

Editorial

Antidepressant drugs and sexual dysfunction*

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**Summary**

Depressive symptoms and depressive illness are associated with impairments in sexual function and satisfaction but the findings of randomised placebo-controlled trials demonstrate that antidepressant drugs can be associated with the development or worsening of sexual dysfunction. Sexual difficulties during antidepressant treatment often resolve as depression lifts but may persist over long periods, and can reduce self-esteem and affect mood and relationships adversely. Sexual dysfunction during antidepressant treatment is typically associated with many possible causes, but the risk of dysfunction varies with differing

antidepressants, and should be considered when selecting an antidepressant.

Declaration of interest

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There is a close relationship between the presence of depressive symptoms and reported sexual difficulties and dissatisfaction. Systematic reviews of the epidemiology of sexual difficulties, dysfunction and dissatisfaction indicate that sexual problems are common in men and women in all societies, and they are more frequent in older individuals and among those with chronic medical conditions, including depression.^{1,2} Recognising the strong association between sexual difficulties and the presence of depressive symptoms, an international consensus statement on sexual dysfunction in chronic illness recommends screening for depression.³ Given its effects on mood, energy, interests and self-esteem, it should be expected that depression will lower sexual interest and satisfaction; and this is the case, more so in younger patients.⁴ But depression may also exert adverse effects on other aspects of the sexual response including the ability to achieve and maintain penile erection or attain adequate vaginal moistening, ejaculation or orgasm, and distressing hypersexuality has also been reported.⁵ When considering the relative risks for and management of sexual dysfunction associated with antidepressant treatment, the adverse effects of depression itself and of any coexisting physical illness can be easy to overlook.

Relative incidence of sexual dysfunction during antidepressant treatment

Antidepressants have differing effects on sexual function, presumably due to variations in their pharmacological properties. Selective serotonin reuptake inhibitors may exert untoward effects on sexual functioning both through central (neurotransmitter)⁶ and peripheral (neurotransmitter and vascular)⁷ effects. An early meta-analysis of studies with differing methodologies (including open-label, double-blind, cross-sectional, and retrospective investigations) suggests that sexual dysfunction is no more common with agomelatine, amineptine, bupropion, moclobemide, mirtazapine or nefazodone than it is with placebo, in contrast

to the situation with other antidepressants.⁸ A more recent meta-analysis of randomised controlled trials indicates that bupropion is associated with a lower rate of treatment-emergent sexual dysfunction than is seen with escitalopram, fluoxetine, paroxetine or sertraline;⁹ this is possibly due to the predominantly noradrenergic–dopaminergic mechanism of action of bupropion. A systematic review suggests mirtazapine is less likely than other antidepressants to cause adverse sexual effects, and this is probably due to its antagonist effects on the 5-HT_{2C} receptor.¹⁰ Randomised controlled trials with agomelatine suggest it has fewer adverse effects on sexual functioning than other antidepressants,¹¹ which is more likely to be as a result of its antagonist effects on the 5-HT_{2C} receptor rather than the agonist effects at melatonin receptors.

Assessing sexual functioning in patients with depression

Patients and health professionals alike can find it difficult to mention and discuss sexual symptoms, and reliance on spontaneous reporting of difficulties leads to a substantial underestimate of the prevalence of sexual problems.¹² Comprehensive assessment of a patient with depression reporting sexual difficulties while undergoing antidepressant treatment may be time-consuming, but can be facilitated through the use of screening or severity questionnaires, such as the Arizona Sexual Experiences Scale, Changes in Sexual Functioning Questionnaire, Psychotropic-Related Sexual Dysfunction Questionnaire and the Sex Effects Scale, although these cannot fully substitute for a sensitive but comprehensive interview.¹² Scales such as these have adequate psychometric properties (including validity, reliability and sensitivity to change) and so can be used to monitor sexual function and satisfaction prior to and during antidepressant treatment. There are many risk factors for development of sexual dysfunction (such as male gender, older age, lower academic achievement, lack of full-time employment, physical ill health, multiple drug treatment, excess alcohol consumption and troubled interpersonal relationships): but not all of these are amenable to intervention.

Improvement and deterioration of sexual function during antidepressant treatment

Reduction of depressive symptoms through successful antidepressant treatment can be accompanied by reported improvements in

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sexual desire and satisfaction.¹³ Many men troubled by persistent premature ejaculation can derive benefits from treatment with clomipramine or selective serotonin reuptake inhibitors, on either a daily or 'as required' basis.¹⁴ However, antidepressant treatment is also associated with the worsening of pre-existing sexual dysfunction, and with the development of new sexual difficulties in previously untroubled patients. Incidence estimates vary widely, depending on the methodology used, but in excess of 45% of patients with depression may experience 'treatment-emergent sexual dysfunction' associated with antidepressant drugs.¹⁵ Unfortunately, the long-term course of sexual dysfunction associated with antidepressant treatment is uncertain.

Management of sexual dysfunction in depression

The presence of antidepressant treatment-emergent sexual dysfunction can significantly reduce quality of life and self-esteem, and impose burdens on interpersonal relationships, over and above those associated with depression.⁵ Sexual dysfunction may also cause some patients to stop treatment, although the evidence for this is sparse. Many strategies have been proposed for managing patients troubled by sexual dysfunction associated with antidepressant drugs, but the number of randomised placebo-controlled trials is limited, and there is an absence of randomised controlled data evaluating the effect of psychological interventions.¹⁶

Choosing an antidepressant from the list of those regarded as having fewer adverse effects on sexual functioning is reasonable, if patients are concerned to preserve sexual functioning and when other considerations allow; but some of these antidepressants have other bothersome side-effects, limited availability or questionable efficacy. A reduction in daily dosage is a commonly adopted first-line approach to management¹⁷ but this should be undertaken cautiously and preferably in patients who have successfully completed continuation treatment. 'Drug holidays' (with brief interruptions of treatment) have been adopted with some antidepressants¹⁷ but only a proportion of patients describe improvements in sexual function; depressive symptoms tend to worsen and discontinuation symptoms can be troublesome.

Many compounds have been advocated for relieving sexual dysfunction associated with antidepressant drug treatment, although relatively few have been subject to rigorous evaluation.¹⁵ Randomised placebo-controlled trials indicate efficacy for bupropion, buspirone, olanzapine, testosterone gel¹⁸ and the phosphodiesterase-5 inhibitors sildenafil (in male and female patients¹⁹) and tadalafil (in male patients²⁰). Although switching from one antidepressant to another seems reasonable and is a commonly adopted practice,¹⁷ placebo-controlled evidence of efficacy for this approach rests on a study of switching from sertraline to nefazodone (which is no longer widely available).¹⁶

Future and current practice

Coming years may see the adoption of laboratory approaches to identifying patient subgroups at increased risk of developing sexual side-effects of antidepressant treatment, through knowledge of genetic polymorphisms or other biological markers. Also, treatment options may be widened through the advent of new treatments with a lower risk of causing sexual problems. For the time being, management rests largely on sensitive enquiries to establish whether sexual difficulties are present; choosing antidepressants with a lower propensity to worsen sexual dysfunction, when other considerations allow; carefully reducing antidepressant dosage, when this is feasible; and in gaining greater

familiarity with the potential benefits and drawbacks of adjuvant treatments.

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