**IMPACT OF MENTAL DISORDER AND PSYCHOTROPIC MEDICATIONS ON SEXUAL HEALTH**

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**Conflict of interest**: Dr. Montejo has been a consultant for, received grant/research support and honoraria from, and been on the speakers/advisory board of Eli Lilly, Forum Pharmaceuticals, Rovi, Servier, Shyre, Lundbeck, Otsuka, Janssen, Pfizer and Roche. Laura Montejo has no conflict of interest.

In the last three years, on behalf of his employer (University of Southampton), Professor Baldwin has received research funding from H. Lundbeck A/S, Liva Nova, Mundipharma and Pfizer Ltd. In the same period, he has received personal honoraria (lecture fees) from AstraZeneca, Janssen and Pierre Fabre.

**Abstract**

Sexual dysfunction often accompanies psychiatric illness and can be impacted either by the mental disorder itself or by use of psychotropic treatments. Many sexual symptoms resolve as the mental state improves, but treatment-related sexual adverse events tends to persist over time, and are unfortunately under-recognised by clinicians and scarcely investigated by pharmaceutical companies in clinical trials. There are important variations between different compounds in the incidence of treatment-emergent adverse sexual effects, associated with differences in mechanisms of action. Treatment-emergent sexual dysfunction adversely effects quality of life, and may be a factor in reducing treatment adherence. Antidepressants with a predominantly serotonergic activity, antipsychotics likely to induce hyperprolactinaemia, and mood regulators with hormonal effects are often linked to moderate or severe sexual dysfunction, including decreased libido, delayed orgasm, anorgasmia and arousal difficulties.

Psychosis and bipolar disorder can interfere with sexual function and satisfaction but many patients wish to preserve a previously satisfactory sexual activity. In many other patients, a lack of intimate relationships and chronic deterioration in mental and physical health can be accompanied by both a poor sexual life and more frequent risky sex behaviour than in the general population. Young male patients show poor compliance with long-term psychotropic drug treatments and this can adversely affect global clinical outcomes.

At present, optimised management of patients with sexual dysfunction associated with psychotropic drugs hinges on making careful but sensitive enquiries to establish whether sexual difficulties are present, and on making best use of available treatments. This.

**Keywords (10)**: antidepressant, antipsychotic, mood regulator, mental illness, depression, psychosis, bipolar disorder, sexual dysfunction, sexual health, quality of life.

**Introduction**

Psychosexual medicine and psychiatry are overlapping disciplines and there is much interest among psychiatrists in improving their theoretical knowledge and clinical skills in sexual medicine. Adverse sexual effects are frequent with commonly prescribed psychotropic drugs such as selective serotonin reuptake inhibitors (SSRIs) and prolactin-raising antipsychotics. Deterioration of libido, and arousal and orgasmic dysfunction are frequent complaints, adversely affecting quality of life. Sexual dysfunction tends to be under-reported and under-recognised and systematic enquiries are needed to assess the incidence, severity and impairment associated with untoward sexual effects of psychotropic drugs.

Recent developments in the field include recognition of the beneficial effects of a healthy sex life in patients with mental disorders, and the need to incorporate this aspect of assessment and management with routine clinical practice[[1]](#endnote-1); and greater understanding of the adverse effects of psychotropic drugs on sexual life, either through serotonergic mechanisms or induced hyperprolactinemia with some commonly prescribed antipsychotics.

**Bipolar Disorder and Sexual Dysfunction.**

 ***Influence of Bipolar disorder on Sexuality***

Bipolar disorder (BD) can involve sexual disturbances directly related to the illness phase in manic, mixed and depressive episodes. Male and female patients in manic or hypomanic episodes often experience hyper-sexuality, have an increased incidence of risky sexual behaviors, to have more couple relationships and more promiscuous behavior[[2]](#endnote-2). By contrast, in depressive episodes, reduction in sexual desire is common. Sexual dissatisfaction is associated with BD, possibly because severe mental disorders have an overall negative impact on daily life and functioning, including negative effects on sexual life and satisfaction [[3]](#endnote-3).

When differing variants of bipolar disorder are compared, sexual interest appears greater in BD type I [[4]](#endnote-4). When compared to patients with other severe mental illnesses, patients with BD tended to have more stable sexual partners and more frequent sexual intercourse than patients with schizoaffective disorder or schizophrenia [[5]](#endnote-5). When compared to females, males with BD tend to have more sexual partners, were more likely to engage in homosexual relations and were more likely to have sexual intercourse with strangers [[6]](#endnote-6). Sexual dysfunction is a common residual symptom in euthymic patients with BD, and has a significant negative impact on quality of life similar to that with residual depressive symptoms and occupational stigma[[7]](#endnote-7). Moreover, impairment in desire, excitement and ability to achieve orgasm was significantly associated with suicide plans or a feeling that life is not worth living [[8]](#endnote-8). In addition, SD has been identified as a predictor of poor medication adherence [[9]](#endnote-9).

Meta-analysis indicates a statistically significant association between the history of sexual abuse and a lifetime diagnosis of anxiety disorder, depression, eating disorders, sleep disorders and suicide attempts. Unfortunately, no longitudinal studies assessing BD were found in this field[[10]](#endnote-10) . Sexual aggression is common in youth with BD particularly in subjects with lifetime history of comorbid posttraumatic stress disorder (PTSD)[[11]](#endnote-11). Prompt identification and treatment of these youth is highly needed.

Routine enquiries about sexual life, including questions about sexual drive during manic episodes, accompanied by simple psychoeducation, is highly recommended in bipolar patients to mitigate the physical, psychic and family consequences of risky sex and unwanted sexual activities.

**Influence of the BD treatment in sexuality.**

Pharmacological management in BD involves the use of lithium, anticonvulsants, antipsychotics, antidepressants or benzodiazepines, either in monotherapy or in combination therapy, depending on the clinical characteristics of the patient and phases of the illness. One of the more common side effects is SD which has a high impact on quality of life and is rated by patients as one of the most disabling problems.

*Lithium* is one of the first-line treatments [[12]](#endnote-12), but several studies suggested some negative impact of lithium on sexual function, as it may reduce sexual thoughts and desire, worsen erectile function and decrease sexual satisfaction [[13]](#endnote-13). Approximately one-third of patients receiving lithium experience SD, which usually involves more than a single domain of sexual functioning, in both male and female patients 4. Patients were significantly less likely to experience sexual intercourse, sexual fantasies, sexual desire, pleasure and satisfaction, and 30% of patients attribute this to lithium treatment [[14]](#endnote-14). Despite this, it seems that lithium has less adverse impact in sexual function when compared with other treatments in BD [[15]](#endnote-15) and with other atypical antipsychotics [[16]](#endnote-16). Concomitant benzodiazepine prescription with lithium is associated with an increased risk of SD. SD does not appear to be associated with serum lithium levels[[17]](#endnote-17).

*Antiepileptics (AEPs)* are often associated with SD in patients with epilepsy (between 35-55% of patients)[[18]](#endnote-18) but there is limited evidence of these adverse effects in patients with BD. Valproate (VPA) and carbamazepine (CBZ) are commonly used in BD and have been associated with SD due to reduced levels of testosterone, mainly CBZ [[19]](#endnote-19). Oxcarbazepine and lamotrigine have not been associated with changes in hormonal levels and SD [[20]](#endnote-20).. Topiramate, pregabalin and gabapentin may cause SD, while oxcarbazepine, lamotrigine and levatiracetam may improve sexual functioning [[21]](#endnote-21).

Endocrine changes include an increase in follicle-stimulating hormone (FSH) and sexual hormone-binding globulin (SHBG), and a decrease in dehydroepiandrosterone sulfate (DHEAS) and free androgen index (FAI) in males with SD in comparison with normal sexual function 18 . Prolactin levels typically remain within normal limits with AEPs [[22]](#endnote-22) .

*Valproate* is an enzyme inhibitor, and is associated with endocrine disturbances including high serum testosterone, androstenedione and DHEAS concentrations. The increase in androgen levels is associated with a higher incidence of menstrual disorders, polycystic ovarian syndrome, and hyperandrogenism [[23]](#endnote-23), [[24]](#endnote-24). Decreased sexual desire and anorgasmia have been described in women with BD treated with valproate [[25]](#endnote-25). In men, valproate therapy may cause abnormalities in androgens levels, sperm motility, and erectile dysfunction [[26]](#endnote-26).

*Carbamazepine* is often associated with sexual dysfunction with reduced levels of estradiol, progesterone and testosterone, and may cause hypogonadism, amenorrhea and decreased sexual function and sexual desire 14, [[27]](#endnote-27).. CBZ may increase SHBG concentrations, leading to diminished bioactivity of testosterone and estradiol and sexual side effects such as reduced libido and erectile dysfunction but not with orgasmic dysfunction in males with epilepsy [[28]](#endnote-28) .

*Oxcarbazepine* is not usually associated with changes in hormonal levels and SD 12 but there are occasional reports of anorgasmia and retrograde ejaculation[[29]](#endnote-29),[[30]](#endnote-30). *Lamotrigine* is associated with a lower risk of SD and is not associated with sexual adverse effects in patients with BD [[31]](#endnote-31),[[32]](#endnote-32).

*Treatment strategies*

There is little evidence relating to management of SD associated with mood stabilizers. As a general approach, optimizing drug doses to the lowest effective dose, switching to alternatives, or some add-on strategies may be useful [[33]](#endnote-33).

A small randomized placebo-controlled trial suggests adjunctive aspirin (240 mg/day) may improve erectile dysfunction in patients undergoing lithium treatment [[34]](#endnote-34). There is currently no information on the potential utility of PDE5 inhibitors such as sildenafil, but it seems reasonable to consider it based on clinical experience in other patients. There is some evidence that switching from enzyme-inducing (VPA, CBZ) to non-enzyme-inducing anticonvulsant drugs (oxcarbamazepine, lamotrigine) can be beneficial[[35]](#endnote-35). In epileptic patients, switching to lamotrigine can be associated with an improvement in desire, frequency, interest, pleasure, excitement and orgasm in women, but only in the pleasure dimension in men [[36]](#endnote-36). Addition of lamotrigine to CBZ or VPA can ameliorate SD in male patients [[37]](#endnote-37).

**Psychosis and sexual dysfunction.**

**Influence of psychosis on sexuality**:

Disturbances in sexual functioning in patients with schizophrenia may arise from multiple factors, including negative symptoms (apathy, avolition and lack of motivation), depressive symptoms, consequences of prefrontal dysfunction, and adverse effects of some antipsychotics [[38]](#endnote-38). People diagnosed with psychotic disorders often have unmet needs relating to sexuality and intimacy which impact negatively on recovery and the ability to lead a fulfilling life. Psychosis tends to be a barrier to the expression of sexuality and intimacy [[39]](#endnote-39). It can be difficult to study sexuality in some cultures as open discussions about it are discouraged. However, a questionnaire study found a high frequency of SD in female patients with schizophrenia in India (70%) [[40]](#endnote-40). An investigation of SD in Chinese patients with schizophrenia found a similar frequency (70%) [[41]](#endnote-41). A recent Korean study found that sexual satisfaction was negatively correlated with age and length of illness in schizophrenic patients receiving risperidone [[42]](#endnote-42) .

Medications provoking prolonged hyperprolactinaemia may affect sexual functioning at the onset and progression of the puberty. A recent study found an increased risk of abnormal sexual maturation in female adolescents treated with paliperidone extended-release over 2 years [[43]](#endnote-43).

*Benefits of sexual life in Psychosis:*

Despite what many cliniciana believe, adequate sexual expression can improve overall well-being, restore confidence and dignity, and allow the individual to overcome problems such as negative symptoms, social disengagement and stigma. Patients with a partner and active sex life differ little from the general population in their assessment of the beneficial attributes of sexuality.

A study comparing sexual and emotional life in 100 patients with psychosis and controls found that the affective environment surrounding the sexual approach includes not only coitus but also kisses, caresses and massages [[44]](#endnote-44). Sexual activity improved self-esteem, feelings of acceptance and additionally the sleep, anxiety and mood in patients, in a similar way as in healthy controls. Many patients suffered from antipsychotic-related sexual dysfunction and many of them were dissatisfied with their sexual life. Only few patients had regular sexual intercourse, but sexual and emotional relationships were considered highly relevant in at least 65% of patients with schizophrenia, who were more concerned about affection and companionship than about physical pleasure. The presence of delusions and hallucinations was not necessarily accompanied by the end of sexual life and pleasure. Only 13% were able to maintain a steady partner. and only 20% had coital activity, but more than half of patients believed that sex life was still important to them. Masturbation was often the only possibility for expressing sexual impulses and achieving sexual pleasure.

*Risky sexual behaviour*

Many patients use prostitution as the sole way for obtaining sexual pleasure (twice as common in the male general population), and put their health at risk through sexually transmitted diseases including HIV by not using condoms[[45]](#endnote-45).. An investigation comprising 546 patients in Spain which involved interviews about lifetime sexual behaviour including homosexual relations, HIV carriers and individuals suffering from AIDS, and sex workers, found that 87.7% of patients had sexual intercourse but many of them had potentially ‘risky sex’: including homosexual relations (10%), and sex with a HIV-positive partner (8%). Approximately one-third of patients (and 50% of male patients) had paid for sex (29% had never used condoms). Overall 49.79% of the total sample and 46% with HIV-positive partners reported never using condoms. Patients had a higher percentage of homosexual contacts and lower rates of condom use, even in higher risk situations, than in the general population. These findings emphasise the need to systematically evaluate potentially risky behaviours, and provide education designed to promote safer sexual practices. A genetic factor common to schizophrenia and HIV infection has recently been associated with risky sexual behaviour [[46]](#endnote-46). Multidisciplinary consensus has been developed to facilitate the detection and evaluation of risky sexual behavior in psychiatric patients [[47]](#endnote-47),[[48]](#endnote-48).

The presence of psychotic symptoms should not be incompatible with healthy sexual relationships. Whilst not all patients attach a similar importance to sexual life, many young patients who previously had satisfactory sexual relationships are not prepared to lose this aspect of interpersonal functioning after diagnosis and starting pharmacological treatment. Many young male patients who drop-out from continued antipsychotic medication cite the onset of sexual dysfunction, especially erectile and orgasm problems in the short term and loss of desire over the longer term, as reasons for stopping treatment

**Antipsychotics and Sexual Dysfunction:**

*Frequency and symptoms.*

SD is common during short- and long-term treatment with APs, and associated with a considerable impact in adult and adolescent patients [[49]](#endnote-49). Depending on the measurement method, it affects between 38-86% of patients[[50]](#endnote-50),[[51]](#endnote-51),[[52]](#endnote-52) ,[[53]](#endnote-53) including remitted patients [[54]](#endnote-54) and patients experiencing first episodes of schizophrenia [[55]](#endnote-55), with higher frequencies if specific interviews and/or questionnaires are used.

Symptoms include decreased desire, difficulties in sexual arousal, penile erection, vaginal lubrication, and orgasm, and reduced sexual satisfaction. The most frequent symptoms in clinical practice include orgasmic and erectile difficulties in the short term and decreased desire in longer term. The most frequent pattern in male patients is the combination of lowered libido with erectile dysfunction which is usually unacceptable [[56]](#endnote-56),[[57]](#endnote-57) symptoms appearing a few days after starting treatment: some patients wonder whether SD represents an additional symptom of psychosis 54,[[58]](#endnote-58).

*Aetiological factors*

Several factors are important, including blockade of dopaminergic activity, hyperprolactinemia (HPRL), and α1-receptor blockade [[59]](#endnote-59). HPRL and its related hypogonadism seems to be strongly implicated in SD[[60]](#endnote-60): it is often accompanied by infertility, amenorrhea, gynecomastia and galactorrhoea [[61]](#endnote-61),[[62]](#endnote-62) . Higher plasma prolactin levels are associated with higher rates of erectile and ejaculatory dysfunction in patients with first episodes of schizophrenia 56 . The importance of hyperprolactinaemia in sexual and physical health in patients with schizophrenia has been emphasised[[63]](#endnote-63).

Dopamine-blocking and hyperprolactinaemia-inducing antipsychotics such as haloperidol, risperidone, paliperidone and amisulpride are more likely to be associated with decreased libido and/or arousal difficulties. By contrast, aripiprazole, quetiapine, olanzapine and ziprasidone have been linked to low rates of SD (16-27%) in open studies [[64]](#endnote-64),[[65]](#endnote-65) and in meta-analysis [[66]](#endnote-66). A lower risk for SD and prolactin elevation was seen with aripiprazole once-monthly when compared to long-acting paliperidone, this difference being associated with a greater improvement in quality of life [[67]](#endnote-67).

Erectile dysfunction with antipsychotic drugs may be specifically related to endothelial dysfunction linked to decreased nitric oxide (NO) production from inhibition of endothelial NO synthetase [[68]](#endnote-68) and vasoconstriction from any beta 2-adrenergic effects [[69]](#endnote-69).

*Under-reporting of sexual dysfunction*

Sexual dysfunction tends to be under-estimated, for several reasons including lack of confidence in health providers, shame, cultural difficulties and lack of interest of psychiatrists. The extent of sub-optimal communication about sexuality in patients with a psychotic disorder assessed within routine clinical practice is considerable, affecting 50-73% of patients with SD 54. Failure of adequate discussion is more common in female patients, of whom 80% had not discussed sexual function with their mental health care providers[[70]](#endnote-70). Cross-cultural factors are important, as a recent survey conducted in India found that the majority (73.2%) of professionals did not enquire about SDs in routine clinical settings, many admitting that they lacked expertise [[71]](#endnote-71).

In addition to sub-optimal communication about sexuality with health professionals, many patients with severe mental illness have received little i sexual education, and have insufficient time allocated for the discussion of emotional relationships, sexual expression, and avoidance of riskier sexual activity.

*Assessment of SD*

Reliable comparisons between antipsychotics are difficult due to the wide variety of assessment techniques[[72]](#endnote-72). Only 6 questionnaires have been validated to measure SD in psychotic patients: following a systematic review of psychometric and other properties, only the ASFQ [[73]](#endnote-73), CSFQ-14[[74]](#endnote-74), and PRSexDQ-SALSEX [[75]](#endnote-75) were found to address all stages of sexual functioning, so makings these questionnaires preferable for clinical practice and research [[76]](#endnote-76).

*Influence in poor compliance*

SD does not typically resolve spontaneously, but tends to persist for prolonger periods. Unfortunately, sexual difficulties represent one of the areas of practice with the most unmet needs.

Young men with psychosis consider that impairment of sexual function is the most important adverse effect of antipsychotic medication, (followed by extrapyramidal symptoms, weight gain, and sedation) in provoking a lack of treatment adherence [[77]](#endnote-77),[[78]](#endnote-78). Poor treatment compliance was found in both male (36%) and female (20%) patients, when using a specific questionnaire (PRSexDQ-SALSEX), when measuring either previous withdrawals or probable future drop-outs from antipsychotic treatment 54,72. Although female patients may be less worried than male patients about sexual difficulties, younger women are more likely to experience hormone-related side effects than are older women.

In a USA-based nationwide survey of patients with schizophrenia, side effects relating to prolactin and other endocrine disturbance were significantly related to lower levels of treatment adherence [[79]](#endnote-79). Again, cross-cultural factors are probably important, as in investigation in India, using the PRSEXDQ-SALSEX questionnaire, found that most patients (91.7%) reported good to fair tolerance of any sexual side-effects 73 .

*Management strategies*

Decreasing the dosage, switching the antipsychotic, ‘drug holidays’, add-on strategies with a dopamine agonist, addition of aripiprazole, or use of a phosphodiesterase-5 inhibitor have all shown some beneficial effects.

However, reducing antipsychotic dosage may sometimes engender relapse, so switching strategies to another antipsychotic medication may be preferable in managing many patients with treatment-emergent SD. Switching to aripiprazole was found successful in different studies, improving delayed ejaculation/orgasm in some naturalistic settings [[80]](#endnote-80), normalizing prolactin levels [[81]](#endnote-81) and maintaining the clinical efficacy of previous treatment [[82]](#endnote-82). A careful switching protocol is needed to avoid the reappearance of troublesome psychotic symptoms[[83]](#endnote-83) [[84]](#endnote-84). Adjunctive aripiprazole reduces antipsychotic-Induced hyperprolactinaemia [[85]](#endnote-85) and SD [[86]](#endnote-86). When differing strategies were compared, switching to aripiprazole monotherapy was found superior to the addition of aripiprazole in patients with schizophrenia. Positive results have also been reported, after switching to quetiapine[[87]](#endnote-87) or ziprasidone[[88]](#endnote-88) in 3 to 6-month prospective studies.

A Cochrane Review of randomized controlled trials involving patients with schizophrenia and SD found that sildenafil can improved erectile function and general sexual satisfaction when compared with placebo, and that switching to olanzapine and quetiapine may improve sexual functioning in male and female patients [[89]](#endnote-89).

A recent multidisciplinary consensus process on management of this problem concluded that switching an antipsychotic to a non-hyperprolactinaemic one is probably the best way to ameliorate APS-related sexual dysfunction, with aripiprazole being the first-line option[[90]](#endnote-90). Systematic screening for SD is strongly recommended [[91]](#endnote-91) . Psychosocial interventions, i.e. psychoeducation, supportive psychotherapy and psychiatric rehabilitation also play a crucial role in the management of SD, with the restoration of sexual function as an achievable recovery target 39.

There is a need for further research to establish optimal treatment approaches in the management of SD associated with psychosis, but at present drugs with a lower frequency of sexual dysfunction should be considered as potential first-line options in patients with an active and satisfactory sexual life. Certain medications, with the effectiveness of traditional antipsychotics but with a lower potential for causing sexual problems are available, and use of these medications may improve sexual functioning, quality of life, and treatment adherence.

**Depression and sexual function**

Sexual problems are common in all societies, being more frequent among older individuals and in people with chronic medical conditions [[92]](#endnote-92),[[93]](#endnote-93) The Global Survey of Sexual Attitudes and Behavior, of over 27,000 men and women aged 40-80 years, identified ‘early ejaculation’ as the most common sexual dysfunction, affecting 14% of men, with ‘erectile difficulties’ having a prevalence of 10%: all sexual dysfunctions in men being more prevalent with older age [[94]](#endnote-94). The Men’s Attitudes to Life Events and Sexuality Study, among individuals aged 20-75 years, found a 16% prevalence of ‘erectile dysfunction’, the proportion being higher in older respondents and in men with depression, cardiovascular disease or hypertension [[95]](#endnote-95). The Women’s International Study of Health and Sexuality, in over 4,500 individuals aged 20-70 years, found ‘hypoactive sexual desire disorder’ to have a prevalence ranging between 16-46%, in pre-menopausal to surgically post-menopausal women [[96]](#endnote-96). The Third National Survey of Sexual Attitudes and Lifestyles, in over 15,000 individuals aged 16-74 years, found 41.6% of men and 51.2% of women reported problems in sexual response, though self-reported distress about sexual life was much less frequent (9.9% and 10.9%, respectively): after adjustment for potential confounders, the presence of depressive symptoms was the only specific condition associated with low sexual satisfaction [[97]](#endnote-97),[[98]](#endnote-98).

Depressive symptoms are strongly associated with sexual difficulties and dissatisfaction and screening for depression has been recommended in patients with sexual dysfunction and chronic illness 94. Conversely examination of the bidirectional association between depression and sexual dysfunction suggests depressed patients should be screened for sexual dysfunction [[99]](#endnote-99). A longitudinal study found the prevalence of sexual problems in depressed individuals to be approximately twice the prevalence in controls (50% vs. 24%)[[100]](#endnote-100). Recurrent depressive disorder seems especially associated with sexual problems: for example, the United States Study of Women’s Health Across the Nation found that women with recurrent episodes (but not those who experienced only a single episode) were more likely to report problems in sexual arousal, physical pleasure and emotional satisfaction, when compared to controls[[101]](#endnote-101). The Netherlands Mental Health Survey and Incidence Survey-2 found the presence of 12-month mood disorders (and also the presence of an anxiety disorder or a substance use disorder) was associated with a significantly lower likelihood of reported sexual satisfaction [[102]](#endnote-102).

Depression affects mood, energy, interest, capacity for pleasure, self-confidence and self-esteem, so it should be expected that depression would lower sexual interest and satisfaction: and this effect seems more marked in younger patients[[103]](#endnote-103) . Depressive symptoms commonly coexist with anxiety symptoms, which are also associated with reported sexual difficulties and dissatisfaction 105,[[104]](#endnote-104),[[105]](#endnote-105) and with obsessive-compulsive symptoms, themselves associated with loss of sexual pleasure and sexual dissatisfaction [[106]](#endnote-106),[[107]](#endnote-107). But depression can exert adverse effects on all aspects of the sexual response, including the ability to achieve and maintain penile erection, to attain adequate vaginal lubrication, and to achieve ejaculation or orgasm[[108]](#endnote-108). Most antidepressants can exert unwanted effects on sexual function and satisfaction, but the adverse effects of depression itself (and of comorbid mental or physical disorders and concomitant medication) are often overlooked when considering the management of patients with sexual dysfunction associated with antidepressant treatment.

**Assessing sexual difficulties in depressed patients**

Patients and health professionals can feel embarrassed to mention and discuss sexual symptoms, and consultation 101,[[109]](#endnote-109)and recognition rates in primary medical care are low [[110]](#endnote-110). Unfortunately, reliance on spontaneous reports of sexual adverse events leads to a substantial under-estimate of sexual problems [[111]](#endnote-111),[[112]](#endnote-112). Screening and severity questionnaires can facilitate recognition and assessment [[113]](#endnote-113)but cannot fully substitute for a comprehensive but sensitive assessment. The Arizona Sexual Experiences Scale, the Changes in Sexual Functioning Questionnaire, the Psychotropic-Related Sexual Dysfunction Questionnaire and the Sex Effects Scale all have adequate key psychometric properties (validity, reliability and sensitivity to change) and have been recommended for assessing sexual function and satisfaction before and during antidepressant treatment 116 .

Risk factors for developing sexual dysfunction during antidepressant treatment include male gender, older age, lower academic achievement, absence of full-time employment, physical ill-health, multiple drug treatment, and troubled interpersonal relationships. Inter-individual variation in pharmacokinetic parameters may be important, as ‘poor metabolizer’ status for cytochrome P450 2D6 contributes to sexual dysfunction with paroxetine [[114]](#endnote-114),[[115]](#endnote-115) as does a genetic variation in P-glycoprotein which affects transfer of paroxetine across the blood-brain barrier [[116]](#endnote-116).

**Worsening of sexual function during antidepressant treatment**

It has proved difficult to accurately identify the incidence of ‘treatment-emergent’ sexual dysfunction (encompassing both the worsening of pre-existing problems and the development of new sexual difficulties in previously untroubled patients) during antidepressant treatment. Two international studies of the prevalence of sexual dysfunction in depressed patients undergoing treatment with either an SSRI or serotonin-noradrenaline reuptake inhibitor (SNRI), which both accounted for self-reported sexual problems before starting treatment and the potential adverse effects of concomitant medication, found that 27-65% of female and 26-57% of male patients experienced either a worsening of pre-existing difficulties or the emergence of new sexual difficulties in the early weeks of treatment [[117]](#endnote-117),[[118]](#endnote-118).

An early meta-analysis which included studies with differing designs (incorporating open-label, double-blind, cross-sectional and retrospective investigations) found that ‘treatment-emergent sexual dysfunction’ was no more common with the antidepressants agomelatine, amineptine, bupropion, moclobemide, mirtazapine or nefazodone than with placebo: all other antidepressants were significantly more likely than placebo to be associated with ‘sexual dysfunction’ (as a unitary category), and nearly all were significantly more likely than placebo to be associated with dysfunction in each phase of the sexual response [[119]](#endnote-119). Bupropion appears associated with a significantly lower rate of treatment-emergent sexual dysfunction than with the SSRIs escitalopram, fluoxetine, paroxetine or sertraline[[120]](#endnote-120): which may reflect the predominantly noradrenergic-dopaminergic mechanism of action of bupropion [[121]](#endnote-121). A second meta-analysis, of 58 randomised controlled trials and 5 observational studies, found only minor differences between most antidepressants, although there were relative disadvantages for paroxetine and venlafaxine, and relative advantages for bupropion [[122]](#endnote-122). A systematic review of the relative efficacy and tolerability of mirtazapine and comparator antidepressants found mirtazapine to be less likely than other antidepressants to cause adverse sexual effects[[123]](#endnote-123) :possibly reflecting its antagonist effects at alpha-2 adrenergic receptors and at 5-HT2C receptors [[124]](#endnote-124).

Some novel antidepressants may have a relatively low propensity for adverse effects on sexual function [[125]](#endnote-125). Randomised controlled trials with agomelatine suggest it has fewer adverse effects on sexual functioning than some other antidepressants, which is probably due to its antagonist effects at the 5-HT2C receptor, rather than the agonist effects at melatonin receptors [[126]](#endnote-126),[[127]](#endnote-127),[[128]](#endnote-128),[[129]](#endnote-129) although the absence of effects on nitrergic relaxation of corpus cavernosum smooth muscle may also be relevant [[130]](#endnote-130). Vilazodone appears to have a low incidence of spontaneously reported adverse effects on sexual function, which may be related to partial agonist effects at the 5-HT1A receptor: it does not differ from placebo in improvement of sexual function during acute treatment of major depressive episodes, and the ‘number needed to harm’ for sexual adverse effects has been estimated as 7 in men, and 23 in women [[131]](#endnote-131),[[132]](#endnote-132),[[133]](#endnote-133) . Treatment with the novel ‘multimodal’ antidepressant vortioxetine is associated with a low incidence of reported adverse effects on sexual function in men (3-5%) and women (1-2%) which may relate to its antagonist effects at the 5-HT3 receptor, and to indirect effects in increasing the availability of dopamine and noradrenaline [[134]](#endnote-134) paper 2015 in press?? Please confirm.

**Improvement in sexual function during antidepressant treatment**

Not all sexual effects of antidepressants are unwanted in all patients. Although behavioural approaches to premature ejaculation are effective in most patients [[135]](#endnote-135), many men (including those without depression) troubled by persistent problems can benefit from treatment with either the tricyclic antidepressant clomipramine or SSRIs [[136]](#endnote-136). The short-acting SSRI dapoxetine is efficacious in treating premature ejaculation, with either daily dosing or ‘on demand’ dosage [[137]](#endnote-137): it has similar efficacy to paroxetine [[138]](#endnote-138) though may be less well tolerated [[139]](#endnote-139). A systematic review of randomized placebo-controlled trials with trazodone (which has partial agonist effects at 5-HT1A receptors and antagonist effects at 5-HT2A and α-1 adrenergic receptors) indicates that it can be efficacious in reducing ‘psychogenic’ erectile dysfunction, when prescribed at higher daily dosage (150-200 mg) [[140]](#endnote-140).

Many patients experience treatment-emergent sexual dysfunction whilst taking an antidepressant 120,121, but in others the reduction of depressive symptoms through successful treatment can be accompanied by reported improvements in sexual desire and satisfaction [[141]](#endnote-141),[[142]](#endnote-142). Improvement in sexual function appears more common among patients who respond to antidepressant treatment [[143]](#endnote-143). The proportion of patients who stop treatment because of sexual problems is not established [[144]](#endnote-144),[[145]](#endnote-145), and neither is the time-course of sexual dysfunction in patients who continue with antidepressant treatment [[146]](#endnote-146).

**Managing sexual dysfunction in depressed patients**

Many interventions have been proposed for managing patients who report sexual dysfunction associated with antidepressants, but there is limited randomised controlled data evaluating the effectiveness and acceptability of psychological and pharmacological interventions [[147]](#endnote-147), and no approach can be considered ‘ideal’ [[148]](#endnote-148),[[149]](#endnote-149).

When patients are concerned to preserve usual sexual functioning, choosing an antidepressant thought to have fewer adverse effects is reasonable, when other considerations allow. However, some of these antidepressants have other side effects, limited availability, or questionable efficacy. Sexual side effects of some antidepressants may be dose-related, so reduction in daily dosage is commonly adopted as a first-line approach to management[[150]](#endnote-150) . However, dosage reduction may contribute to depressive symptom relapse, and should only be considered when patients have achieved full remission, and after satisfactory completion of continuation treatment. Regular brief interruptions of treatment (so-called ‘drug holidays’) have been proposed [[151]](#endnote-151) but sexual function will improve in only a proportion of patients and with only some antidepressants: depressive symptoms may worsen, and troublesome discontinuation symptoms can emerge, making this approach potentially hazardous 151.

Many adjuvant interventions have been proposed for relieving sexual dysfunction associated with antidepressants but few have been subjected to rigorous evaluation. Randomised placebo-controlled trials provide evidence of possible efficacy for bupropion and olanzapine [[152]](#endnote-152), testosterone gel [[153]](#endnote-153), and the phosphodiesterase-5 inhibitors sildenafil (both in male and female patients [[154]](#endnote-154),[[155]](#endnote-155)) and tadalafil [[156]](#endnote-156). Comparative studies are rare, but a placebo-controlled study found no evidence of efficacy for augmentation with mirtazapine or yohimbine in female patients [[157]](#endnote-157). Augmentation of antidepressants with aripiprazole can improve sexual interest and satisfaction in depressed women, independent of an improvement in depressive symptoms [[158]](#endnote-158). Switching from one antidepressant drug to another seems reasonable and is commonly adopted 153, but placebo-controlled evidence of efficacy rests on a single study of switching from sertraline to (now withdrawn) nefazodone 150 . Switching from one drug to another may lead to discontinuation symptoms, and the replacement drug may prove less effective in controlling depressive symptoms 155 . A single study found regular exercise prior to sexual activity improved sexual desire and global sexual functioning in depressed women taking antidepressants [[159]](#endnote-159).

Nitric oxide (NO) is involved in the physiology of the male and female sexual response. In men, nitric oxide in the corpus cavernosum of the penis binds to guanylate cyclase receptors, which results in increased levels of cyclic guanosine monophosphate (cGMP), leading to smooth muscle relaxation (vasodilation) in the intimal cushions of the helicine arteries, which in turn leads to vasodilation, increased blood flow into the spongy tissue of the penis, and subsequent erection. The adverse effect of escitalopram on erectile function in rats may be due to reduced nitric oxide bioavailability mediated by increased nicotinamide adenine dinucleotide phosphate oxidase activity and reactive oxygen species production [[160]](#endnote-160). Sildenafil, tadalafil and vardenafil are potent and selective inhibitors of cGMP-specific phosphodiesterase type 5 (PDE-5), which is responsible for degradation of cGMP in the corpus cavernosum. The molecular structure of sildenafil resembles that of cGMP, and sildenafil acts as a competitive binding agent of PDE-5 in the corpus cavernosum, resulting in more cGMP and facilitation of erection [[161]](#endnote-161). In women, the role of NO and its interplay with oestrogen is less well understood, but the PDE-5 inhibitor enhancement of nitric oxide–cGMP in non-adrenergic-non-cholinergic signalling for women seems similar to the effect in men; and NO release results in vasodilatation in clitoral and vaginal tissues [[162]](#endnote-162).

A series of randomised placebo-controlled trials demonstrate that PDE-5 inhibitors are efficacious in resolving sexual dysfunction associated with antidepressants 157,158,159. Studies of men with erectile dysfunction and depressive symptoms (but not undergoing antidepressant treatment), also show that prescription of PDE-5 inhibitors is often accompanied by a reduction in depressive symptoms, enhanced quality of life, and improved interpersonal relationships [[163]](#endnote-163),[[164]](#endnote-164),[[165]](#endnote-165). Furthermore, preclinical studies suggest nitric oxide activity is an important vulnerability factor in the Flinders rat depressive phenotype [[166]](#endnote-166); that passage of PDE-5 inhibitors across the ‘blood-brain barrier’ can occur [[167]](#endnote-167); that sildenafil has antidepressant-like effects after central muscarinic receptor blockade [[168]](#endnote-168); and that sildenafil administration can reverse reduced social interactive behaviour 170 . PDE-5 inhibitors are often helpful in when managing patients with sexual dysfunction associated with antidepressants, but side effects such as headache, dyspepsia, and visual disturbances, and the need for cautious use in patients with cardiovascular disease are all potential limitations.

**Conclusion**

Mental illness and many psychotropic drugs impair sexual function and reduce sexual satisfaction. Systematic enquiries in all patients about previous and current sexual life are needed to assess potential sexual dysfunction, and to manage it with the aims of preserving quality of life, maintaining emotional experiences and continuing partner relationships. Treatments with fewer adverse sexual effects should be considered as potential first-line options in patients interested in maintaining a sexual life. Managing treatment-emergent side effects adequately is crucial to facilitate compliance and achieve the best possible outcomes.

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