Why did three journals reject my puberty-blocker study? Trans children deserve to know the facts

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What happens during puberty? And

what happens if we try to stop it? It's one of the most fraught questions of our time. Given its significance and the vulnerability of the people it involves, you might be surprised to learn that there have been more studies assessing the impact of puberty blockers on cognitive function in animals than humans. Of the 16 studies that have specifically examined the impact of puberty blockers on cognitive function, 11 have been conducted in animals. And most found some detrimental impact on cognitive function when the researchers gave these drugs to mice, sheep or monkeys.

The sheep studies were particularly interesting as they used twin lambs, administering the puberty blockers to only one in the pair. More than one year after stopping the medication, the sheep

who had taken the puberty blockers had still not "caught up" with their untreated siblings in their ability to complete a test of spatial memory. It can, however, be fairly argued that we can only extrapolate so much from the abilities of sheep to remember the way through a maze of hay bales. It is really the studies in humans that are of most interest to those considering prescribing or taking these drugs.

Yet such studies are hard to come by. There are only five that have looked at the impact of puberty blockers on cognitive function in children, and only three of these have looked at these effects in adolescents given the medication for gender dysphoria. In one of these studies, the researchers didn't measure how well the children were doing before they administered the drugs, so it is difficult to know whether

the subsequent difficulties they had on a strategy task could be attributed to the medication. A second study established an excellent baseline, and the researchers employed a gold-standard measure to test the cognitive abilities of the children in the programme before they started the puberty blockers.

Unfortunately, they didn't re-administer these tests to assess the impact of the medication, but chose instead to report how many of a subset of these children completed a vocational education and how many completed a higher vocational education years later. No outcomes at all were reported on 40% of the children who started out in the study. The final study, however, was beautifully designed: the researchers assessed IQ prior to the administration of puberty blockers and regularly

monitored the impact of the treatment over 28 months on a comprehensive battery of cognitive tasks. The results were concerning and suggested an overall drop in IQ of 10 points which extended to 15 points in verbal comprehension. But regrettably, this was a single case study, and while alarming, the conclusions we can draw from one person's experience are limited.

Last year, I wrote a paper to summarise the results of these studies. The paper explained in relatively simple terms why we might think that blocking puberty in young people could impact their cognitive development. In a nutshell: puberty doesn't just trigger the development of secondary sex characteristics; it is a really important time in the development of brain function and structure. My review of the medical literature highlighted that while

there is a fairly solid scientific basis to suspect that any process that interrupts puberty will have an impact on brain development, nobody has really bothered to look at this properly in children with gender dysphoria.

I didn't call for puberty blockers to be banned. Most medical treatments have some side effects and the choice of whether to take them depends on a careful analysis of the risk/benefit ratio for each patient. My paper didn't conduct this kind of analysis, although others have and have judged the evidence to be so weak that these treatments can only be viewed as experimental. My summary merely provided one piece of the jigsaw. I concluded my manuscript with a list of outstanding questions and called for further research to answer these

questions, as every review of the medical literature in any field always does.

As a scientific paper, it was not ground-breaking — reviews rarely are. But by summarising the research so far, I thought it would serve as a convenient resource for the numerous authorities currently examining the efficacy of these treatments. It also provided key information for parents and children currently considering medical options. Every patient needs to be aware of what doctors do and do not know about any elective treatment if they are going to make an informed decision about going ahead. Doctors have a duty of candour to provide this.

"Doctors have a duty of candour."

I was surprised at just how little, and how low quality, the evidence was in this field. I was also concerned that clinicians working in gender medicine continue to describe the impacts of puberty blockers as "completely physically reversible", when it is clear that we just don't know whether this is the case, at least with respect to the cognitive impact. But these were not the only troubling aspects of this project. The progress of this paper towards publication has been extraordinary, and unique in my three-decades-long experience of academic publishing.

The paper has now been accepted for publication in a well-respected, peer-reviewed journal. However, prior to this, the manuscript was submitted to three academic journals, all of whom rejected it. "Academic has paper rejected from

journal" is not headline news. I have published many academic papers and have also served on the editorial boards of a number of high impact scientific journals. I have both delivered and received rejections. In high-quality journals, many more papers are rejected than accepted. The reasons for rejection are usually a variation on the themes that the paper isn't telling us anything new or that the data is weak and doesn't support the conclusions that the authors are trying to draw. In a paper that is reviewing other studies, reasons for rejection typically include criticisms of the ways the authors have looked for or selected the studies they have included in their review, with the implication that they may have missed a big chunk of evidence. Sometimes the subject of the review is too wide, too narrow or too niche to be of value to the wider

readership.

While imperfect, anonymous peer review remains the foundation of scientific publishing. Theoretically, the anonymity releases reviewers from any inhibitions they may have in telling their esteemed colleagues that, on this occasion, they appear to have produced a pile of pants. When it works well, authors and editors receive a coherent critique of the submitted manuscript, with reviewers independently highlighting — and ideally converging — on the strengths and weaknesses of the paper. If done sloppily, or if the reviewers have been poorly selected, the author may be presented with a commentary on their work that is riddled with misunderstandings and inaccuracies. Requests for information already provided are common, as are

suggestions that the author include reference to the anonymous reviewer's own body of work, however tangential to the matter in hand. I have been on the receiving end of both the best and worst of these practices over the course of my career. However, I have never encountered the kinds of concerns that some of the reviewers expressed in response to my review of puberty blockers. In this case, it wasn't the methods they objected to, it was the actual findings.

None of the reviewers identified any studies that I had missed that demonstrated safe and reversible impacts of puberty blockers on cognitive development, or presented any evidence contrary to my conclusions that the work just hasn't been done. However, one suggested the evidence may be out there, it just hadn't been published.

They suggested that I trawl through non-peer reviewed conference presentations to look for unpublished studies that might tell a more positive story. The reviewer appeared to be under the naïve apprehension that studies proving that puberty blockers were safe and effective would have difficulty being published. The very low quality of studies in this field, and the positive spin on any results reported by gender clinicians suggest that this is unlikely to be the case.

SUGGESTED READING

Why I stopped being a good girl

BY HADLEY FREEMAN

Another reviewer expressed concerns that publishing the conclusions from these studies risked stigmatising an

already stigmatised group. A third suggested that I should focus on the positive things that puberty blockers could do, while a fourth suggested there was no point in publishing a review when there wasn't enough literature to review. Another sought to diminish an entire field of neuroscience that has established puberty as a critical period of brain development as "my view".

In a rather telling response, one of the reviewers used religious language to criticise the paper. They argued that the sex-based terms I had employed to describe the children in the studies — natal sex, male-to-female, female-to-male — indicated a pre-existing scepticism about the use of blockers. They suggested that the very presence of these terms would cause people who prescribe these medications to "outright dismiss the article", and went on to say

that by using these terms the paper was "preaching to the choir" and would do a "poor job of attracting new members to the fold". However, the most astonishing response I received was from a reviewer who was concerned that I appeared to be approaching the topic from a "bias" of heavy caution. This reviewer argued that lots of things needed to be sorted out before a clear case for the "riskiness" of puberty blockers could be made, even circumstantially. Indeed, they appeared to be advocating for a default position of assuming medical treatments are safe, until proven otherwise.

Yet "safe and fully reversible" can never be the default position for any medical intervention, never mind a treatment that is now deemed experimental by authorities in Europe and the UK. Extraordinary claims demand

extraordinary evidence, and the only extraordinary evidence here is the gaping chasm of knowledge, or even apparent curiosity, of the clinicians who continue to chant “safe and completely reversible” as they prescribe these medications to the children in their care. It is not the job of a scientific paper to “bring people into the fold”; it is the job of clinicians to understand the evidence base of the treatments they offer and communicate this to the patients they are treating.

I sincerely hope that any arrest in brain development associated with puberty blockers is recoverable for young trans and gender diverse people, who are already facing significant challenges in their lives. I would welcome any research that indicates that this is the case, not least for the significant insights that would present to our current

understanding of puberty as a critical window of neurodevelopment in adolescence. Puberty blockers almost invariably set young people on a course of lifetime medicalisation with high personal, physical and social costs. At present we cannot guarantee that cognitive costs are not added to this burden. Any clinician claiming their treatments are "safe and reversible" without evidence to back it up is failing in their fundamental duty of candour to their patients. Such an approach is unacceptable in any branch of medicine, not least that dealing with highly complex and vulnerable young people.

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