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Antidepressant-induced sexual dysfunction in men

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ABSTRACT

Most of the available antidepressant medications, including tricyclic antidepressants, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, and dual noradrenergic/serotonergic reuptake inhibitors have been reported to be associated with sexual dysfunction in both sexes. This manuscript reviews evidence concerning the relative incidence of treatment emergent sexual dysfunction in men being treated with antidepressant drugs. Both double-blind controlled trials and large clinical series report a high incidence of sexual dysfunction, especially ejaculatory delay, with serotonergic drugs. The incidence of sexual dysfunction in men appears to be much lower with drugs whose primary mechanism of action involves adrenergic or dopaminergic systems.

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1. Introduction

The relationship between depressive disorder, its treatment, and sexual dysfunction is complex. There is a high co-morbidity of sexual dysfunction with depressive disorder (Makhlouf et al., 2007) and some aspects of sexual function, especially libido, may improve with successful treatment. However, some psychopharmacological agents used to treat depression, anxiety and other psychological problems may themselves induce sexual dysfunction, especially delayed ejaculation. Thus it is often difficult to ascertain what is caused by the disease as opposed to its treatment, or by other factors. A complaint of sexual dysfunction could indicate non-response to treatment as well as a drug side effect. (Lahon et al., 2011).

Most of the commonly prescribed antidepressant drugs are associated with sexual side effects and these side effects are often the cause of treatment non-compliance. One study (Monteiro et al., 1987) found that approximately 20% of patients on clomipramine became non-compliant with treatment because of anorgasmia or delayed ejaculation. Some clinicians decades ago were aware that tricyclic antidepressants and monoamine oxidase inhibitors could cause sexual dysfunction (Beaumont, 1977). In fact, there were even case reports by some clinicians that the delay in ejaculation induced by these agents could be used to treat premature ejaculation (Eaton, 1973). However, most clinicians were apparently unaware of these side effects. Clinicians were more concerned with other troublesome side effects such as sedation, weight gain, dizziness, hypotension, and anticholinergic side effects as well as the risk of cardiac arrhythmias and the sudden onset of severe life threatening hypertension. When the serotonin reuptake inhibitors were introduced, clinicians had a class of drugs devoid of the side effect burden of the earlier agents. Initially, most clinicians were unaware that these agents also cause sexual dysfunction. With continued experience, more and more clinicians became aware that these agents were also associated with sexual side effects (Balon, 2007). Eventually, the pharmaceutical industry began advertising that some agents had a lower sexual side effect burden than their competitors (Segraves, 2007). These promotional efforts had the benefit of educating clinicians about the sexual side effect potential of these agents.

Recognition of drug-induced sexual dysfunction is important clinically for a number of reasons. It may be a cause of treatment non-compliance (Segraves, 2007) or complicate recovery from depressive disorder in other ways. Decreased self-esteem is often part of the symptomatic presentation of depressive disorder. Antidepressant-induced sexual dysfunction may further impair the patient's sense of self-worth and competence. Stable interpersonal relationships play an important role in the recovery from depression. Psychotropic-induced sexual dysfunction may place an additional stress on intimate relationships (Labbate, 2008). Thus, the study of antidepressant-induced sexual dysfunction has important clinical ramifications.

2. Methodology

It is of note that many of the antidepressants when first introduced were thought to have minimal sexual side effects (e.g., fluoxetine 1.9% based originally on *self*-reports). In fact, controlled clinical trials indicated a low incidence of sexual dysfunction on many agents. Then clinicians began reporting cases and clinical series of sexual problems seemingly induced by antidepressant agents. Subsequent clinical trials with differing methodology, especially direct inquiry as opposed to spontaneous self-report, indicated that the observations made by astute clinicians were indeed correct and that the original estimates of the

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incidence of sexual dysfunction based on clinical trial data were faulty (Segraves, 2007).

Although various estimates of the incidence of sexual dysfunction induced by various antidepressant agents have been published, the reality is that the estimated incidence of antidepressant-induced sexual dysfunction depends on the methodology utilized and one cannot truly speak of a universally accepted methodology and incidence figure for any of the agents being utilized. At best, one can discuss probable differences in incidence of sexual dysfunction induced by differing pharmacological agents. Incidence figures vary widely depending on whether direct inquiry was utilized, the instrument utilized, and the threshold established for the diagnosis. For example, it has been reported that there is a four-fold difference between the percentage of patients spontaneously reporting sexual dysfunction versus those reporting such problems after direct inquiry (Montejo-Gonzalez et al., 1997). At this point, the accepted standard for investigating the prevalence of sexual dysfunction in drug trials is some form of direct inquiry, either by interview or questionnaire. The types of studies available also vary widely. Most of the controlled double blind studies were financed by pharmaceutical companies in order to market their product as having a lower incidence of sexual dysfunction than competing agents. Many of these studies compare their agent with a competitive product in the market, often to a product with a known propensity to induce sexual dysfunction. Thus we have evidence of the proposed superiority of one product as compared to one other product. These one to one comparison studies offer a piecemeal understanding of antidepressant-induced sexual dysfunction. Again, most of these studies employ differing methodology. The studies comparing multiple agents are usually cross sectional and most often have not employed any type of untreated control group, have not employed random assignment to agents utilized and many don't have baseline measures of sexual function. Unfortunately, these studies may represent our only source of data comparing multiple agents using the same methodology. Some of these studies employ very large samples sizes which might mitigate against the effect of contaminating variables such as co-morbid physical and mental disease on the study of the effect of antidepressants on sexual function

Thus, one needs to use caution in interpreting the findings reported in these studies. However, if a number of studies with inadequate methodology report similar results, one can suspect that the differences reported are replicable and thus maybe valid. Another issue rarely addressed is whether the illness itself is in remission with treatment. As mentioned earlier, untreated depression itself is associated with sexual difficulties. There are more valid methodological issues. The method of assessing sexual dysfunction should be validated and the dosages of the agent utilized must be specified as there appears to be a dose response effect on sexual side effects (e.g., Benazzi and Mazzoli, 1994). Studies utilizing low dosages may report negligible incidence of sexual problems whereas those utilizing higher doses may report a higher incidence. Another issue of importance to the clinician is whether a statistically significant difference between two agents is clinically significant. A very large study may find a statistically significant difference between agents, which although of theoretical interest, has minimal application in clinical psychiatry. Some studies report the incidence of sexual dysfunction separately for each sex. Unfortunately, many do not.

3. Definition and recognition of anti-depressant-induced sexual dysfunction

Two major diagnostic systems are utilized to diagnose antidepressant induced sexual dysfunction — DSM-5 and the ICD-10.

The DSM-5 definition of a substance/medication-induced sexual dysfunction is listed in Table 1. This definition states that the problem begins after exposure to a substance which is capable of producing sexual dysfunction. Clearly, the wording of the definition is awkward because of a decision to combine criteria for sexual dysfunction induced by drug abuse with sexual dysfunction induced by prescribed medication. In the ICD-10, the diagnosis begins with the specific substance believed to be the cause of the problem.

Table 1
Substance/medication-induced sexual dysfunction diagnostic criteria (DSM-5, American Psychiatric Association, 2013).

A. A clinically significant disturbance in sexual dysfunction is predominant in the clinical picture.
B. There is evidence from the history, physical examination, or laboratory findings of both (1) and (2).

1. The symptoms in Criterion A develop during or soon after substance intoxication or withdrawal or after exposure to a medication.
2. The involved substance/medication is capable of producing the symptoms in Criterion A.

C. The disturbance is not better explained by a sexual dysfunction that is not substance/medication-induced. Such evidence of independent sexual dysfunction could include the following:

The symptoms precede the onset of the substance/medication use; the symptoms persist for a substantial period of time (e.g., about 1 month) after
The cessation of acute withdrawal or severe intoxication; or there is other
Evidence suggesting the existence of an independent non-substance/
medication-induced sexual dysfunction (e.g., a history of recurrent
non-substance/medication-related episodes).

D. The disturbance does not occur exclusively during the course of delirium.
E. The disturbance causes clinically significant distress in the individual.
Note: The diagnosis should be made instead of a diagnosis of substance intoxication or substance withdrawal only when the symptoms in Criterion A predominate in the clinical picture and are sufficiently severe to warrant clinical attention.
The diagnosis should be coded using the codes for specific substance use.
It should be also *specified if*:
With onset during intoxication: If the criteria are met for intoxication with the substance and the symptoms develop during the intoxication.
With onset during withdrawal: If criteria are met for withdrawal from the substance and the symptoms develop during, or shortly after, withdrawal.
With onset after medication use: Symptoms may appear either at initiation of medication or after a modification or change in use.
Specify current severity:
Mild: Occurs on 25%–50% of occasions of sexual activity.
Moderate: Occurs on 50%–75% of occasions of sexual activity.
Severe: Occurs on 75% or more of occasions of sexual activity.

In clinical contexts, it is often difficult to ascertain whether or not sexual dysfunction is drug-induced, part of the symptomatic presentation of depressive disorder, or related to other factors. Depressive disorder with loss of ability to

experience pleasure and social withdrawal may affect ability to experience intimacy. Loss of interest in sex is the most common sexual difficulty associated with depression. Sexual difficulties have a high incidence in patients with major depressive disorder (Kennedy et al., 2000). One epidemiological study found that loss of sexual interest was an indicator of depression in most age groups except for women aged 70 and above (Kivela and Pahkala, 1988). Depression can also be associated with erectile disorder and difficulty reaching orgasm. Separating the effect of the depressive disorder from the effect of medications used to treat the disorder can be quite difficult in clinical practice. It has been suggested that the clinician always obtains information about baseline sexual function prior to administering a drug which might have adverse consequences on sexuality. In actual clinical practice, this step may be omitted by a busy clinician. Thus often the clinician attempts after the fact to discover what the level of sexual function was prior to drug administration. Many patients are poor historians which complicates determination of etiology and severity. The determination may be especially difficult with complaints of low sexual desire. Most clinical trials simply assess for the presence of statistically significant differences between compounds on questionnaires. These questionnaires may vary considerably in how well they are validated

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