Articles

Teens and Research

Should We Enroll Adolescents in Trials of Deep Brain Stimulation for Anorexia Nervosa?

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Abstract: On seeing promising results in a small number of patients, some researchers are conducting trials to determine whether deep brain stimulation (DBS) is an effective treatment for anorexia nervosa (AN). This article asks whether we should open enrollment in trials of DBS for AN to adolescents. Despite concerns about informed consent, parental consent, and unforeseeable psychological sequelae, the article concludes that the risks to anorexic adolescents associated with participation in trials of DBS are reasonable considering the substantial risks of not enrolling teens with AN in research on DBS. The seriousness of AN, its high incidence in teens, and serious shortfalls in the AN treatment literature point to the need for improved, evidence-based treatments for teens with AN. This unmet need generates an obligation on the part of researchers and physicians to promote and conduct research on AN in adolescents.

Keywords: deep brain stimulation; anorexia nervosa; adolescents; informed consent; parental consent; research ethics

Introduction

Anorexia nervosa (AN) is characterized by a distorted body image and excessive dieting that leads to severe weight loss with a pathological fear of becoming fat.[1] AN disproportionately affects adolescents, causes serious and severe medical crises, and has the highest mortality rate of all mental illnesses. Though 80% of individuals diagnosed with AN will fully or partially recover with prolonged treatment, 20% do not respond to available treatments. Despite the fact that those in the 20%, who have so-called long-standing AN (L-AN), seem to require differential treatment from those in the earlier stages of the disease, there has been only one controlled study on treatment of L-AN in adults, and no studies of treatment of L-AN in adolescents.[2]

One possible treatment is currently under investigation. Deep brain stimulation (DBS) has been approved for use in treating refractory obsessive-compulsive disorder (OCD) and is under investigation for a handful of other psychiatric illnesses: chronic depression, Tourette syndrome, addiction, overeating, and, more salient for this article, AN. This article explores whether we should open enrollment in future trials of DBS for AN to adolescents who have failed to recover despite repeated treatment attempts. Current trials of DBS limit enrollment to patients over 20, despite the fact that the highest incidence of AN occurs among adolescents. I review the scientific factors about AN and about DBS relevant to considering the ethical

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question at hand and argue that the risks to adolescents with AN associated with participation in trials of DBS are reasonable considering the substantial risks of not allowing teens with AN to participate in clinical research. Teens with AN have been overprotected from research to their detriment.

Anorexia Nervosa

The natural course of AN and the efficacy of available treatments must be considered in an assessment of the ethical acceptability of conducting high-risk research in adolescents with AN. They include the prevalence and incidence, impact and mortality, evidence base for standard treatments, and prospects for recovery.

Prevalence and Incidence

Lifetime prevalence is the proportion of people who have had a particular disease or disorder at any point in their lifetime. A recent large-scale survey of adults and adolescents in the United States concluded that the lifetime prevalence of AN is 0.9% among all women and 0.3% among female adolescents ages 13–18.[3] Studies in other countries report lifetime prevalences of AN at up to 4.3% of women.[4] The lifetime prevalence of AN among men is considerably lower than that among females.[5] Studies typically underestimate the actual prevalence of AN, because patients tend to conceal their illness.

Although prevalence is an indicator of the impact of a disease on public health and the demand for care, incidence is a better indicator of patterns of disease onset. Incidence is the number of new cases in a population over a specific period. The incidence rate of AN is commonly expressed in terms of new diagnoses per 100,000 individuals per year. The reported incidence of AN ranges from 4.7 to 7.7 per 100,000 women per year. This statistic includes women of all age groups. But several incidence studies show that AN disproportionately impacts adolescents.[6,7] The peak age of onset of AN is between 13 and 18 years.[8] Although onset of AN is rare in children, it does occur in children under 12 years old.[9] The incidence statistics quoted derive from retrospective studies of healthcare records and so do not capture new cases of AN among patients who do not seek treatment. The already high—and rising—incidence of AN in adolescents and children demands attention to the etiology and impact of illness on adolescents specifically, as well as treatment protocols with their specific needs in mind.

Impact and Mortality

Even though the lifetime prevalence and incidence of AN are low relative to other mental illnesses[10] and other eating disorders,[11] the severity and impact of AN has been repeatedly demonstrated through studies of social impairment, medical complications, and comorbidity. The impact of AN on the developing adolescent is particularly severe. AN has profound psychological consequences that can impact adversely the developmental tasks of adolescence and young adulthood. Depression, anxiety, social withdrawal, difficulty eating in social situations, heightened self-consciousness, and fatigue associated with AN may isolate an individual from the tide of normal development.[12] Serious growth retardation, pubertal delay or interruption, peak bone mass reduction, and abnormalities in brain structure

can occur early in the course of the illness.[13] Cardiovascular, gastrointestinal, and hormonal abnormalities are also common.[14]

Most concerning, AN has the highest mortality rates among all mental illnesses and eating disorders.[15,16] High mortality rates are due not only to medical complications but also to suicide, the second most common cause of death among those with AN.[17] The impact of AN and risk of death increase as the illness continues, suggesting a need for early treatment, as well as a need for specialized care as AN progresses to a more severe and long-standing stage.

Prospects for Recovery

All told, about 50% of AN patients make a full recovery with prolonged behavioral and/or medical treatment, 30% make only partial recoveries, and 20% do not recover, even with repeated attempts at treatment.[18,19] A substantial number of AN patients continue to display clinically significant symptoms for years and, in some cases, for decades. Adolescents are more likely to recover than those first diagnosed as adults, likely due to the inclusion of family therapy in adolescent treatment protocols. Adolescent onset is widely considered an indicator that a patient will have a positive outcome but is not unequivocally supported as a favorable prognostic factor in all studies.[20] Those diagnosed before puberty, for example, typically have worse outcomes.[21,22] It is not known why some individuals recover and others do not, and no longitudinal data exist from which a clinician can gauge with confidence the outcome of treatment.[23] Inevitably, many patients diagnosed with AN, including adults, adolescents, and children, will progress to long-standing AN.

There is no consensus definition or hard-and-fast rule for designating a patient as having long-standing AN, also called end-stage AN, chronic AN, or severe and enduring AN. I use the term "long-standing AN" (L-AN) because it does not imply that AN at this stage is untreatable, as "chronic" and "enduring" might imply. Some working definitions have been proposed and are used to guide clinical practice and research: entrenched patterns of AN behavior, enduring body mass index under 17.5, duration of illness greater than 10 years, extremely limited social life, or repeated treatment failures.[24] To my knowledge, there are no available statistics on the demographics or epidemiology of L-AN specifically. This may be due to the lack of consensus over its definition, or poor follow-up at this stage of illness.

Unfortunately, there are few therapeutic options for L-AN.[25] A conventional therapeutic regime for L-AN does not differ from the approach used during early stages of AN. It consists of refeeding to stabilize weight, followed by some form of therapy, sometimes with pharmaceutical management of depressive symptoms and delusions. An ongoing cycle of refeeding, followed by therapy for some time, and then relapse into significant weight loss, which necessitates further refeeding, is the norm for those who live with L-AN. Management of the L-AN patient may devolve into relatively unfocused, intermittent supportive interventions. Goals of care become unclear as patients grow more resistant to therapy. Clinician burnout and frustration are common among those who treat patients with L-AN.[26]

Evidence Base for Standard Treatments

Recovery from AN is marked by normalization of the core symptom characteristics of anorexia nervosa, that is, involving weight, menstruation, and eating behavior.

Standard treatment involves stabilization of medical symptoms, sometimes with refeeding, followed by behavioral interventions (i.e., cognitive behavioral therapy, cognitive analytic therapy, and nutrition programs) and/or medical management of symptoms (i.e., antidepressants, hormones, and nutritional supplements).

A recent comprehensive review of the evidence for AN treatment concluded that evidence for AN treatment is weak. Only 32 studies identified as addressing treatment efficacy for AN were published between 1980 and 2005, and there are serious shortfalls in the AN treatment literature.[27] It is devoid of medical studies for adolescents, as drug trials have focused exclusively on adults; moreover, males are underrepresented in clinical trials of AN, and the majority of trials fail to report the race and ethnicity of participants. No clinical trials for AN address the optimal approach to inpatient weight restoration, the first step of any treatment protocol. This is especially concerning given the potentially lethal combination of fluid and electrolyte shifts that refeeding initiates.[28] Most pertinent for the purposes of my argument, there has been only one controlled study of the treatment of long-standing AN in adults,[29] and there have been no controlled trials on the treatment or management of L-AN in adolescents, despite the fact that some have argued for distinct treatment protocols at this stage of illness.[30,31] The prevailing need for effective methods of management, if not treatment, of L-AN is largely ignored in the clinical literature.

Ethically Salient Scientific Factors

Several of the scientific factors about AN are ethically salient to determining whether to enroll anorexic adolescents in clinical research on AN. AN is prevalent in children and adolescents and has a significantly higher incidence in adolescents than in any other age group. As we see diagnoses of AN in children and adolescents rise, we face a persistent lack of evidence to guide treatment decisions. This means that developing definitive treatment for AN in the adolescent population, especially for those with L-AN, is in the long-term interest of every adolescent AN patient, as well as their parents.[32]

The literature on treatment for AN points to an unmet need among all AN patients, and among adolescents in particular. Clinicians routinely make choices for their adolescent patients that are not based on scientific evidence. Though clinicians know that family therapy is more efficacious than other therapeutic options in adolescents, not all adolescent patients have the stable home life necessary for its success, and studies have shown that it will not be efficacious in all cases even when done correctly. Finally, the fact that no studies exist focusing primarily on the treatment and management of L-AN indicates that there is a full 20% of the population of AN patients for whom no vetted therapeutic option exists. We can assume that among that 20% are adolescents diagnosed early, but for whom existing treatment failed.

The unmet need for evidence-based treatment of L-AN among adolescents provides a professional, if not moral, obligation on the part of researchers and clinicians to promote and conduct research on L-AN.[33] To meet this unmet need, I propose three recommendations.

First, researchers should find consensus definitions of the various stages of AN and should use those definitions consistently across studies to allow accurate comparisons. Duration of illness greater than 10 years is used as an indication of L-AN because studies have shown that recovery is least likely after that point.

Clinicians and researchers should not use the point of no return as a clinically significant marker, however, because it implies that no attempt to treat L-AN will be efficacious. Ongoing AN-associated behaviors and low body weight after a number of failed treatment attempts are more inclusive definitions of L-AN, as treatment-refractoriness does not exclude adolescents from a classification of L-AN. This is a positive result, as identification of adolescents with L-AN is crucial to foster research on adolescents at this stage of the disease, whose particular needs are not well understood, and certainly not met by the existing literature on AN treatment.

Second, researchers should separate adult and adolescent populations for research purposes. High incidence among adolescent females and males indicates that AN may be experienced differently among adolescents and adults. Clinicians' experiences with adolescents corroborate a difference between adolescent and adult AN.[34,35] Treatment options need to be tailored specifically to adolescents' psychological and developmental needs.

Finally, research should focus on patients identified as having L-AN, and particularly on L-AN in adolescents, for whom the long-term psychological and medical consequences are especially severe. Adolescents with L-AN likely require different treatment than adolescents in earlier stages of treatment and may require different treatment than adults with L-AN, given their unique developmental needs. Research in adolescents, as well as in adults, with L-AN is urgently needed to determine whether this is the case, and to develop treatments to mitigate the psychological, social, and medical impact of adolescent AN. Research on the efficacy of DBS presents an opportunity to meet this need.

Deep Brain Stimulation

Commonly called a "pacemaker in the brain," DBS provides direct stimulation to areas of the brain targeted for their relevance to the disease being treated. Electrodes, or leads, are placed on the target area of the brain and connected to a battery-driven stimulator that is surgically implanted in the chest. Once the leads and battery-driven stimulator are correctly implanted, the leads provide constant stimulation to the target area. The goal of DBS is to normalize the functioning of areas of the brain that function abnormally in the context of disease or illness; stimulation is ongoing for as long as is required to normalize functioning. For example, constant, long-term stimulation of areas of the motor cortex effectively alleviates symptoms of some treatment-refractory movement disorders, such as Parkinson's and dystonia. Ongoing research has, for about a decade, explored the efficacy of DBS for treatment of mental illness. DBS is approved for use in treatment of chronic OCD in adults[36] and is under investigation in a handful of other illness, including depression and, of course, AN.

Various scientific factors are relevant to determining whether trials of DBS for treatment of AN should be open to adolescent patients: DBS in children for other indications, the evidence that it is an efficacious treatment for AN, and the risks of DBS.

DBS in Children for Other Indications

There is a precedent for using and studying DBS during childhood and adolescence. The FDA approved a humanitarian device exemption (HDE) for DBS of

the global pallidus internus, an area on the motor cortex, for use in treating dystonia in children and adults in 2003. Dystonia is a movement disorder in which sustained muscle contractions cause twisting and repetitive movements or abnormal postures. Approval of the HDE authorized marketing of DBS for dystonia even though the effectiveness of the device for treating dystonia had not been demonstrated. In approving the HDE, the FDA determined that DBS does not pose an unreasonable or significant risk of illness or injury, and that the probable benefit to health outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment. Most significantly, the FDA approved DBS for dystonia in all patients over 7 with treatment-refractory dystonia.[37] At least 39 patients under 18 have undergone DBS for dystonia, including 21 patients under 12 years old.[38]

Researchers confronted several problems when treating children with DBS for dystonia. They had to accommodate children's small size, decreased muscle and soft tissue mass, and growth potential. Researchers now typically implant the battery-driven stimulator at the rectus abdominis to increase soft tissue coverage. Doing so reduces the battery pack's prominence.[39] (Stimulators are typically implanted at the collarbone in adults.) Despite increased incidence of postsurgical complications in children who have undergone DBS, researchers' observations and accommodations suggest that DBS is a life-saving and beneficial option for pediatric patients with intractable dystonia.[40]

Researchers have also studied DBS's efficacy in treating Tourette syndrome in adolescents. Tourette syndrome is a chronic, childhood-onset neuropsychiatric disorder. It consists of motor tics and at least one vocal tic lasting longer than one year. It has a profound psychosocial and neurocognitive impact on sufferers. At least six adolescents have undergone DBS for Tourette syndrome.[41] Adolescents were often lumped in with adults in publications of small case series of the outcomes of DBS in Tourette syndrome. Some authors suggest that DBS in younger patients may be associated with better tic control and functional outcomes.[42] Others argue that tics that could result in permanent injury may justify DBS at an earlier age.[43] Tourette syndrome–associated behaviors improved with DBS in most cases, and studies reported no serious adverse effects. DBS was not effective in managing symptoms in all cases, however, and one adolescent patient requested to remove the device.[44]

DBS for AN

There are three reasons to believe that DBS might be an effective treatment for AN: (1) theoretical plausibility, (2) case reports from trials of DBS for OCD and depression, and (3) case series of DBS for AN.

Over the past two decades, breakthroughs in brain chemistry and neuroimaging have improved our understanding of the neurobiological bases of AN. Brain chemistry is disturbed in anorexic patients. Their levels of serotonin and leptin, which are associated with mood and appetite regulation, are abnormally high. Studies show differences in serotonin and dopamine receptor activity, indicating dysregulation of mood, anxiety, appetite, and impulse control.[45,46] In addition, brain scans show that some areas of the brains of anorexic individuals appear to be overactive, whereas others are underactive compared to controls. Anomalies are found in the cingulate gyrus, the nucleus accumbens, and the insula. All three of these midbrain structures are implicated in other psychiatric illnesses and signal dysregulation of emotions,

anxiety, and reward processing.[47,48,49] A neurobiological understanding of AN supports the hypothesis that DBS may be an effective treatment for AN because DBS aims to restore normal functioning to areas of the brain that function abnormally during illness.

Two case reports from trials of DBS for depression and OCD spurred interest in using DBS for treatment of AN. Mimi Israel et al. published a case report on Ms. A., who was treated with DBS for chronic depression. A. had suffered from AN since age 17. At age 52, A. underwent DBS. Four years later, in addition to recovering from depression, A. had maintained a healthy BMI. She had one relapse into AN following a friend's suicide but otherwise required no further interventions for AN.[50]

Shortly thereafter, Nicole McLaughlin et al. published a case report of a woman whose AN was markedly improved after undergoing DBS for OCD. The patient had childhood-onset OCD and AN. She underwent DBS at age 48. By the four-year follow-up, she had increased her food intake and variety. She attended events that involved eating and reported that she "doesn't mind" going out to eat.[51]

Publication of these case reports prompted further study of DBS specifically for AN, and a few case series were subsequently reported. The first case series, published by Jing Wang et al., involved only two young women. The study took place in Xi-an, China. The measure of success in this study was maintenance of a normal BMI, as well as improvement in symptoms of depression, anxiety, and obsessive-compulsive disorder; personality; intelligence; memory; quality of life; and social functioning. This study did not report on the average duration of illness prior to undergoing DBS, but both patients were over 18. Its authors concluded that DBS in the nucleus accumbens was an effective treatment for severe AN in young women.[52]

Around the same time, a second study in Shanghai showed promising results in four adolescents. The average age of the patients before surgery was 16.5 years, and the average duration of illness was 19 months. Hemmings Wu et al. reported an average 65% increase in body weight at the 48-month follow-up.[53] Despite promising results, the authors were criticized for having enrolled minors. Critics alleged that the researchers may have violated ethical principles by enrolling patients who had not exhausted treatment options or failed current treatment guidelines.[54] Selecting subjects earlier in the progression of AN may have inflated results that may not be generalizable to adolescents with L-AN.

A group of researchers from Toronto published a case series of DBS for AN composed of six women with AN ranging from 24 to 57 years old.[55] Their mean duration of illness was 18 years. Together, the study participants had been hospitalized almost 50 times. Nine months after starting DBS, three of the patients had sustained a body weight in the normal range. Two patients stayed more or less the same. One patient—the sole subject who did not suffer from a psychiatric disorder in addition to anorexia—deteriorated during the nine months after DBS began. The study methodology, inclusion criteria, and postsurgical consequences of DBS were much more rigorously described in the Toronto study than in the Shanghai and Xi-an studies, but the follow-up was shorter.

Risks Associated with DBS

DBS requires brain surgery, an inherently risky procedure. Placement of the DBS leads is associated with a 2%–3% risk of intracerebral hemorrhage and a 5%–8%

risk of infection. There is a 0.6% risk of death related to surgery.[56] Common adverse effects include seizure, infection, and pain.[57]

Patients with AN would face increased medical risks from surgery; anesthesia is especially risky. Although only local anesthesia is used during lead placement, typically general anesthesia is used to surgically implant the battery-driven stimulator. AN causes a host of cardiovascular, respiratory, and endocrine abnormalities that complicate anesthetic management.[58] Like children with dystonia, patients with AN have decreased muscle and soft tissue mass, and growth potential would have to be accommodated.

Other effects of DBS are not easily quantifiable, or even describable. DBS can have a profound effect on the lives, specifically the emotional lives, of those who have undergone the treatment for mental illness, for example, treatment-refractory depression. Several bioethicists and clinicians have written about the effects of DBS on quality of life, identity, and free will.[59,60,61,62] Some patients report feeling alienated from their desires and their self-conception post-DBS. In rare cases, patients have requested that stimulation be stopped and the leads and battery-powered stimulator removed following unforeseen psychological effects.

For adolescents who undergo DBS, the potential negative effects of DBS, whether psychological or biological, will last longer. Though DBS is reversible in that stimulation can be turned off and the device can be safely removed, it may produce intangible, lifelong psychological effects. These effects are not well understood and have never been tracked in adolescents. Beginning DBS during adolescence for treatment of AN will run the risk of adverse medical effects as well as of encountering unknown psychological outcomes. These risks are reasonable only when substantial benefit is expected from the trials and there is substantial risk associated with living with the disease under investigation.

Balancing Risks and Benefits

Having established that there is an urgent need for research on new treatment options for AN, and L-AN in particular, in adolescents, and that DBS shows promising results, I turn to ethical considerations relevant to determining whether studies of DBS's efficacy should enroll teens in addition to adult patients.

Any research study has an impact on not only the study participants involved but also the entire community of those who suffer, or will suffer, from the illness under investigation. Thus, in weighing whether or not research is ethical, we must consider the benefits and risks to two populations: (1) the study participants and (2) the entire affected population with the disease.[63]

The Study Participants

It is widely held that high-risk experimental interventions should be carried out only on patients who have exhausted other treatment modalities. Risky research should enroll those who have the most to gain and the least to lose. In these extreme cases, the risks of intervention are on par with the risks of continuing the status quo, and so the risk of undergoing a highly experimental intervention is deemed reasonable in the context. The same risks are not reasonable for a patient at an earlier disease stage, for whom there remain less risky treatment options to try. Within the population of people with AN, those with the most to gain and the

least to lose are individuals who have already failed to improve after repeated treatment attempts, and so have progressed to L-AN.

Allowing adolescents to enroll in research on DBS carries risks and benefits for the study participants. Potential study participants face the aforementioned risks associated with surgery and unknown psychological sequelae. At the same time, enrolling in clinical research on DBS also provides benefits to study participants. Benefits include a chance at recovery and heightened surveillance for the duration of the trial, likely several years. If DBS is effective, study participants will obtain early access to treatment.

If adolescents with L-AN are not allowed to enroll in studies of DBS, they risk further organ system failure, cognitive decline, and psychological instability. The longer individuals progress with L-AN, the less likely it becomes that they will ever recover; adolescents who already have refractory AN are unlikely to lead healthy lives. Thus, although DBS for AN carries substantial risk, so, too, does living with L-AN. For young patients entrenched in the behaviors and complicated psychology of AN, DBS may be the best option for restoring normal life. That may be worth the risk of undergoing surgery and stimulation.

The Affected Population

Research into treatments for L-AN is urgently needed. The entire AN population suffers by not having good evidence available to guide clinicians in the treatment of their devastating disease, and the entire group benefits from studying the efficacy of newly available treatments. Moreover, DBS provides not only the opportunity to develop a new treatment for L-AN but also a chance to study the neurobiological underpinnings of AN. Regardless of whether DBS proves an efficacious treatment, its use may improve scientific understanding and lead to treatments down the line. The benefits of an improved understanding of AN will accrue to the affected population regardless of whether adolescents are included in trials of DBS for AN. It's unclear, though, whether or how that knowledge would affect clinical practice for adolescents.

If adolescents are included trials of DBS, clinicians will know sooner rather than later whether DBS is efficacious in treating L-AN in adolescents, adults, neither, or both. Obtaining a positive answer sooner rather than later will prevent morbidity and mortality in adolescent patients, and obtaining a negative answer sooner rather than later opens up research time and effort for other projects. Moreover, even if DBS is not an effective treatment for L-AN in adolescents, patterns may emerge indicating that adolescents and adults require distinct treatment with DBS, improving scientific understanding of L-AN and its effects on developing and developed brains.

Current and future adolescents with AN and L-AN are harmed by not allowing teens to enroll. The status quo of management of L-AN will continue, and it will remain unknown whether DBS is an effective treatment for L-AN in adolescents. To exclude teens from promising research is to exclude other adolescent patients with L-AN from what may be the best treatment available in both the short and long run. Excluding teens from this promising line of research perpetuates the precedent of adolescent exclusion from research. Furthermore, if research continues on adults with L-AN only, and a negative result is found, it is less likely that researchers will explore its use in children. This would be an unfortunate result, as

it may lead to missing a treatment that is effective in younger but not older patients. Adolescents may respond differently, so we should not predicate research on adolescents on data from adult trials in adults.

It is reasonable to conclude that the benefits to study participants and the entire affected population of enrolling willing teens in research outweigh the risks of undergoing DBS.

Countervailing Argument

Informed consent in this study population may present an obstacle to moving forward with research on adolescents with AN and may lead to abuse. Adolescents with AN are doubly problematic research participants, insofar as research in minors requires not only parental consent but also participant assent.[64] Obtaining both may be a challenge. Due to the nature of AN, adolescents with AN may underestimate the gravity of their illness and may express ambivalence about getting better. Parents may be so desperate for a cure that they may be unable to objectively weigh the risks and benefits of DBS. Indeed, both of these problems have been mentioned in previous analyses of ethical issues in studying the efficacy of DBS for treating mental illness.[65,66]

Peter Rabins et al. argue that limiting enrollment to adults protects children from parents who will do anything to help their child get better. Desperate parents may understate risks and tend to overestimate the extent to which their child will benefit from participation in research. To prevent this from happening, the authors explicitly state that research on DBS for mental illness ought to be limited to adults.

Although parental desperation is a problem, it is not unique to trials of DBS for AN in adolescents. Further, there are ways of protecting adolescent research participants despite parental desperation: for example, talking to adolescents without their parents present or appointing an independent third party to consult with parents and potential research participants.[67]

Barriers to establishing assent among adolescents with AN remain, however. Grant et al. did not explicitly prohibit research on DBS in minors. They say: "Prospective patients must demonstrate an ability to consent to participation in a research trial."[68] But there is ample evidence that people, especially young people, with mental illnesses are not capable of providing consent, or assent, as the case may be.

There is an ongoing debate over whether people with refractory mental illness have the decisional capacity to provide informed consent to treatment and biomedical research.[69,70] Psychiatric patients deemed eligible for any experimental intervention, such as DBS, typically are refractory to treatment. However, symptoms of the disease at this stage, such as unwillingness to undergo treatment, also indicate to researchers and ethicists that potential participants lack decisional capacity.

To my knowledge, no one has studied specifically the anorexic individual's decisional capacity to consent to research, but there have been several papers recently on their capacity—or lack thereof—to make other medical decisions.[71,72,73] Participation in research is one such decision.

One symptom of AN is that affected patients underestimate the gravity of their illness and the negative consequences of their choices—two fundamental components of decisional capacity. Additionally, young people with AN exhibit

ambivalence about entering treatment. They tend to refuse or resist treatments despite insisting that they want to recover. For example, one adolescent with AN says:

> I wanted to be healthy but I didn't want to be bigger, and I just couldn't, couldn't get myself out of that trap. . . . So I'd start say where one day I'd eat more and I'd think I can do this, I can do this; and then I'd wake up the next morning and I'd think I can't believe what I've just done. I'd never get more than a day or two days into it, before panicking completely and just thinking "I can't do this!"[74]

In the words of another adolescent, "But again it's the two headed thing one part of you says, like, you need some help . . . but the other part of you is screaming at you to run 600 miles in the opposite direction . . . you're caught between a rock and a hard place."[75] And finally, another adolescent said:

> I remember at the time . . . being outwardly very, like, no I don't want to go [to adolescent inpatient unit] . . . really protesting against it and really like, no I don't want this and it's horrible and they were saying you have to and I was actually thinking inside well maybe it's a good idea, but I wasn't admitting it to anyone. I was, like, no I don't want to go. But I was also kind of thinking that actually maybe it was a good idea.[76]

These quotes point to what researchers have called a "substantial inner conflict" among patients with AN.[77] Evidence of substantial inner conflict prompted the same researchers to conclude that young people, including adolescents, with AN lack decisional capacity to make treatment decisions on the basis that they base decisions, for example, a refusal of treatment, on a consideration that they later recognize as having been overvalued.[78,79]

We can extend Tony Hope et al.'s argument to research decisions. Given their tendency to underestimate the gravity of their illness and substantial inner conflict, adolescents with AN may also be unable to make decisions about research. Interestingly, however, the same argument is used to justify forced refeeding and involuntary treatment programs. The double standard should be obvious. Adolescents with AN are considered too vulnerable to be subjected to possibly risky research, but not too vulnerable to be subjected to risky, painful, and unwanted treatment, even when there is no scientific basis for believing that treatment will work. Considering the lack of scientific evidence that any treatment is an effective cure for chronic AN, all "attempts at treatment" for chronic AN are experimental. Viewed that way, it makes no sense to exclude teens from one risky experimental treatment yet force them against their will to undergo another.

I propose that we should interpret the substantial inner conflict evident in these quotations as pleas for help. Inconsistency in the desire to treat their AN is a way of saying, "help me find another way." Adolescent patients may know well enough that they do not want to return to a particular therapist or inpatient hospital unit. Refusal of treatment should be seen not as a lack of decisional capacity but, rather, as a yearning for another way to be treated. Participation in research provides another way to help both study participants and all affected by AN, and certain adolescents may even welcome the alternative option.

This is not to suggest that adolescents should be forced to participate in research, or manipulated in any way. Indeed, regulations governing research in children specifically prohibit enrolling minors in research absent their assent.[80] Though they do not have the legal capacity to consent to research, adolescents must be involved in the process of eliciting consent to research from their parents or guardians. Participant assent is not only ethically required in this case but also essential to the success of surgery to implant DBS devices. Placing the leads for DBS requires patients to be awake and compliant during the surgical procedure. Adolescent patients must be fully committed to surgery, must understand its reality, and must be acquiescent to the demands of the surgical procedure.

Conclusion

Even if opening trials of DBS to teens with AN is justified, as I have argued, there remain barriers to their participation in research. Establishing a consensus definition for stages of the disease is a necessary first step toward including adolescents in clinical research, not only research on the efficacy DBS but other endeavors as well. Some authors are working toward this goal.[81,82] Further, the rarity of L-AN among adolescents underscores the need to enroll them in research trials of DBS for AN in order to produce generalizable results about its efficacy. This is the only way to determine whether DBS is a safe and effective treatment for L-AN in adolescents. If adolescents are not enrolled in trials as adult participants benefit from DBS, we might expect an uptick in requests for compassionate use of DBS in treatment-refractory adolescents. Adolescents may be treated in "*n* of 1" studies, producing results that do not extrapolate to other adolescents with L-AN. This would be a regrettable result, as it is critical that we learn as much as possible from each opportunity to research DBS in adolescents with L-AN so that research produces generalizable results. Learning is facilitated by larger, controlled studies. Finally, it may turn out that no adolescents or parents would provide consent to high-risk research on the efficacy of treatment of L-AN, even if they were invited to participate in such research. Further empirical study is needed to gauge the willingness of this small community to improve the health outcomes for all teens with AN by participating in research.

Despite these barriers, there is a compelling case that trials of DBS for AN ought to be opened to treatment-refractory adolescents. The seriousness of AN, its high incidence in teens, and serious shortfalls in the AN treatment literature point to the need for improved, evidence-based treatments for teens with AN. This unmet need generates an obligation on the part of researchers and physicians to promote and conduct research on AN in adolescents specifically. The process of meeting that need may require risk taking on the part of study participants, but that risk is reasonable given the benefits of obtaining definitive answers to the question of whether DBS is an effective treatment for teens with L-AN, and given the substantial risks associated with the current management of L-AN.

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