.13	0.89
Sexual arousal	7	153.00	143.00	15	120	120.00	6	133.0	143.0	0.25	0.80
Ability to achieve orgasm	10	191.50	175.50	10	55	55.00	8	159.5	175.5	0.37	0.71
Satisfaction with orgasm	14	231.00	192.50	6	21	21.00	8	154.0	192.5	0.89	0.38
Enjoyment of sex	10	197.00	170.00	11	66	66.00	7	143.0	170.0	0.64	0.52

N, number of observations; z, result of Wilcoxon matched-pairs test; Prob>z, probability of rejecting null hypothesis that paired observations are the same.

All computed observations given to two decimal points

Table 8.6

ASEX scores at follow-up interview, grouped by gender

		Score						
		1	2	3	4	5	6	missing
		Increasing impairment →						
Male patients (n=20)								
Item 1	Sex drive	1	1	4	3	4	7	0
Item 2	Sexual arousal	1	2	3	7	3	4	0
Item 3	Erection	0	2	4	6	4	4	0
Item 4	Reach orgasm	0	1	5	6	3	5	0
Item 5	Satisfaction	2	4	4	3	2	5	0
Female patients (n=28)								
Item 1	Sex drive	0	2	5	7	4	10	0
Item 2	Sexual arousal	0	3	3	8	7	6	1
Item 3	Lubrication	0	5	5	7	4	4	3
Item 4	Reach orgasm	0	3	4	7	7	4	3
Item 5	Satisfaction	1	3	12	1	3	5	3

By convention, sexual dysfunction is considered present according to the ASEX scale, when either the total score is 19 or greater, or when an individual item score is 5 or greater, or when any three of the five individual items have a score of 4 or more. Table 8.7 gives the proportion of male and female patients fulfilling each of these criteria, together with the proportion of patients who fulfil any of the three criteria. The criteria using either the total ASEX score or an individual ASEX item score of 5 or greater identify fewer cases of sexual dysfunction, than does the criterion based on scores of 4 or more on 3 or more ASEX items. Because of the small numbers, no gender comparisons were made.

Comparison of proportion with sexual dysfunction according to ASEX and questionnaire

Prior to this study, no attempt had been made to determine the threshold for probable sexual dysfunction according to the score on the sexual function and enjoyment questionnaire. Using the three ASEX criteria for probable sexual dysfunction described above, a total questionnaire score of -5 or less identifies a similar proportion of subjects (59.1%) as is identified by either of the first two ASEX criteria (62.5% with both methods). Using a different criterion, of any questionnaire individual item score of -2, identifies a proportion of patients (68.2%) that lies between the proportion defined by the first two ASEX criteria, and the third (i.e. a score of 4 or more on 3 or more items) (79.2% of patients). Table 8.8 gives the proportions identified by these criteria in the overall sample, and in the two sub-groups of male or female patients.

DISCUSSION

Study findings

The overall findings of the current investigation in a small specialist secondary care sample of patients with complex mood and anxiety disorders indicate that sexual dysfunction declines slightly (i.e. sexual function improved) over five years. During this period considerable changes occurred in prescribed treatment and in psychiatric morbidity, defined according to the number of current MINI diagnoses. At the original assessment, 31 patients (70.5%) had probable sexual dysfunction, defined according to total score on the sexual function and enjoyment questionnaire, this number declining to 26 patients (59.1%) after an average follow-up period of 5.08 years. Only 9 of the 48 patients (18.8%) had an unchanged number of MINI diagnoses. Most patients (29, 60.4%) had undergone at least one change in their antidepressant treatment.

The pattern of decline of sexual dysfunction differed between the sub-groups of male and female patients. In men, the proportion with sexual dysfunction, according to total questionnaire score, declined from 70.0% to 63.2%, whereas the decline in proportion in women was more marked (from 70.8% to 56.0%). Furthermore, in women the mean score on each questionnaire item increased, indicating an

Table 8.7

Proportion of patients fulfilling ASEX criteria for presence of sexual dysfunction

	Men N =20		Women N =28		Total N =48	
Criterion	n	%	n	%	n	%
Total ASEX score of 19 or more	13	65.0	17	60.7	30	62.5
ASEX item score of 5 or more	12	60.0	18	64.3	30	62.5
3 ASEX item scores of 4 or more	15	75.0	23	82.1	38	79.2
Any of these criteria	15	75.0	24	85.7	39	81.3

Individual ASEX items coded as 'missing' are scored as 0

Table 8.8

Proportion of patients fulfilling proposed sexual function and enjoyment questionnaire criteria for probable presence of sexual dysfunction

	Original assessment						Follow-up assessment					
	Men		Women		Total		Men		Women		Total	
	N = 20		N = 24		N = 44		N =19		N = 25		N = 44	
Criterion	n	%	n	%	n	%	N	%	n	%	n	%
Total score of -5 or less	14	70.0	17	70.8	31	70.5	12	63.2	14	56.0	26	59.1
Any item score of –2	15	75.0	19	79.2	34	77.3	13	68.4	17	68.0	30	68.2

Any patient with individual items coded as 'missing' is excluded from the analysis

N number of patients with fully completed questionnaire

n number of patients fulfilling that criterion

improvement in sexual function, whereas in men there were improvements in mean score on three of the five items. The reduction in the proportion of men with sexual dysfunction over time is an intriguing finding, given that epidemiological studies typically indicate that sexual function in men declines with increasing age. However use of the Wilcoxon matched pairs signed ranks test determined that the original and follow-up scores did not differ significantly, in either male or female patients. Furthermore, both the greatest increase (0.6 on enjoyment of sex item, in women) and the largest decrease (0.35 on ability to ejaculate) in the mean questionnaire item scores were less than one 'point', and of uncertain clinical significance.

The proportion of subjects with sexual dysfunction varied according to the differing ASEX criteria that were employed - from 30 patients (62.5%) using the criterion of a total ASEX score of 19 or greater, to 39 patients (81.3%) using the combination of all three ASEX criteria. This rather broad range is potentially troublesome, and 'tighter' criteria would be helpful. The development of a threshold for defining sexual dysfunction according to the score on the sexual function and enjoyment questionnaire was beyond the scope of this investigation, but use of a total DASEX score of -5 or less identifies a similar proportion of subjects to the proportion identified by the first two ASEX criteria.

Study weaknesses

The design of the study has a number of drawbacks that together limit the potential value of the findings. As mentioned in chapter three, the patient sample is drawn from a specialist secondary care service for patients with complex mood and anxiety disorders, and the findings may therefore not be applicable to the broader population of patients receiving treatment with antidepressant drugs. Despite considerable effort, only 48 (57.8%) of the original sample of 83 patients could be interviewed, and although the proportion of men and women in the original and follow-up sample is similar, the numbers are such that meaningful gender comparisons could not be made. Furthermore, the follow-up group may not necessarily be representative of the original patient sample. The mean scores on the questionnaire items at the original assessment indicate that the male subjects had worse sexual function, and the female subjects had better function, than the total population of male and female patients in the original sample of 83 patients.

Another area of weakness is in the method of defining the presence of sexual dysfunction. Whilst the ASEX scale has become the most widely used scale in psychopharmacological treatment studies, the use of varying criteria to identify sexual dysfunction makes the scale difficult to use and troublesome to interpret. The sexual function and enjoyment questionnaire was used in the randomised controlled trial of paroxetine and a comparator SNRI (described in chapter four), and considered generally acceptable by patients and doctors. Furthermore, in that study certain questionnaire items showed both change over time and the ability to differentiate between treatments with differing pharmacological properties. This suggests that

the questionnaire could be a useful alternative to the ASEX scale, but it cannot be adopted more widely before its other psychometric properties have been determined.

It is tempting to examine the change in mean score on the individual questionnaire items over time, but this would be unwise for three reasons. Firstly, the magnitude of the difference in mean scores is slight and of doubtful clinical significance, so statistical analysis would produce questionable results. Secondly, the subject numbers are rather small, and the probabilities of type I and type II errors would be great. Thirdly, the most useful statistical test is based on the assumption that questionnaire item scores are normally distributed, whereas examination of the raw data reveals that they show considerable skew.

Implications for clinical practice and research

The study findings suggest that some patients with sexual dysfunction, originally associated with antidepressant treatment, will improve over time; but this study was unable to demonstrate when that improvement occurred. This improvement is more noticeable in women than in men, as approximately 20% of women with sexual dysfunction at the original assessment did not fulfil proposed sexual function and enjoyment questionnaire criteria at the follow-up assessment, whereas this change was seen in only 10% of men. This degree of symptomatic resolution should be considered, when evaluating the efficacy of potential new treatment approaches, and emphasises the need for a placebo-controlled study design.

Most patients, however, remain troubled by marked sexual difficulties, despite the passage of time, considerable changes in psychiatric diagnosis, and changes in prescribed antidepressant and other treatments (some of which are associated with sexual dysfunction). The findings of the randomised controlled trials in patients with major depressive episodes reported in previous chapters indicate that varying aspects of sexual function improve during the acute and continuation phases of double-blind antidepressant treatment. However the findings from this study in a different patient group undergoing more naturalistic treatment indicate that sexual dysfunction usually persists over the long-term. As such, it would seem inappropriate to withhold consideration of new treatment approaches in this group, in the expectation that matters will improve, as this will only be the case in a small proportion of patients.

Future research might seek to examine the pattern of change in sexual function over long-term antidepressant treatment, once the continuation phase of treatment is complete. Such research would also require assiduous monitoring of changes in prescribed medication and in physical health. Consideration should also be given to examining serial changes on both the ASEX and sexual function and enjoyment questionnaire, together with a global measure of sexual dysfunction, perhaps based upon the CGI-I scales. This would allow the sensitivity and specificity of the ASEX and questionnaire to be examined, would permit further examination

of their thresholds for identifying patients with probable sexual dysfunction, and delineate their respective sensitivity to change with treatment.

CHAPTER 9 : CONCLUSIONS

The previous eight chapters have reviewed the literature on sexual function in depression (chapter one), and have described a series of investigations of sexual dysfunction among patients taking antidepressant drugs (chapters two to eight). Before making some suggestions for future research, I will briefly summarise the findings of the individual studies, and highlight recent relevant publications.

The literature review of the epidemiology of sexual dysfunction in the general population and in patients with depression indicates that sexual problems are common in the community and in primary care, and more common in people with depression. Two recent papers, published since the literature search, provide further evidence supporting these findings. In a cross-sectional study in 13 general practices in London, 22% of men and 40% of women fulfilled ICD-10 diagnostic criteria for at least one sexual dysfunction. In women, independent predictors for dysfunction were increasing age, physical ill-health, sexual dissatisfaction, and psychiatric 'caseness'; in men, the only predictor was bisexual orientation (Nazareth *et al*, 2003). In the second investigation, sexual problems were reported by 34.8% of men and 53.8% of women, aged 16-44 years, in a probability sample household survey (Mercer *et al*, 2003). Consultation rates for sexual problems were low in both studies: for example, 22% of women and 17% of men with lack or loss of sexual desire in primary care (Nazareth *et al*, 2003), and 10.5% of men and 21% of women with sexual problems in community settings (Mercer *et al*, 2003).

The literature review of sexual dysfunction associated with antidepressants reveals that few studies have sufficiently rigorous design to allow an accurate assessment of the incidence of sexual dysfunction arising during antidepressant treatment. However, all four of these studies indicate that sexual dysfunction is significantly more common with certain antidepressants than with placebo. Similar methodological problems are seen in studies that attempt to show the relative incidence of sexual dysfunction with different antidepressants, although five out of eight comparator-controlled studies of adequate design indicate a significant advantage for one drug over another. A recent review supports the need for caution when claiming that certain antidepressant are less likely to cause sexual problems than others, and emphasizes the need for further well-designed studies (Labbate *et al*, 2003).

The review of treatment strategies for the management of sexual dysfunction associated with antidepressants reveals the small number of randomised double-blind placebo-controlled studies. The best evidence appears to be for switching to nefazodone in patients with sexual dysfunction associated with sertraline, and for the addition of sildenafil in men with erectile dysfunction. However, nefazodone is no longer available for clinical use in the United Kingdom; and because of the association of erectile failure with cardiovascular disease,

prescription of sildenafil is limited by contraindications in patients with hypotension, unstable angina and recent myocardial infarction, and by untoward reactions with nitrates. As such, there is still a need for more placebo-controlled switching or augmentation studies in patients with sexual dysfunction associated with antidepressants.

The findings of the double-blind randomised controlled trial of nefazodone and paroxetine reported in chapter two indicate that two antidepressants which have similar overall efficacy in acute and continuation treatment can nevertheless exert significantly different effects on sexual desire, as estimated by item 14 (genital symptoms) of the HAM-D. This finding was also seen in the randomised controlled comparison of nefazodone and sertraline (Feiger *et al*, 1996), and for this reason I chose to examine changes in score on this item in the subsequent studies described in chapters four, five and seven. Admittedly, item 14 is a limited measure of one aspect of sexual function, and these studies therefore also incorporated more detailed assessments of sexual function and satisfaction. This investigation confirms that sexual difficulties are reported only rarely as an adverse event during antidepressant treatment.

The point prevalence study described in chapter three confirms that sexual problems are common among secondary care patients taking antidepressant drugs, and supports the contention that the method of enquiry affects the reported prevalence (Harrison *et al*, 1986; Monteiro *et al*, 1987; Baldwin, 2001), as 44.6% of patients reported problems when given the opportunity, compared to 84.3% who described changes on the sexual function and enjoyment questionnaire. Detailed enquiry shows that most patients had at least one possible cause of sexual dysfunction, in addition to the presence of affective illness and antidepressant treatment. This reinforces the need for comprehensive assessments of sexual function before starting antidepressants, to avoid erroneously attributing any sexual problems to treatment. This chapter also reports the first use of the sexual function and enjoyment questionnaire. Few patients declined to complete the questionnaire, and the majority completed it within ten minutes, with low rates of missing data (6.3%), and it is for this reason that it was incorporated as an outcome measure in the study described subsequently.

The findings of the international multi-centre double-blind randomised controlled trial of paroxetine and an SNRI reported in chapter four indicate that the sexual function and enjoyment questionnaire can be used repeatedly in secondary care settings. Missing data were seen only rarely with men, but more commonly with women, particularly for the 'enjoyment' item (4.4% missing in men, 15.9% in women). As in chapter two, the study shows that antidepressants with similar overall efficacy had significantly different effects on libido (item 14). There were also significant differences between treatments in other aspects of sexual function, as assessed by changes on the sexual function and enjoyment questionnaire; with significant advantages for the SNRI over paroxetine on ejaculation early in the study, and for paroxetine over the SNRI on other questionnaire items early and late in the

study. The questionnaire appears sensitive to change and able to differentiate between pharmacological properties of antidepressants that may affect sexual function.

Somewhat similar findings are seen in the multi-centre double-blind randomised controlled trial of reboxetine and paroxetine reported in chapter five, where the antidepressants had similar overall efficacy in acute treatment. There were non-significant trends for an advantage for reboxetine over placebo on HAM-D item 14, it being possible that this could have reached conventional levels of statistical significance if more than 70 patients had been recruited in the United Kingdom study centres. There were significant differences between treatments with advantages for reboxetine on one visual analogue item (ability to become sexually excited) of the Rush Sexual Inventory, and non-significant trends on two other items. The findings of this study support the results of two other recent investigations, in which reboxetine had advantages over an SSRI (fluoxetine, citalopram), in improving sexual function (Clayton *et al*, 2003; Bodlund *et al*, 2003).

There were no significant differences between treatments, either in antidepressant efficacy or effects on sexual dysfunction, in the multi-centre double-blind randomised controlled trial of escitalopram and paroxetine reported in chapter six. The study findings therefore contrast with the results of the preceding investigations, perhaps because the two treatments share considerable pharmacological properties. Paroxetine and escitalopram differ only slightly in their potency and selectivity for re-uptake of serotonin, and on the basis of this study this appears insufficient to result in significant differences in antidepressant efficacy or on effects on sexual function or satisfaction.

Given the need for evidence-based treatments for the management of patients with sexual dysfunction associated with antidepressants, the results of the placebo-controlled augmentation study of the investigational compound CEB-1555 described in chapter seven are disappointing. There was a numerical advantage for CEB-I555 over placebo on the primary outcome measure, and on most of the secondary outcome measures, but the differences between treatments were mostly small and statistically significant. CEB-155 was significantly more efficacious than placebo on just one secondary outcome measure (ASEX item 3, difficulty in achieving and maintaining erection), but the difference between treatments in mean score at study end-point (0.4) is unlikely to be clinically important. The study findings contrast with those from other studies of drugs with 5-HT_{1A} agonist properties (Landen *et al*, 1999; Davidson and Gilbertini, 2002); a pooled analysis of these and any other unpublished studies would be helpful, to establish whether drugs with this mechanism of action should be developed further, as potential treatments for sexual dysfunction associated with SSRI treatment.

The five-year follow-up study reported in chapter eight represents the first longitudinal investigation of sexual dysfunction in a secondary care sample of patients undergoing antidepressant treatment. Because of the degree of patient drop-out (42%) only tentative comments can be made. Despite changes in diagnoses, treatment, and the passage of time, sexual function appeared to improve, particularly in women (where the proportion with probable sexual dysfunction declined from 708% to 56.0%). However, it should be emphasized that individual sexual function and questionnaire scores did not differ significantly in either male or female patients. The study design also allowed a comparison of scores between the ASEX and sexual function and enjoyment questionnaire, and the delineation of probable thresholds for sexual dysfunction on that questionnaire.

Having completed this series of investigations, a number of potential research directions are apparent. For clarity, these are listed below.

1. Many investigations into the problem of sexual dysfunction associated with antidepressants have been flawed in design, and therefore much remains unclear about the incidence of sexual problems during treatment. More randomised placebo-controlled studies with a baseline assessment of sexual function are needed.

2. There is still a need for placebo-controlled studies of treatment approaches to the management of patients with established sexual dysfunction associated with antidepressants. These should be performed in remitted patients, preferably with no history of sexual dysfunction prior to the onset of depression.

3. Attempts should be made to identify predictors for developing sexual dysfunction with antidepressants, including demographic, clinical, psychosocial or neurobiological factors. This will necessarily involve close collaboration between differing disciplines. For example, recent research has identified genetic polymorphisms for the development of weight gain with atypical antipsychotic drugs (Reynolds *et al*, 2002), and this approach may be helpful in the area of sexual dysfunction.

4. The findings reported in this thesis suggest that antidepressant drugs with 5-HT_{2A} antagonist properties or selective noradrenaline re-uptake inhibitory properties may be associated with less sexual dysfunction than SSRI antidepressants. Further randomised controlled trials incorporating a sexual function scale are needed to confirm or refute these results.

5. There is scope for the development of antidepressant drugs with preferential effects on preserving sexual function, but reliance on the incidence of treatment-emergent sexual adverse effects is an insufficient assessment of this potential advantage.

6. There are many questionnaires and scales for assessing sexual function and satisfaction, but there is at present no consensus on which scale has optimal validity, reliability, sensitivity and ease of use. Further comparisons between scales are needed.

The studies also suggest a number of potential modifications to current clinical practice. Again for the sake of clarity these are listed below.

1. The term 'sexual dysfunction' obscures the precise nature of any sexual problem, and doctors should be more familiar with the range of difficulties experienced by depressed patients both before and during treatment.

2. Whilst it is common to ask depressed patients about loss of libido at the first consultation, to support the diagnosis of depression, few clinicians enquire about disturbances in other areas of sexual function. The readiness with which patients completed sexual function scales and questionnaires in these studies, and occasional favourable comments on being asked about an important aspect of interpersonal relationships suggest that more detailed enquiries into sexual function at first assessment are feasible, which may prevent erroneous attribution of problems to the effects of treatment.

3. The differences between antidepressants in effects on sexual function in the studies described in this thesis, and in previous investigations reported in chapter one, are in general insufficient to lead to preferential prescribing of one drug over another. The potential for sexual dysfunction during treatment is but one consideration among many, when selecting a particular antidepressant for a particular patient.

David Baldwin
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