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FEATURE

TRANS CARE

Gender dysphoria in children: puberty blockers study draws further criticism

An opportunity to strengthen the evidence base for these treatments in a particularly vulnerable group of patients may have been missed, say **Deborah Cohen** and **Hannah Barnes**, who catalogue new concerns about NHS research practices and decisions to lower the minimum age for treatment before results were published

Deborah Cohen *correspondent*, Hannah Barnes *senior journalist*

BBC Newsnight

The NHS Gender Identity Disorder Service (GIDS), based at London's Tavistock and Portman NHS Foundation Trust, is England's only provider of NHS specialist treatment for young people with gender dysphoria.

In 2010 GIDS and University College London's Institute of Child Health applied for ethical approval to conduct a cohort study offering puberty blockers to a "carefully selected group of adolescents" with gender dysphoria in early puberty.

But questions continue to emerge about the researchers' conduct of this early intervention study.

We reported in July that potentially crucial information may have been missing from the study's protocol and patient information sheets, casting doubt as to whether participants gave informed consent.[1] Critics had said that the researchers had downplayed interim findings that might suggest increased suicidality. And the researchers had not submitted the annual progress reports required by the NHS Health Research Authority (HRA), which promotes patients' interests in health research. Also, despite the full study findings remaining unpublished, the NHS changed its policy to allow GIDS to prescribe these drugs to children under 12 in established puberty.

Here we present new allegations that the researchers might have broken rules when seeking ethical approval. They might also have misinterpreted another study's findings about potentially worrying effects of the drugs on changing bone density.

Contested area of research

Gender dysphoria, a conflict between a person's biological sex (or "assigned" gender) and the gender with which they identify, can cause distress.[2]

Puberty blockers are drugs that stop the rise in sex hormones that prompts development of secondary sex characteristics. In theory they might give children time to explore their gender identity without the additional distress of their bodies changing. But evidence about outcomes, side effects, and unintended consequences is lacking.[3 4]

GIDS uses off-label triptorelin, which suppresses gonadotrophin release from the pituitary gland. In girls it reduces the secretion of luteinising hormone and follicle stimulating hormone; in boys it shuts down gonadal testosterone production.

GIDS says this is a "contested field of work": some groups argue for earlier treatment with cross sex hormones—testosterone or oestrogen—to enable transition, while others oppose all physical treatments in adolescence, including puberty blockers.

In the early 2000s the NHS was seen by gender specialists worldwide as a conservative outlier, offering puberty blockers only to young people aged 16 or over. Recognising the weak evidence base, the British Society of Paediatric Endocrinology and Diabetes in 2009 recommended earlier use of puberty blockers but only as part of a research study. This way young people could be monitored and outcomes added to the literature to inform clinical practice.

Protocol and patient information sheets

Michael Biggs, an Oxford University sociologist, used freedom of information requests to obtain the early intervention study's protocol and information sheets for young people and parents, which we have seen.

He has alleged that GIDS has suppressed "negative" data.[5]

The protocol said that the study would recruit 10-15 young people, aged 12 to 15, a year for three years starting in April 2011 and would run for six years. GIDS says the study concluded in February 2019. The full results are not yet published.

Correspondence to: D Cohen deborah.cohen02@bbc.co.uk

The outcomes cited were the "psychological, social and physical benefits and risks" in blocking sex hormone production.

We sought the views of methodologists and clinical trial statisticians, but few were prepared to speak publicly for fear of reprisal. However, they noted that the cohort study had no control group; that outcome measures were not well defined; and that there was no definition of what would constitute a serious adverse event. Similar concerns are common to many studies of puberty blockers in young people with gender dysphoria.[4]

The experts we spoke to said that the protocol and information sheets were missing potentially significant information. The sheets said, "Hormone blockers will make you feel less worried about growing up in the wrong body and will give you more time and space to think about your gender identity."

But one concern about the treatment is that it may in some way be putting young people on a path towards medical and, perhaps, later surgical transition, as indicated by a Dutch study of 70 young people aged 12-16 that had similar eligibility criteria to the early intervention study. The Dutch study found: "No adolescent withdrew from puberty suppression, and all started cross-sex hormone treatment." [6] That is, all children who took puberty blockers went on to the next stage of transitioning to the opposite gender. Protocols should summarise the evidence to date, says the NHS Health Research Authority.[7] The early intervention study's protocol, however, did not mention the Dutch study and its findings.

The early intervention study's principal investigator, Russell Viner, professor of adolescent health at UCL and president of the Royal College of Paediatrics and Child Health, was aware of this other work. He wrote in the application to the research ethics committee, "The Dutch group reports that no one entered in their study has changed their mind during the eight years in which the Dutch group has offered hormone blockers. Their eligibility criteria are similar to those of our study."

In a joint response to us about why they chose not to mention the Dutch study in their study documentation, GIDS and Viner said, "There is no evidence to establish an association between use of the blocker and the persistence of gender dysphoria. This is a hypothesis."

GIDS said it was confident that its study participants gave informed consent: "Our lead paediatric endocrinologist always raised the possibility that blocking puberty may crystallise gender identity [with gender dysphoria persisting]."

An NHS policy change: based on what evidence?

In 2014, just after the study had finished recruiting participants, NHS England approved policy changes to permit GIDS to offer puberty blockers as described in the study protocol, "following evaluation." In addition to lowering the age limit from 16 to 12, as per the study, puberty blockers could now also be considered for children under 12 in established puberty.[8]

It is unclear which data this evaluation included, and neither GIDS nor NHS England responded to our requests to see this evaluation.

NHS England said that the policy was changed on the basis of "international evidence and clinical expertise."

The former minister for mental health Jackie Doyle-Price told the House of Commons in July that NHS England was doing a "proper review of the research around this service and the ethics of it to establish a proper framework for consent, recognising that we are looking at treatments that may have long-term consequences."[9]

GIDS, however, has spoken encouragingly about the study in the media and at conferences. In 2014, the year the NHS changed policy, the *Mail on Sunday* reported Polly Carmichael, director of GIDS, as saying, "The results thus far have been positive."[10]

GIDS declined to share these results, "which could prejudice publication of the study," but said, "It is usual to look at emerging data to evaluate the intervention." It added that the "qualitative interviews and satisfaction data were positive," saying, "Indeed, at six and 12 month interviews, all young people stated that they wished to continue accessing the blocker."

Preliminary data released

The researchers released some preliminary data for 30 of the 44 young people in the study, presented to the Tavistock's board by Carmichael in 2015 and documented in meeting minutes.[11] The researchers flagged up their finding of a "significant increase" in the number of children agreeing to the statement "I deliberately try to hurt or kill myself" after taking puberty blockers for one year.

Because of the uncontrolled study design, interpretation of these data is difficult. It's not clear whether this apparent increase in self harm and suicidality was caused by the drug or something else.

Regardless, Susan Bewley, emeritus professor (honorary) of obstetrics and women's health at King's College London, said that these findings should have warranted further investigation. "Good medical practice would normally be very reflective about an increase in harms," she said.

"Seeing a change in suicidality is very worrying . . . We've got form in medicine of having bad science, where we've given treatments that have increased suicidality in teenagers before."

GIDS said that the data were from a "small sample" and therefore no "meaningful conclusion" could be drawn. It added, "All patients were seen regularly by mental health professionals. They concluded that there was no evidence of harms that could be directly attributed to the treatment and that continuation of the study was appropriate."

Obligatory annual progress reports

The researchers didn't provide the HRA with any of the annual progress reports it requires researchers to submit. Researchers are advised to mention any concerns that have arisen about participants' safety.

The HRA sent three letters to the researchers in the three years 2013-2015 asking for updates of their study, threatening to withdraw ethical approval otherwise.

It warned, "If you fail to submit regular progress reports—which is a condition of the favourable ethical opinion—the REC [research ethics committee] may wish to consider suspending or terminating its opinion."

The HRA said that it doesn't usually enforce this requirement. However, because of concerns raised, it is now investigating. It has sent all information available to it to a specially formed group to assess the processes followed when ethical approval was granted. The group, comprising senior HRA staff, and supported by a research ethics committee chair and a non-executive director of the authority, is expected to complete its investigation by the end of September.

The HRA said that it is currently consulting on a new strategy for research transparency and what action to take if researchers do not fulfil their transparency responsibilities.

The researchers told us that they didn't think annual reports were required.

How the researchers got ethical approval

Since the HRA launched its investigation, we have seen a letter to the authority from a concerned parent that questioned how the researchers sought ethical approval for the study. Additionally, we have seen the meeting minutes of the ethics committees involved and some correspondence between them and researchers, through freedom of information requests.

In July 2010 the Central London REC1 committee rejected the researchers' first application on methodological grounds. The researchers argued for an uncontrolled cohort study because "less than one quarter would accept randomisation," adding that British children would go abroad if they could not access treatment here.

The committee wasn't persuaded, saying "there was no way to validate" the research without a control group and suggesting other study methods. These included randomisation for a year or adopting a trial design to compare immediately started intervention with delayed start.

It added that to proceed with the proposed study "without due consideration of alternative study design was unethical."

The chair of Central London REC1 told Viner in a letter, "You may submit a new application for ethical review, taking into account the Committee's concerns. You should enter details of this application on the application form and include a copy of this letter, together with a covering letter explaining what changes have been made from the previous application . . . We recommend that the application is submitted again to this Committee, but you may opt to submit to any other Research Ethics Committee within this domain . . . Alternatively, you may appeal against the decision."

Rather than appeal, the researchers reapplied with an unaltered protocol to a second ethics committee of their choosing, Central London REC2, which approved it.

The parent's letter to the HRA alleged that this breached the rules of the National Research Ethics Service[12] (the HRA's predecessor) and noted that all but the lay members of Central London REC2 worked at the same institutions as Viner. The letter said this may be a conflict of interest.

In a covering letter to the second committee, the researchers again argued against the first committee's suggestion of a randomised design. Young people would be "highly unlikely to accept to enter a project which faces them with the uncertainty of whether or not they will receive this treatment based on chance," they wrote.

Whether rules were breached forms part of the HRA's investigation.

A UCL spokesperson said that the team had followed due process: "They followed instructions from the original REC chair by submitting a new application which referenced and addressed the committee's concerns and included a copy of the original REC letter.

"A further opinion was sought from a REC known to have significant experience in dealing with rare diseases in children and the ethical issues therein. For fair comparison, the same protocol was used."

The spokesperson added that the researchers gave due consideration to the methodology recommended by Central London REC1 but concluded that an observation study design was the only practicable option.

Interpreting a bone density study

Questions have also been raised about how the team at GIDS and their colleagues at the University College London Hospitals Paediatric Endocrine Clinic, which administers puberty blockers, have interpreted other research.

The study information sheets told young people that "we do not know how hormone blockers will affect bone strength."

More evidence has since emerged. A 2018 study from the UCLH clinic was presented at a conference in Rome in 2019.[13] The 70 12-14 year olds in this retrospective cohort had bone scans over three years after starting puberty blockers. GIDS has said publicly that the published abstract indicated "no actual change" in bone density and "no true fall as initially suspected." The abstract concluded that "reference ranges may need to be re-defined for this patient cohort."[14]

GIDS interpreted these findings positively: "This confirms that long-term . . . treatment has minimal impacts upon bone health, one of the major concerns about treatment."[15]

However, others are not so optimistic. William Malone, an endocrinologist in Idaho with an interest in puberty blockers, says that the drugs seem to halt the rapid increase in bone density that occurs in adolescence.

He said that GIDS's "conclusion should be the opposite: puberty blockers profoundly inhibit normal bone density development and this should be of great concern to any practitioner using this medication."

In response to this opinion GIDS said, "There is no evidence that the blocker actively and directly causes loss of bone mineral density, but . . . the expected rise that takes place typically in adolescence is delayed."

GIDS pointed to a study of 56 young people who had received puberty blockers, followed by cross sex hormones to transition, that appeared to show some recovery in bone density was possible.[16]

Curiosity is the tenet of good care

GIDS has been criticised recently by current and former employees over the care it offered.[17 18]

In July a former psychologist from GIDS's Leeds service, Kirsty Entwistle, published an open letter to Polly Carmichael, the service director, warning that clinicians were making decisions that would have a major impact on young people's lives without a robust evidence base.[19]

The Tavistock and Portman trust told us it "takes very seriously concerns raised by staff and has robust processes for dealing with these." It added the trust's medical director had "carried out a review of GIDS which found no immediate issues of patient safety."[20]

Marcus Evans was a psychoanalyst and adult psychotherapist at the Tavistock and Portman trust for two decades. He resigned from its board in February this year because he didn't think concerns among staff about GIDS were being taken seriously enough.

He said that he didn't think GIDS had taken enough interest in negative results.

"We're doing the whole area a disservice by this besieged mentality in which you feel that questioning things and having curiosity about what's going on is the enemy of good treatment and care—rather than it's [being] an absolute central tenet of good treatment and care," he told us.

Evans says he was amazed when the Tavistock's medical director told him that GIDS failed to collect information about what happened to young people after they left the service. "In this controversial area, to hear that we don't actually know whether the young people who've been through the service are going on to have hormone blockers or positive sex hormones or going on to have sexual reassignment surgery is very strange."

GIDS said that it did not agree with Evans's assertions about the work of the service.

Bewley says, "It is unacceptable to have lower standards of care for a group that is already marginalised and stigmatised.

"We must not miss the opportunity to do good research now, helping a very good clinic with concerned clinicians actually deal with the uncertainty of what they're doing."

That opportunity might come. In February the National Institute for Health Research awarded the Tavistock and Portman trust £1.3m to follow a group of young people referred to GIDS, no matter what path they choose. This, the trust hopes, will allow researchers to investigate and compare outcomes among young people who go on to use interventions such as puberty blockers and cross sex hormones with those who do not.

A patient's perspective: "We're just so young that we just trust the doctors"

Hannah Phillips, 19, has extensively documented her experience on YouTube.

"The way that I usually describe how gender dysphoria feels to people who aren't in the trans community is that you feel out of place. You feel odd and disturbed every time you look into the mirror. You also have this depression about how you look and how other people see you," she said.

She started taking puberty blockers when she was 16. Phillips says she was told that little was known about the treatment and about potential risks. She wanted to go ahead anyway: "I don't think there could have been anything that the doctors could have said to stop me from wanting to go onto hormone blockers."

She describes herself as a guinea pig at the time. "You're pretty much testing blockers. The only thing they know for sure is that they stop puberty and that your bones go a bit weird, hence why you may have a few bone density tests. The NHS knows absolutely nothing about blockers," she said in a YouTube video.[21]

To patients wanting to take blockers she says, "No one [any patient] really questions whether or not it's harmful to your body . . . We're just so young that we just trust the doctors."

After 15 months taking blockers, Phillips began taking the cross sex hormone oestrogen.

She is positive about her experience at GIDS. "It feels as if someone's finally listening to you, as if someone just understands exactly how you feel, and that they have helping you as their best interest.

"I don't think they should pause the current rules on allowing young people to have access to puberty blockers. But I do reckon that there should be more research."

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Competing interests: We have read and understood BMJ's policy on declaration of interests and have no relevant interests to declare.

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