Puberty-blocking drugs: Te difficulties of conducting ethical research

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A recent Newsnight programme reported that a major UK puberty-blocking trial is under investigation. Doctors at a London clinic provided drugs to block the development of puberty in young adolescents with

gender dysphoria, a condition where the person experiences discomfort or distress because of a mismatch between their biological sex and gender identity.

The trial began in 2011. A year after starting the drugs, the young people were apparently more likely to report thoughts of wanting to harm themselves. The worry is that perhaps the treatment they received was causing them to have these thoughts of self-harm and suicide.

One of the criticisms of the study, put forward on Newsnight, is the design. The study involved giving the drugs to a group of adolescents and monitoring the effects. However, there was no control group, that is, adolescents who did not receive the drugs. This makes it hard to be sure whether the rates of self-harming thoughts are related to the drugs, would have happened anyway, or perhaps were lower than they would have been without treatment.

It is an important issue because there are high rates of self-harm and thoughts of suicide among children and teens with gender dysphoria. A large study from a clinic in Toronto of 572 children with gender dysphoria found a high rate of self-harm or suicidal thoughts, or both. These were younger children who were not likely to have received puberty-blocking drugs. Results showed they were five times more likely than other children (of similar age) to talk about suicide. The rates of these thoughts also increased as the children with gender dysphoria got older.

This means that it is difficult to know how to interpret the reported results from the UK trial, which was run at the Tavistock and Portman hospital. The puberty blockers might have led to more self-harm, or less, or had no effect. We can't tell.

Some commentators on the UK trial have claimed that the study was

flawed because it lacked a control group. But would it have been ethical to perform a controlled trial? To our knowledge, all of the previous studies of puberty blocking in adolescents have had a similar observational design (that is, no comparison group that is not treated). Potentially, this is based on either ethical or practical grounds. The ethical argument is that it would be wrong to withhold treatment from distressed adolescents who may benefit from delaying or halting the physical changes of puberty.

In a forthcoming commentary in the journal *Pediatrics*, we also set out an ethical argument in favour of controlled trials of puberty suppression. We argue that one of the goals of medical ethics is to promote well-being. But in gender dysphoria it is uncertain whether puberty suppression achieves this goal. The drugs have potentially serious physical side effects. The nature and extent of the psychological benefits are unclear and may differ from person to person. It remains uncertain whether they are in the overall best interests of the adolescent.

Questions about autonomy, too

Medical professionals also have an ethical obligation to promote the well-being of patients, and they also have an obligation to promote their autonomy. In the case of adult patients (with capacity), the right thing to do, in the face of uncertainty about the patient's best interests, is usually to respect their wishes.

But autonomy is more complicated in the case of young adolescents. Adolescents have varying degrees of cognitive development, which is relevant to their capacity to make decisions. Autonomy is not merely desiring something, it is genuinely and accurately understanding oneself and the options available, and vividly imagining the consequences of all feasible courses of action. How much does an adolescent understand themselves, and how well have they understood and reflected on the

consequences of their choices? Clearly, there are some situations where it would be a mistake to automatically comply with an adolescent's expressed wishes.

How does this apply to expressed wishes for puberty-blocking drugs in adolescents with gender dysphoria? When either the implications of a medical intervention for well-being are unclear, or the extent of the autonomy of the patient is not fully determined, there is a moral obligation to scientifically study such interventions to determine their impact on well-being and on how they relate to the developing autonomy of the patient.

Randomised trials

Should these studies be randomised controlled studies? Ideally, from a purely scientific perspective, they should. But because of the intense distress of some adolescents with gender dysphoria and the perceived risk of suicide, doctors might feel compelled towards compassionate use. It would be potentially problematic for these doctors to withhold the puberty-blocking treatment for the sake of a trial, or to randomise the patient to non-treatment.

There may be other cases where clinicians are unsure, however, and are prepared to enrol an adolescent in a controlled trial of puberty-blocking drugs. But at this point a significant practical hurdle may arise. Maybe parents or adolescents are unwilling to participate in a trial. They may indicate that they would seek treatment elsewhere (for example, overseas) if treatment is not offered.

If puberty suppression is to be used with uncertain consequences, it is imperative that we study the effects as systematically as possible. Where a controlled trial is impractical, this might be through an observational design. The study design is not ideal from a scientific perspective,

because it limits the ability to draw causal inferences, but it is better than mere anecdote and personal experience, which is all that doctors may have to draw on in clinical practice otherwise.

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