

# Antidepressants and sexual dysfunction: a history

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## Background

In June 2019, in response to a petition lodged by the author in 2018,<sup>1</sup> the European Medicines Agency asked pharmaceutical companies to warn that sexual dysfunction can endure after antidepressant treatment stops.<sup>2</sup>

## History

The effect of antidepressants on sex was first noted in 1960 by Frank Ayd, a psychiatrist and the discoverer of amitriptyline, who linked amitriptyline treatment to a sexual dysfunction distinct from the loss of libido that the melancholic states it was being used to treat can cause.<sup>3</sup>

In the 1970s, George Beaumont, working for Geigy Pharmaceuticals, had the job of finding a niche for clomipramine, now regarded as the most potent antidepressant, but then another molecule in a crowded field. He placed articles in newspapers featuring a minor celebrity, thrilled that her boyfriend's premature ejaculation problem could be managed by 10 mg of clomipramine taken 30 minutes before intercourse – the standard antidepressant dose is 150 mg.<sup>4</sup>

Beaumont also established clomipramine as the premier drug treatment for Obsessive-Compulsive Disorder.<sup>4</sup> As clomipramine use encroached on behaviour therapy for Obsessive-Compulsive Disorder in the 1980s, in public lectures, Isaac Marks, the leading proponent of behaviour therapy, drew attention to the persistent orgasms a patient of his, a nun, experienced after withdrawal from clomipramine. This may be a first linkage of what is now called persistent genital arousal disorder with withdrawal from a serotonin reuptake inhibitor.

In 2001, Sandra Leiblum formally described persistent genital arousal disorder.<sup>5</sup> Although a psychotherapist, she was convinced the persistent arousal four of her patients had was organic rather than psychological. Persistent genital arousal disorder primarily affects women and is now linked to hormonal changes around the menopause as well as discontinuation from serotonin reuptake inhibitor drugs –

which include many antibiotics, antihistamines and analgesics in addition to antidepressants.<sup>6</sup> The women affected have turned to perineal nerve ablation, clitoridectomy, electroconvulsive therapy and other drastic remedies, without benefit.

The Selective Serotonin Reuptake Inhibitor (SSRI) group of antidepressants is derived from clomipramine and was launched in the years around 1990.<sup>7</sup> SSRIs are relatively ineffective for melancholia, a rare disorder compared to the nervous problems for which doctors around 1990 were giving benzodiazepines. The marketing need for the SSRIs was to transform cases of Valium, rather than cases of clomipramine, into cases of Prozac.

Doctors began to hear they could be sued for prescribing benzodiazepines which cause dependence. The real need they were told was to treat the underlying depression, with antidepressants, which did not cause dependence, rather than treat the superficial anxiety with dependence-producing drugs.<sup>7</sup>

In the 1980s, prior to marketing, healthy volunteers in phase 1 studies of SSRIs, however, had become dependent on SSRIs and were left anxious and depressed afterwards.<sup>8</sup> Within three years of paroxetine being on the market, there were more reports in Britain about dependence on it than there had been in 20 years from all benzodiazepines combined.<sup>8</sup>

The initial labels for all SSRIs when these drugs were launched clinically stated that less than 5% of patients in clinical trials reported sexual dysfunction. But in some unpublished phase 1 trials, over 50% of healthy volunteers had severe sexual dysfunction that in some cases lasted after treatment stopped.

Over 50% becomes less than 5% primarily because in clinical trials investigators have innumerable boxes to tick, almost entirely devoted to the question of whether the drug works, and minimal space and time to record adverse events. They may not, therefore, record a problem, in particular one that can be passed off as a feature of the illness.<sup>9</sup>

Phase 1 trials also offer companies a clear view of a drug's adverse effects making it possible to design trials that will not find the problem. In a trial, comparing paroxetine to clomipramine in

Obsessive-Compulsive Disorder (study 29060/136), for instance, the protocol had a Limited Symptoms Checklist with 8 questions centering on sexual dysfunction but investigators, like me, were told not to ask these questions.

The resulting 5% clinical trial figure trumped later evidence from surveys that gave rates of over 50% consistent with the unpublished phase 1 studies. The 5% figure even trumped a marketing of dapoxetine, an SSRI, for premature ejaculation, which depends on the drug impacting on the sexual functioning of close to 100% of the men who take it.

Clinicians were advised to tell patients taking SSRIs that any sexual problems would remit once treatment stopped and that they could even take a break from treatment for a romantic weekend.

The first report to British regulators of a patient with post-treatment genital arousal disorder dates to 1987.<sup>10</sup> The first report of what is now called Post-SSRI Sexual Dysfunction (PSSD) was filed in 1991.<sup>10</sup> It is likely that no doctors are aware of this.

I saw my first patient with what was later called PSSD in 2000; a 35-year-old lady who told me that three months after stopping treatment, she could rub a hard-bristled brush across her genitals and feel nothing.

In 2006, Bahrack<sup>11</sup> and Csoka<sup>12</sup> formally described PSSD. They were helped in this by a lot of sufferers, especially Kevin Bennett who played a key role in being willing to have his name linked to the condition and to be cross-examined at academic meetings. Kevin and other sufferers could reliably date their condition to the early 1990s, so that by 2006 their problems had persisted for over a decade.

In an effort to find a cure, hundreds of women and men in Internet forums have since exchanged information about the effects of drugs acting on serotonin or dopamine systems, phosphodiesterase inhibitors, herbs, metals and operative procedures, all of which had some rationale, but many of which were dangerous, and none of which work. Some forum participants appear to have committed suicide. I have been contacted by Dignitas, the assisted dying centre in Zurich, asking about the nature of this problem because a number of young people have referred themselves there.<sup>13</sup>

The core features of the condition are genital numbing, loss or muting of orgasm and loss of libido. But many are just as concerned by additional features like emotional numbing or derealisation.<sup>14</sup> Both sexes, all ages and every ethnic group can be affected. The problem may begin after only a few doses and leave someone affected for life. Or a relatively mild dysfunction can worsen dramatically when the person stops treatment.

In 2011, an almost identical problem, post-finasteride syndrome (PFS), was reported. Finasteride has been marketed since 1997 to young men with thinning hair.<sup>14</sup>

In 2014, a similar post-retinoid syndrome (PRSD) was described following isotretinoin (Accutane). These problems have also been happening for decades previously.<sup>14</sup> In 2006, a man suffering sexual dysfunction following isotretinoin killed the doctor who prescribed it to him.

With colleagues, in 2018, I reported on 300 cases of enduring sexual dysfunction following antidepressants, finasteride or isotretinoin.<sup>14</sup> We decided to petition the European Medicines Agency to have PSSD recognised on drug labels, hoping recognition might lead to research and treatment.

Another reason was because, in addition to the direct treatment harms, many patients are harmed by the response of their doctors. They are ridiculed for thinking a drug could cause a problem after it leaves the body. They are referred for therapy of childhood issues, or told, if they consult Google, they will have problems for ever, or they may be offered antidepressants.<sup>15</sup>

Why would regulators, who have been sitting on thousands of reports from doctors for years, act in response to us? Reports from doctors to regulators are anonymised. This transforms them into hearsay. Unless a patient and doctor can be cross-examined, it is not possible to establish causality. Aware of this, with the agreement of patients, we sent the European Medicines Agency 84 named patient reports and contact emails and 32 letters from doctors to confirm the patient's identity, their treatment with an SSRI and the lack of a competing explanation for their difficulties. The European Medicines Agency were told we were offering them the possibility to cross-examine patients or their doctors to establish causality.

In contrast to regulators, companies are obliged to follow us up if we report. They seek access to our medical records in order to find ways to explain the problem away. When their drug is the only way to explain the problem, companies include it on their label under 'other reports', which for doctors for the most read as indicating that companies even let us know about reports from 'Flat-Earthers'. PSSD has not appeared there because companies have a get-out – the patients were depressed.

In June 2019, the European Medicines Agency agreed to ask companies to note a problem described nearly 30 years previously.<sup>2</sup>

## Ways forward

Sixty years ago, it rarely took more than a few years between the first reporting of problems such as sexual

dysfunction on amitriptyline, to wider acceptance. PSSD, PFS and PRSD now join a growing group of significant adverse events that have taken over three decades from the point of first description to a linkage to treatment.

Key to reversing the increasing delay in recognising common effects drugs can cause is a willingness on the part of patients and doctors to put their names to reports and be cross-examined. This – not clinical trials – is how to establish drug X causes effect Y.<sup>9</sup>

In May 2019, the *BMJ* featured a study on declining sex in Britain that fingered depression as a leading cause of this decline.<sup>16</sup> Neither the *BMJ* nor media coverage mentioned that neither the nervous problems for which benzodiazepines were given, nor the benzodiazepines caused sexual dysfunction. Antidepressants are more likely than the nervous problems for which they are now given to wipe out our interest in or ability to make love.

Meanwhile 10% of people of sexually active years in developed countries are on antidepressants chronically.<sup>17</sup> Nearly 20% of the population, therefore, may not be able to make love the way they want. In some deprived areas, the figure may be much higher. Some likely comfort themselves with the thought that once they stop treatment, they will get back to normal, when in fact they may be even less able to function.

There is a great need to recognise these treatment-related enduring sexual dysfunctions and pinpoint how they arise and might be treated.

#### Declarations

**Competing Interests:** DH helps run a website RxISK.org which records patient reported adverse events on drugs. This has in recent years provided a forum for patients with enduring sexual difficulties following antidepressants and other drugs. DH has been an expert witness in legal cases involving SSRI antidepressants but no cases involving sexual dysfunction.

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