Post-SSRI sexual dysfunction & other enduring sexual dysfunctions

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Abstract

Enduring sexual difficulties following treatment with selective serotonin reuptake inhibitor antidepressants have been reported to regulators since 1991, but it was only in 2006 that a formal post-SSRI sexual dysfunction syndrome was reported. The clinical, research and regulatory implications of this syndrome are considerable and researchers using epidemiological methods are well placed to map out the contours of the problem and perhaps pinpoint possible treatments.

Introduction

Close to 100% of takers of a selective serotonin reuptake inhibitor (SSRI) have a degree of genital sensory change within 30 min of taking. These effects consist primarily of a reduced sensitivity, often termed ‘numbing’ by those affected but others have genital arousal (irritability). The reduced sensitivity is accompanied by an immediate delay of ejaculation in men and mounting of orgasm in both men and women. After a period of treatment, orgasm may stop and there may be a loss of libido (Healy et al., 2018a).

The ‘numbing’ effect produced by SSRIs has similarities to the effect of rubbing lidocaine into the genital area, which was a prior treatment for premature ejaculation, and SSRIs in single doses are used for premature ejaculation now. The effect is also described in terms of a loss of pleasurable sensation. In some cases, there is an actual genital numbing equivalent to that produced by lidocaine.

These immediate onset sexual effects ordinarily lift when treatment stops. In 2006, reports appeared of a condition now termed post-SSRI sexual dysfunction (PSSD), in which the genital numbing, pleasureless or absent ejaculation/orgasm, and loss of libido remain and may become more pronounced after treatment stops (Bahrick, 2006; Csoka and Shipko, 2006). PSSD can persist for decades afterwards (Healy et al., 2018a, 2018b).

In 2001, persistent genital arousal disorder (PGAD), an enduring disorder of irritable genital sensation was described (Leiblum and Nathan, 2001). This condition is not linked to enhanced libido and does not stem from psychological issues. At present PGAD appears to affect women more than men. This condition seems more likely to happen around the menopause, and while closely related to discontinuation from SSRI medication, can also occur following trauma to the genital area (Healy et al., 2018a).

These genital effects do not occur on antidepressants that do not inhibit serotonin reuptake; other antidepressants and psychotropic drugs can cause erectile dysfunction but not the syndromes of numbness, pleasureless orgasm, loss of libido or persistent arousal.

Two other syndromes have been described which appear closely related to PSSD. One is post-finasteride syndrome (PFS). First described in 2011, this occurs in young men taking finasteride to stall hair loss (Irwig and Kolukula, 2011). It also occurs with other 5α-reductase inhibitors – dutasteride and saw palmetto. Genital anaesthesia, loss of libido and sexual dysfunction are features of this syndrome. Initial finasteride treatment can produce some sexual dysfunction, but this is less common when compared with SSRIs. It is unclear if the sexual dysfunction that appears on treatment is continuous with PFS or distinct from it.

A post-retinoid sexual dysfunction (PRSD) has also been described (Hogan et al., 2014). This also includes genital anaesthesia, sexual dysfunction and loss of libido. There can be some sexual dysfunction on initial treatment in patients taking isotretinoin for acne, but it is not clear what continuity there may be between this and PRSD.

These enduring post-treatment syndromes may interface with tardive dyskinesia linked to antipsychotic drugs in the 1960s. Antipsychotics can cause dyskinesias on treatment, which ordinarily resolve when treatment is stopped. Dyskinesias can also emerge on withdrawal but clear up in time. Tardive dyskinesia is a syndrome that involves dyskinetic movements centred on the jaw and lower facial area, which can emerge on treatment but become more marked when treatment stops. The syndrome can endure for years or decades afterwards.

These legacy effects of antidepressants and antipsychotics have some interface with withdrawal syndromes linked to these drugs. Withdrawal to opioids and alcohol is viewed as
limited to a few weeks, having features not found during admin-
istration of the drug and as ordinarily responding to re-institution
of treatment. Antidepressant and antipsychotic withdrawal how-
ever is linked to dysthymia, which may appear to be continuous
with the original problem but can be demonstrated in healthy
volunteers given these drugs, as well as to other sensory and auto-
nomic disturbances. These states can last for months or longer,
opening up a possible link between enduring sexual syndromes and other legacy effects of antidepressants and antipsychotics
(Healy and Tranter, 1999).

There are variations among antidepressants and antipsychotics
in their likelihood of causing withdrawal problems and likelihood
of causing tardive syndromes but the basis for these differences is
not understood.

Mechanisms

PSSD occurs in all ages, both sexes and all ethnic groups. It can
begin after a few doses of treatment or only become apparent
after years of exposure (Healy et al., 2018a).

There are two issues to account for. One is the original sensory
changes. These almost certainly extend beyond the genital area
but are more salient there perhaps because of the functional con-
sequences. SSRIs also produce a more general dampening of
reactivity – commonly termed emotional numbing. This ‘numb-
ing’ may be linked to the pronounced sensory features that char-
acterise the SSRI withdrawal syndrome, which may be rebound
effects that include spontaneous orgasms and can result in PGAD.

At present, there is no agreement as to how the sensory
changes on SSRIs come about. Lidocaine, which also produces
genital numbing, appears to do so through an action on late
sodium currents (Johannesen et al., 2016) and serotonin reuptake
inhibitors also have effects on late sodium currents (Wang et al.,
2008). Antidepressants with effects on late sodium currents are
also widely used to treat neuropathic pain.

Aiming at finding a treatment, PSSD sufferers have tried a
wide range of agents active on various dopamine and serotonin
receptors along with phosphodiesterase inhibitors, and other
drugs, but these have no therapeutic effect for PSSD, PFS or
PRSD.

PFS sufferers have focused on evidence for androgen insensi-
tivity. It is also the case that SSRIs reduce testicular volume and sperms counts but these effects appear to occur in the absence
of PSSD. At present, no endocrine manipulations appear to
make a difference in PFS, PSSD or PGAD.

The treatment approaches adopted to date have been largely
targeted at reversing the acute sexual effects rather than reversing
the mechanism that leads to enduring effects. This is similar to
research efforts on tardive dyskinesia which for 4 decades have
focused on the dopamine system without finding an answer.

A second issue therefore is one of pinpointing a mechanism
that might underpin enduring effects like these. It does appear
that with time (several years) a degree of spontaneous recovery
happens in some cases. In other cases, there are brief remissions
(days), often triggered by stopping a brief course of another drug
such as an antibiotic. There are grounds to think therefore that
these enduring effects do not stem from permanent damage.

Is this problem best seen as physiological (bio-electric) or
pharmacological? Is the site at which the original sensory changes
are effected central or peripheral? Do they arise in a central
nucleus, at the dorsal root ganglion level, or from local treatment
effects on C-fibres?

Future research

In June 2019, the European Medicines Agency (EMA) acknowl-
edged that sexual dysfunction can persist after treatment with
serotonin reuptake inhibiting antidepressants stops. They have
asked companies to update their product datasheets accordingly.

Now that this problem has been formally recognised, epidemi-
ology can contribute to finding a solution to these problems. First,
using a proxy for PSSD such as prescription of phosphodiesterase
inhibitors in young men, it may be possible to offer some indica-
tion as to the frequency of these problems. Second, using
phosphodiesterase inhibitor use, it may also be possible to track
whether any other medicines cause similar problems. On the
basis of reports to regulators, it is likely that a number of novel
anticoagulants such as rivaroxaban and apixaban along with
tetracycline antibiotics may cause similar problems. The greater
the number of medicines implicated, the more likely a mechanism
will be found. Third, it is quite possible that we already have
agents that can make a difference. These are most likely to be
detected using databases that shed light on who does not develop
these problems.

Acknowledgements. None.

Financial support. None.

Conflict of interest. None.

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