

Antidepressant induced sexual dysfunction Part 2: assessment and management

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Abstract

Sexual dysfunction is a common side effect of treatment with antidepressants, particularly those with a predominantly serotonergic mechanism of action. Although there has been an increasing awareness of the problem in recent years, it is still probably true to say that sexual side effects often go undetected. Antidepressant induced sexual dysfunction has significant implications for a patient's quality of life and that of their family unit. The issue cannot be ignored because it is likely to impact on a patient's sense of wellbeing, their compliance with medication and ultimately the prognosis of their illness. This review is presented in two parts. The first part focused on the prevalence of antidepressant induced sexual dysfunction and its clinical presentation both generally and in the case of individual classes of antidepressants. This second part focuses on the assessment and management of the problem. The aim of this review is to improve overall awareness of sexual side effects and to suggest a rational approach to their assessment and management. It is not intended to be a detailed exploration of underlying causative mechanisms and receptor neurochemistry.

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Introduction

The management of antidepressant induced sexual dysfunction (AISD) can be difficult and strategies aimed at tackling the problem have been largely unsatisfactory. It is only fairly recently with the advent of a number of newer antidepressants that are less associated with sexual dysfunction that viable treatment options have become available. Nevertheless, there remain a significant number of patients for whom these agents are either unavailable or inappropriate, and highly serotonergic antidepressants are still amongst the most commonly prescribed drugs for depression and anxiety disorders. AISD is significant problem associated with serotonergic agents, but a paucity of

clinical trial data makes it difficult to formulate an evidence-based approach to the management of sexual side effects.¹

This discussion of the management of AISD aims to provide two guidelines. The first broadly outlines an approach to the detection and assessment of the problem. The second describes a number of potential management strategies and attempts to combine these into a rational approach to the management of AISD.

Detection, screening and assessment

The sensitive nature of sexual problems makes patients reluctant to report them spontaneously to their clinicians and it is probably also true that clinicians avoid asking questions about sexual side effects for similar reasons. Unfortunately, the rate at which sexual dysfunction is reported varies significantly depending on the method of data collection that is used.^{1,2} The lowest prevalence rates are found with spontaneous self-reporting and higher rates result when confidential questionnaires are used. The highest rates of sexual dysfunction are reported when people are questioned directly about their symptoms. This has two important implications. Firstly, it is not surprising that epidemiological estimates of the prevalence of sexual problems vary widely. Secondly, if clinicians rely on their patients to report sexual side effects spontaneously and do not actively screen for AISD then

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the problem is unlikely to be addressed. The presence of sexual difficulties must be specifically inquired after. The proper management of AISD begins with the detection of the problem in the first instance and a thorough assessment of it in the second.

Detection and screening

It is important to ask direct questions about the presence of sexual dysfunction. However, it is possible to overcome some of the barriers to the detection of sexual side effects by using less intrusive approaches.³ It may be useful to normalise the issue for the patient. This can be done by initially broaching the subject with a discussion of the frequency of sexual disorders in the general population or that associated with specific treatments. Another strategy is to simply provide basic psycho-education on the subject of sexual wellbeing and dysfunction. If the discussion takes place as a normal part of the psychiatric interview and refers generally to sexual activity rather than specific details of sexual behaviour then it is unlikely that the patient will view the questions as intrusive.

The use of a screening tool to identify possible sexual difficulties that may require further discussion can also serve as an introduction to the topic. Such a tool should be brief, non-intrusive, gender specific and identify which phase of the sexual response cycle is involved. It should also be able to separate illness from the effects of medication and monitor change over time.³ The Arizona Sexual Experience Scale is a wide-ranging five-item scale that meets most of these criteria and is quick to administer.⁴ It is, of course, good clinical practice to obtain baseline measures of sexual functioning whenever a diagnosis of depression or anxiety is made or an antidepressant medication is likely to be prescribed. This could involve the use of a rating scale or simply a thorough, well-documented clinical assessment both at baseline and after treatment has been commenced.

Assessment

Once it has been ascertained that sexual dysfunction is indeed present then further assessment should be considerably more detailed. The outline in Figure 1 illustrates an ideal approach to the assessment of AISD.³ It is acknowledged that such a thorough assessment may not always be practical or even appropriate. If a thorough sexual history has been taken before initiating antidepressant treatment then the majority of the flow diagram would be unnecessary.

Any evaluation of sexual dysfunction requires an understanding of normal sexual functioning and the human sexual response cycle. An assessment should identify not only the specific sexual symptoms, but also which phase or phases of the sexual response cycle are involved. It is also important to ascertain whether the sexual symptoms meet diagnostic criteria for a sexual disorder as described in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV).⁵ Each disorder should be sub-typed as lifelong or acquired and as generalised or situational.

It is obviously also important to assess pre-morbid and life-long sexual functioning compared with the current presentation. A person's subjective sense of sexual satisfaction is an important aspect of sexual functioning that is often overlooked and is not accounted for in the DSM-IV.³ Sexual satisfaction may be affected by diminished function in a specific phase of the sexual response cycle or by the global decrease in pleasure that is associated with depression and its treatment. Poor overall sexual satisfaction

is a common complaint of people with AISD.

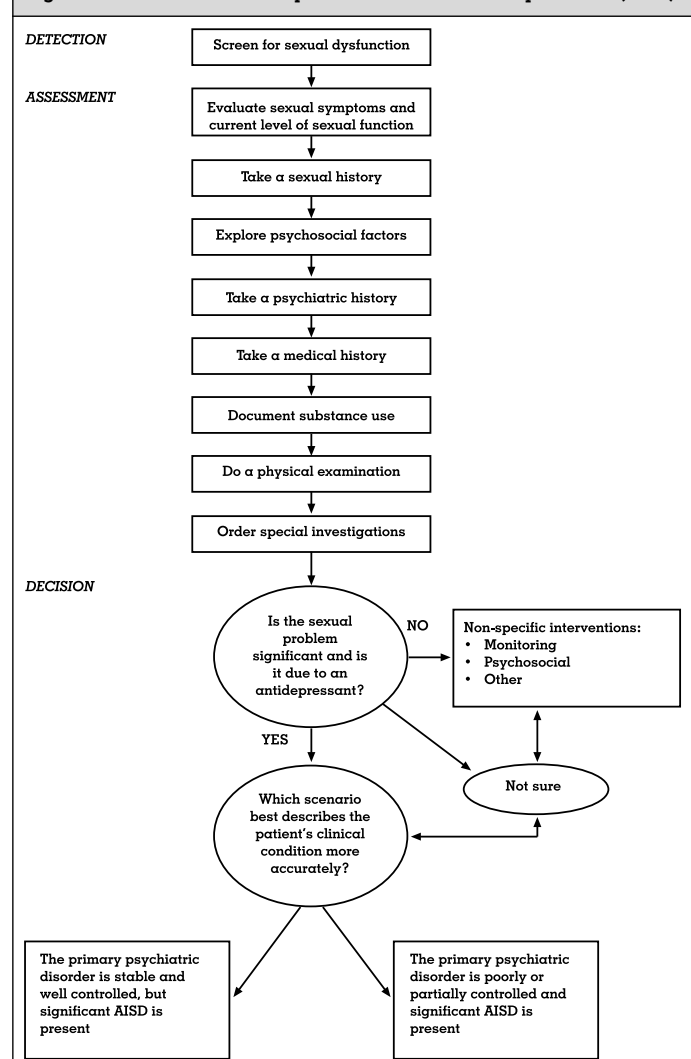
The assessment of sexual dysfunction, particularly in the case of anxiety and depressive disorders, can be complicated by difficulties in determining the relative contribution of the illness itself, of medication, and of underlying pre-existing sexual dysfunction.⁶ A thorough understanding of the sexual problem in its broader context is essential as this should determine the best management strategy to employ.

It is also important that ongoing monitoring for improvement or a lack thereof occurs over time. The use of a rating scale as an assessment instrument can again be very useful; the Arizona Sexual Experience Scale can measure change over time as well as screen for sexual symptoms. The more detailed Rush Sexual Inventory is also widely used and monitors change, but it takes longer to administer and can be considered intrusive.⁷

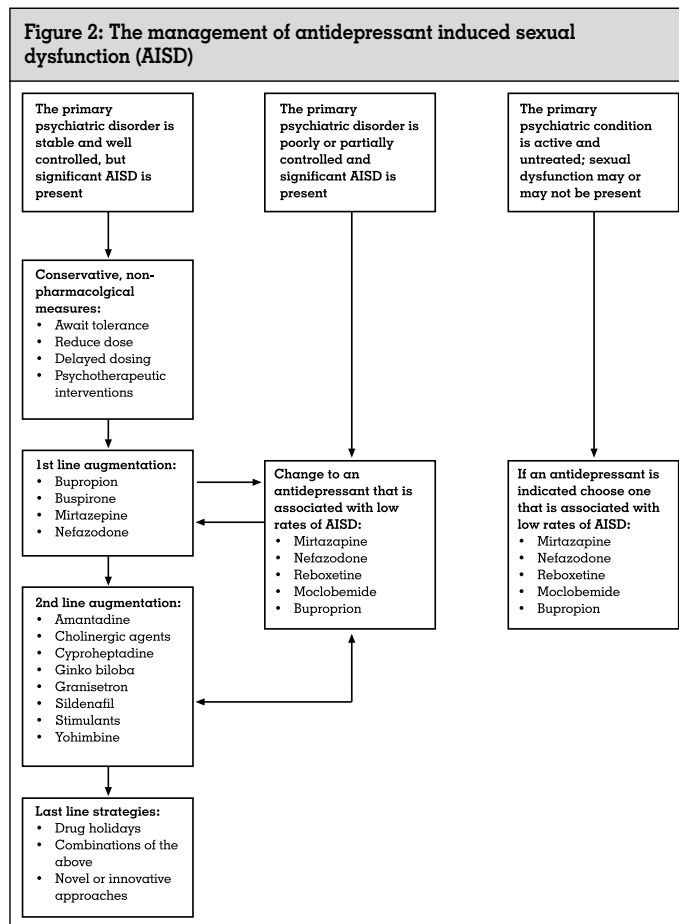
Management strategies

Once a problem with sexual function has been identified and determined to be secondary to the effects of an antidepressant there are a number of possible strategies for managing the condition. It is convenient to divide these strategies into three broad categories: conservative or non-pharmacological approaches, changing the antidepressant medication and adjunctive strategies. Notwithstanding the lack of good evidence-

Figure 1: Assessment of antidepressant induced sexual dysfunction (AISD)



based data, Figure 2 outlines a rational approach to the treatment of AISD. Any decision about which option to choose, and the decision about whether to do anything at all, will be an individual one and should be made in close co-operation with the patient.



Conservative, non-pharmacological approaches

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

The most common approach is to wait and see whether tolerance develops to the side effects. It has been reported that in 42% of cases of AISD the approach used is to await spontaneous remission.⁸ There is evidence to suggest that this will be an acceptable strategy for a small proportion of people.⁹ It has been reported that the spontaneous remission of AISD occurs in approximately 10% of cases and that a further 11% will experience a partial remission.¹⁰ However, the majority of patients will find this an unsatisfactory option, particularly if antidepressant therapy is likely to be ongoing. Although it is reasonable to wait and see for a period of time and to monitor for any spontaneous improvement,

this approach is often incorrectly used as a way to avoid addressing the problem.

A number of other minimally disruptive strategies have been used to manage AISD. It may be useful try and time the patient's ingestion of medication so that it does not correspond with sexual activity. The term delayed dosing has been used to describe this practice and usually the person will only take their daily dose of antidepressant medication after they have engaged in sexual activity.¹¹ Drug holidays or stopping the medication for short periods particularly when sexual activity is anticipated, may also be useful.¹² These two strategies are obviously more likely to be useful with the shorter acting antidepressants, but unfortunately they also carry with them a risk of discontinuation symptoms. Drug holidays are seldom used.⁸ Dosage reduction can some times be helpful.¹³ Unfortunately, all three of these strategies are associated with the risk of relapse or recurrence and patients should be warned that depressive or anxiety symptoms could re-emerge. The patient, family and clinician should monitor the mental state carefully when employing these strategies.

Psychotherapeutic interventions may be a further option. Although the main cause of the sexual problem is the antidepressant, it is worth remembering that sexual activity does not take place in a vacuum and that psychosocial factors are almost certainly at play. It may well be useful to employ behavioural and cognitive behavioural techniques, relationship counselling and perhaps a range of other psychotherapies that are the cornerstone of sex therapy. Unfortunately, little is known about the efficacy of these approaches in AISD and further investigation is needed in this area.¹⁴ Nevertheless, basic psychosocial interventions should be a part of any management plan and not be left as a last resort, particularly when the risks of changes to medication are high.

Changing the antidepressant

Because less invasive strategies may in fact end up being more disruptive than invasive strategies, it is therefore often more logical to switch to a different antidepressant. Generally one would choose an alternative antidepressant that is less associated with the specific sexual difficulty being experienced. Switching to a non-serotonergic antidepressant or to another serotonergic antidepressant that is less associated with sexual problems may be an appropriate strategy for some patients.¹⁵ Examples of suggested antidepressants are bupropion, nefazodone, mirtazapine and reboxetine.^{11,16} The sexual side effect profiles of these agents have been described previously. The potential side effects of these drugs should be matched to the patient's clinical condition, physical condition, sensitivity to side effects and experience of sexual dysfunction.

Guidelines produced by the American Psychiatric Association recommend the substitution of antidepressants causing sexual dysfunction with one of these newer drugs in cases where patients complain of sex problems.¹⁷ In about 39% of people physicians manage AISD by changing antidepressant treatment.⁸

The drawback of this strategy is that any change of medication is accompanied by risk of relapse or recurrence. The fact that a patient recovered from their depressive or anxiety disorder on one agent is no guarantee that another agent will be as efficacious. There is also no guarantee that the patient will be free of sexual difficulties on the new medication, or that they will not experience some other equally or more distressing side effect. Furthermore, a change to a different antidepressant will simply not be an option

for a significant proportion of patients. This may be due to the severity of their past episodes and the risks associated with relapse, a previous history of poor response or intolerable side effects on those agents, or such mundane factors as cost and availability.

Adjunctive strategies

Because the above options are of limited usefulness and at best are only viable for a modest percentage of patients suffering from AISD, adjunctive strategies have been enthusiastically pursued. The term adjunctive refers to the use of a second or add-on agent to augment the pharmacological action of the antidepressant. In the case of AISD it is hoped that use of an augmenting agent will modify the side effect profile of the first drug. Unfortunately, adjunctive therapies are rarely proposed to patients and there is a limited amount of clinical trial evidence on their use for this problem.^{8,11} Controlled data is lacking and is mostly in the form of case reports and small open label studies. As a result these adjunctive strategies are based mainly on a combination of current understanding of the mechanism of antidepressant action and the neurobiology of the sexual response phenomenon. The decision is often based more on the anecdotal experience of the treating clinician than any solid evidence base. The use of a number of agents for the pharmacological treatment of AISD has been suggested. They have usually been used anecdotally as augmenting agents to target sexual side effects in cases where patients continue to take their antidepressant therapy.

Dopamine clearly plays an important role in the neurochemistry of the sexual response cycle and several open studies and case reports have suggested the usefulness of agents augmenting dopaminergic neurotransmission as adjunctive therapies. Bupropion, taken either daily or on an as needed basis may be beneficial, particularly for disturbances of orgasm.^{18,19,20} Doses of between 75mg and 150mg per day in divided doses are recommended for patients on SSRIs or venlafaxine.²¹ The usual precautions for bupropion should be taken and possible drug interactions considered. Amantadine, a dopaminergic agonist, has been reported to be useful, again for orgasmic dysfunction.^{22,23} A dose of 100mg twice daily has been recommended, but caution is advised in those patients predisposed to psychosis.²¹ The usefulness of ropinirole has also been suggested.²⁴

A variety of stimulants including pemoline (18.75mg to 75mg per day), dextroamphetamine (5mg to 40mg per day) and methylphenidate (5mg to 40mg per day) have been reported to be of value.^{25,26} However, their use as augmentation strategies is not without its own risks, most notably agitation, insomnia and misuse. Positive effects have been demonstrated on desire, arousal and orgasm in those patients taking SSRIs and venlafaxine.

The cholinergic enhancers bethanechol (10mg to 50mg per day) and neostigmine (50mg taken one hour before sex or up to 200mg per day in divided doses) have been used with some success for arousal difficulties on antidepressants with anti-cholinergic side effects.²¹

Noradrenaline is involved in the sexual response cycle and noradrenergic agents have also been investigated. Yohimbine, a α -2 adrenergic receptor antagonist, was reported to be of use for all phases of the sexual response cycle.^{27,28,29} A dose of 5.4mg has been suggested, but caution is advised as the agent can exacerbate anxiety and precipitate panic attacks.²¹

An open trial of sildenafil reported efficacy in AISD.³⁰ The efficacy of sildenafil for the treatment of AISD has been confirmed in

a 6-week, randomised, placebo-controlled trial of 90 men and also for the treatment of ejaculatory delay caused by SSRIs.^{31,32} A dose of 50mg to 100mg per day is suggested for difficulties with desire, arousal and orgasm.²¹ The agent is contra-indicated for use with nitrates and the usual precautions should be followed when prescribing sildenafil.

However, it is agents that modify serotonergic neurotransmission that have the greatest face validity in the treatment of SSRI induced sexual dysfunction. This is not surprising considering the modulatory influence of serotonin in the sexual response cycle and the proposed mechanisms by which serotonergic antidepressants are thought to cause AISD. Cyproheptadine, a 5HT₂ and histamine antagonist, is perhaps the most widely used agent for this indication, though evidence for its benefits on orgasm are those best documented.^{33,34,35,36,37,38,39} The recommended dosage range is 4mg to 12mg as required.²¹ Cyproheptadine useful for the AISD associated with both SSRIs and venlafaxine, but it can be sedating and has been associated with the re-emergence of depressive symptoms. Agents which antagonise 5HT₂ receptors, such as nefazodone (50mg to 150mg per day), have been shown to be useful as augmentation agents.⁴⁰ This is in addition to the fact that they appear to be associated with lower levels of sexual dysfunction than SSRIs, when used alone in the treatment of depression. Mirtazapine (15mg to 45mg per day), an antagonist of 5HT₂, 5HT₃ and α ₁ and α ₂ adrenergic receptors, similarly, is associated with lower levels of antidepressant induced sexual dysfunction and may be useful as an augmentation strategy. Both nefazodone and mirtazapine appear to be most useful for orgasmic disturbance.²¹ The potential risks of using multiple antidepressants in combination should not be overlooked when choosing this option.

Ginkgo biloba has been reported as useful for difficulties with libido, arousal and orgasm at doses between 180mg and 240mg per day in divided doses.²¹ However, negative studies do exist for the treatment of AISD with both Ginkgo biloba and sumatriptan.^{41,42}

In a single case report granisetron, an anti-emetic with 5HT₃ antagonism as its mechanism of action, has been reported as useful in this indication.⁴³ A previous positive open label study has suggested that granisetron may be a promising agent meriting study under double blind conditions.⁴² The recommended dose is 1mg per day as required. Two small negative studies have, however, failed to establish the usefulness of granisetron.^{44,45}

Conclusion

Current data regarding of AISD and its management is lacking, but a growing body of evidence points the way to what is likely to represent a rational approach to the problem. The flow diagrams provided in this review represent the author's opinion and clinical experience against the background of current literature. The management flow diagram in particular reflects a balance between the existing level of evidence for particular interventions and that intervention's relative tolerability.

It is impossible in such a broad guideline to take into account the myriad of individual factors that might impact on the decision as to which intervention is most appropriate for a particular patient. In all instances the use of these strategies should be preceded by a thorough assessment and be individually tailored to the patient's specific needs. A patient's response or failure to respond to an intervention should be actively followed-up by ongoing monitoring.

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