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Professor Guido Rasi
Executive Director
European Medicines Agency
Spark Building
Orlyplein 24,
1043 DP Amsterdam,

Dear Professor Rasi

Responding to a petition sent to you in June 2019 by a large group of clinicians and researchers, EMA indicated they would ask companies to mention enduring sexual dysfunction in the labels of antidepressants.

Many of those affected with PSSD had hoped for more than the very minimal set of words that has resulted. A young Dutch man (22 years old) committed suicide several weeks ago frustrated at the continuing lack of research and hope of a cure. I can send you the details of the website his mother, a doctor, has set up in his honour.

An Italian group of sufferers have been chasing AIFA asking if there is anything more AIFA can do to help. AIFA, as I understand it, have responded that more work is needed, interrogating databases etc to determine if there is a real problem.

AIFA suggested:

A). It is difficult to know whether PSSD is a treatment related condition, given that the nervous problems SSRIs are given for can cause sexual dysfunction

B). The condition is relatively recently described.

C). There are no studies that have investigated a causal link between treatment and PSSD.

D). The relatively few reports of PSSD compared with the number of prescriptions make it difficult to decide if there is a signal or not.

While this position might sound reasonable to an outsider, it is neither good for patients with PSSD, nor for perceptions of regulation.

Regulation
When responding to people with PSSD and the media, I stress that EMA and other regulators do not have a public health function other than checking whether there is support for the wording of claims made for drugs and devices by companies. Few patients understand this. Few take note when regulators mention not wishing to interfere in the relationship between doctors and patients.

On the other hand, regulators appear to stray into the health domain when they talk about licensing treatments on the basis of a risk-benefit analysis, a formulation that leaves many doctors figuring EMA are endorsing taking risks.

I asked Jordi Llinares at a recent meeting about EMA risk benefit analyses and he made it clear these are primarily made on the basis of RCTs.

Clearly EMA license drugs on the basis of RCTs conducted to investigate a primary endpoint – which companies and EMA call "the benefit". This is 1 of the 100 things a drug does. The extreme focus on one effect, which is the whole point of an RCT, means that the 99 other drug effects are poorly collected, or not noticed, or deliberately ignored.

"The benefit" is what companies want to make money from. In the case of the SSRI "benefit", there is no evidence for saved lives or restoration of function. Instead rating scale changes allowed regulators let companies advertise "a benefit", which was less of a "benefit" than the "benefit" provided by an older generation of antidepressants.

This "benefit" is not the commonest thing SSRIs do. Their commonest effect is that they numb genitals of over 90% of takers, within 30 minutes of taking a first pill. Company RCTs looking for a less common but commercially interesting "antidepressant" effect, completely missed this genital effect that should have been unmissable. This almost inevitable effect is still not mentioned in drug labels, 30 years later, even though dapoxetine is licensed for Premature Ejaculation (P.E.) and other SSRIs are used for P.E. on the basis of this effect.

Current labels claim sexual dysfunction was found in less than 5% of people in SSRI trials. Following the logic above, an estimate like this could arise simply as a result of the RCT focus on a primary endpoint which, as mentioned, can lead investigators to miss things that are more common than the primary endpoint. The fact that this can happen upends the standard narrative that RCTs give us the best possible information about drugs, and we can supplement the information they offer with pharmacovigilance input to pick up the rare events or events that happen after lengthy exposure to treatments that RCTs miss.

One consequence of this state of affairs is that while risk-benefit assessments may have a value for companies, they are clinically and scientifically meaningless if RCTs can completely miss the commonest effects of a drug and by implication can miss 90+% of a drug's other effects – rather than just miss rare effects or effects with a delayed onset..

In the case of the SSRIs and sex, the failure to notice sexual issues was aggravated by companies deliberately not collecting the data. In SSRI healthy volunteer trials, conducted in the 1980s, trials that did not have an extreme focus on a primary endpoint, over 50% of volunteers reported significant sexual difficulties some of which endured after treatment stopped. In later clinical trials, investigators like me were encouraged to think of sexual problems being linked to mood and in some cases were explicitly told not to ask questions about sex. I can give you details of both healthy volunteer and later clinical trials.

Consistent with the healthy volunteer studies, there were reports to regulators by 1991, almost immediately after first marketing of the SSRIs, showing that in some case this sexual dysfunction could endure after treatment – Post SSRI Sexual Dysfunction (PSSD).

The healthy volunteer studies undermine, AIFA. EMA and other regulatory responses that these conditions might stem from the illness rather than treatment. Melancholia, which is very rare, can lead to lowered libido but the kind of depression for which SSRIs are given does not lower libido. Indeed, just like people comfort eat when they have "nerves" so they often have more sex in an attempt to handle their "depression".

A second clinical feature that undermines EMA's current position is that in the case of PSSD, patients can rub chilli paste into their genitals and not feel it. If you have any evidence that any psychiatric condition produces an effect like this, I would love to see it.

Between 10-15% of the populations of many European countries now take antidepressants, over 90% of whom are on treatment for over a year with a growing number on treatment for 5 to 10 years or more, primarily because they cannot stop. This difficulty in stopping was another problem noted in the healthy volunteer trials of these drugs in the 1980s – a problem companies have handled for 3 decades by a deceptive use of language and not publishing the data from healthy volunteer trials.

Given that over 10% of the population are on drugs that compromise our ability to make love the way we might wish to, anything up to 20% of us may not in fact be having the sexual relations we might wish to have and would otherwise be able to have. There were articles about this in the popular press featuring prominent people as far back as the last millennium – which again I can send if you wish.

In some Welsh towns the figure for people unable to make love may be closer to 50%. Of some note, perhaps, this is primarily a native European issue – a large presence of immigrant communities will lower the figures, as people from these communities are less likely to be on SSRIs.

Some of those on treatment will live with the hope that once they stop their medicine all will be well when things may be much worse if they develop PSSD. There is in fact no way of knowing how many people have PSSD if the vast majority of people who take these drugs chronically can't get off them.

This factor might allow EMA to claim that the apparent frequency of PSSD is quite low but making a claim like this would be "economical with the truth" – as the British put it. Claims like this will likely also contribute to further suicides as they give the impression the problem is not important.

Cause and effect

Faced with convincing reports of an effect on treatment, companies are under a legal obligation to investigate. They seek access to the patient or the patient's medical records to see if there is another way to explain the proposed effect. If, in individual cases, they find no other way to explain an effect, they include this effect in the label of the drug under "other reports". They do not undertake epidemiological or other large database studies before doing so. They establish cause and effect in a way that I and most people can understand rather than turn to ways that both you and I know would support claims that effects have not been proven and further research is needed – ad infinitum.

Many companies have asked me for access to information on the people with PSSD that RxISK has on file. I have not been willing to comply so far as this is a group of people that treatment has rendered vulnerable and an insensitive handling of the matter by companies more interested to defend their drug than to defend patients could lead to further suicides.

As part of the recent petition to EMA, the petitioners included named patient details and records with supportive letters from doctors indicating these patients had been taking an SSRI and the doctor could see no other way to explain the problem other than the effect of the drug. Our hope was that EMA might handle this matter more sensitively.

EMA were told that this material was being sent with patient consent in order to offer EMA a chance to follow up these patients and their doctors in the way companies do. But rather than do this, EMA removed the names of the patients and their contact details.

When asked about this EMA mentioned patient confidentiality, which seems either a case of unthinking bureaucracy or else points to the fact that EMA and other regulators have a very

different model for establishing cause and effect to the one companies, doctors and most lay people have.

Risk-Benefit

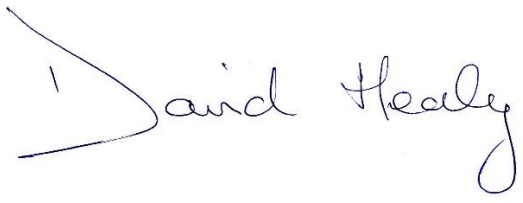
To return to the risk-benefit issue, companies saw a number of ways they could gain from introducing the idea of risk-benefit into our collective lexicon in the early 1990s. One advantage to companies was letting them argue that if regulators approved a "benefit" based on an RCT, it might be more difficult for regulators to advocate for warnings on medicines – as in the case of the SSRIs and suicide. Warn and regulators could be criticised for deterring people from seeking a benefit that might have saved their lives. This argument seems to have hamstrung regulators, even though the clinical trials show an increase in suicidal events on treatment.

In the case of PSSD, young people are now committing suicide and approaching assisted dying programs because they interpret the lack of a warning to mean that no-one is interested in this problem and no work is being done on finding a remedy. They are correct, in my opinion, to read matters this way. They would likely think EMA/AIFA deeply cynical if they realised, as most insiders like you and I do, that decades of research could be put into databases without coming up with anything useful, least of all a remedy. Some might ask if this delay is what EMA intended.

I recognise that the issues of SSRI antidepressants and sex raise profound issues about what companies and regulators are doing. The matter of what might be done to help patients however is rather straightforward. This is not a matter on which remaining quiet about a hazard will be to the benefit of any current or prospective patients, who might get the benefit without the hazard, in that everyone who takes these drugs will have sexual dysfunction of some sort.

My primary purpose in writing is to support the many people with PSSD, whose hopes were raised by EMA in June, but who now feel their position is little better than it was before June. I would also appreciate hearing your views on the more general regulatory issues questions of Sex and SSRIs raise.

Yours sincerely



David Healy MD FRCPsych

cc. J Raine MHRA.