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Controversies in pediatric obsessive-compulsive disorder

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Although obsessive-compulsive disorder (OCD) has been recognized, described, and studied for several hundred years, research into how OCD presents in children and adolescents has only truly been occurring for the past three decades. While enormous amounts of knowledge have been generated during this time by psychiatrists, psychologists, and other researchers, there are nonetheless a number of highly controversial areas in the field where the literature is unclear, contradictory, or just not well-developed. This review will detail the most prominent disagreements and areas of uncertainty surrounding our current evidence-based understanding of pediatric OCD. These will include whether OCD itself should be classified as an anxiety disorder or should form the core of a different class of disorders; the optimal means of treatment and the role of combining pharmaceutical with psychosocial therapies; how best to disseminate evidence-based treatments; the potential role of autoimmune disorders associated with streptococcal infections in causing OCD; the structure of OCD, including the number of subtypes of the disorder; and the relative contributions of genetics versus environment to the chances of an individual developing OCD. The article concludes with recommendations for lines of research to assist in clearing up some of these controversies.

KEY WORDS: Obsessive-compulsive disorder - Child - Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections - Psychopharmacology - Cognitive behavior therapy.

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References to symptoms of what we now call obsessive-compulsive disorder (OCD) date back hundreds of years to the 17th century. From Lady Macbeth's excessive handwashing to Martin Luther's excessive scrupulosity, case studies and reports from history make it clear that OCD has been with the human species for a very long time.[1] Attempts at systematic research on OCD began in the early 1800s, when it was often considered a form of insanity, although this gradually developed into "insanity with insight" as it was acknowledged that persons suffering from OCD did not have the disconnect from reality seen in psychosis.[2] A more contemporary understanding began by the early 19th century, with several psychological frameworks for understanding why people had OCD competing for attention. Sigmund Freud's hypotheses regarding obsessional thoughts battled Pierre Janet's views of abnormal personality in the minds of clinicians.[3] Although influencing later conceptions, these have fallen by the wayside as new perspectives on OCD have developed in the last century. Interestingly, as in much of psychiatry, the primary focus of work on OCD until fairly recently has been focused on adult cases.

Despite documenting pediatric OCD cases over a century ago [4] and examining prevalence rates in the 1940s,[5] it was not until the efforts of Judith Rapoport in the 1970s that psychiatric research into the treatment and understanding of pediatric OCD began in earnest.[3] Indeed, since the early 1990s there has been an explosion of activity in the field and our knowledgebase has been greatly enhanced. Nonetheless, there are still a number of questions that remain unanswered or controversial about pediatric OCD:

— Etiologically, what is the relative contribution of genetics compared to environmental factors? What genes, biological factors, or psychosocial factors are most important in determining if and when someone develops OCD? Can streptococcal infections that cause autoimmune problems cause OCD symptoms to appear literally overnight in some children?

— Conceptually, is OCD best classified in its traditional role as an anxiety disorder, or should it form the core of a new class of disorders? What is the structure of OCD in children and adolescents? What subtypes, if any, should we concern ourselves with?

— Regarding treatment, what should be considered our most evidence-based approach? What is the relative efficacy and effectiveness of psychtropic medications compared with psychological therapies? How can we as a field best disseminate such treatments?

The purpose of this article was to review in depth these questions, examining what we know and do not know on these issues. In line with the questions above, first we will examine etiological controversies, followed by conceptual concerns, and finishing with treatment issues and with recommendations for further research to address these issues.

Controversies in etiology

While there has been debate regarding the amount of contribution genetics plays in the transmission of obsessive compulsive symptoms and disorder, most experts agree that there is strong evidence for genetic determinants serving an important role in the etiology of OCD.[6] While once considered to be predominately psychological in origin,[7] the familial nature of OCD has been described since the 1930s [8] and rigorous research has shown contributions of specific and common underlying genes in the occurrence of obsessive-compulsive (OC) symptoms in children.[9] Genetic research in OCD has benefited from twin, family, and segregation studies that indicate a breakthrough in upcoming years for localizing specific susceptibility genes for the disorder.[10] At present, the primary controversy is the amount of genetic contribution to the disorder, or heritability, which genes are primarily responsible, and the way those genetic contributions manifest.

Genetic contributions to OCD

Perhaps the most convincing evidence that genetic factors play a role in the transmission and expression of OC symptoms comes from twin studies.[11] Twin studies of OCD have a long history, beginning in 1929 [9] and are particularly beneficial when examining genetic contributions to the etiology of psychopathological phenomena.[12] While overall estimates of heritability of OC symptoms in children range from 45-65%,[13] twin studies of OCD suggest that monozygotic twins have the highest concordance rates between 80-87%, followed by dizygotic twins with concordance rates between 47-50%.[6] These concordance rates are by far the highest of all anxiety disorders.[14]

When examining the risk for additional family members, however, studies show that the age of onset of OC symptoms must be taken into account.[15] For example, Rosario-Campos *et al.*[11] found that an age of onset of OC symptoms before puberty has been associated with higher rates of OC symptoms and OCD among first degree relatives, leading to the conclusion that only some forms of OCD are familial, with childhood onset OCD likely to be more heritable than others. Additionally, a genetic relation has

been hypothesized between obsessive compulsive disorder and Tourette's syndrome (TS).[16] For example, Grados *et al*.[17] found that lifetime tic disorders are more frequent in individuals with OCD when compared to control participants without OCD. Likewise, Kalra and Swedo [18] found that boys with childhood onset OCD have a higher rate of comorbid tic disorder, and a higher genetic contribution to disease. Grados *et al*.[17] argued that the final clarification of the genetic or familial relationship between OCD and tic disorder would require finding genetic loci or susceptibility genes for one or both disorders.

Although researchers have been attempting to localize specific genes contributing to OCD for some time, a common problem faced is that of replication failures.[12] Since OCD is a heterogeneous disorder, the most systematic approach to gene discovery to relies on segregation, linkage and association studies of both twins and families.[10] Segregation analyses are often a preliminary step in genetic epidemiology and provide initial evidence that a specific gene has a significant effect on a particular trait.[19] While segregation analyses to date have been unable to establish the transmission model,[15] they have consistently predicted the existence of a major gene locus that goes beyond purely polygenic effects.[13]

Most genes that have been proposed as candidates are involved in the metabolism of central nervous system neurotransmitters.[10] The most studied candidate genes for OCD include catechol-O-methyl-transferase (COMT), monoamine oxidase-A (MOA), dopamine transporter (DAT), dopamine receptors DRD1, DRD2, DRD3, DRD4, serotonin transporter SERT and g-HT2A and 5HT1B.[20] Of these, the most promising for OCD transmission and expression would appear to be 5HTTLPR and 5HT1B in the serotonin systems and GRIN2B and SLC1A1 in the glutamate systems.[20]

It is believed that the serotonin system likely facilitates the expression of symptoms in OCD, based on findings that SSRIs are effective in reducing OC symptoms.[16] Additionally, data from pharmacological, genetic, and imaging studies indicate that the serotonin receptor 5-HT serves a role in OCD. Relatedly, genetic variants affecting glutamate neurotransmissions are implicated.[6] For example, the glutamate receptor ionotropic-N-methyl-D-aspartate-subunit 2B (GRIN2B) has been identified as a candidate gene and the GABA type B receptor 1 may be a susceptibility factor in the disorder.[6] Additionally, the glutamate transporter SLC1A1, located on chromosomal region 9p24, codes for the excitatory amino acid carrier EAAC1, which has been shown to cause altered glutamatergic neurotransmission and is implicated in the pathogenesis of OCD. SLC1A1 is highly expressed within the cerebral cortex, striatum, and thalamus.[6] These brain regions are connected to the cortico-striatal-thalamic circuit that is consistently implicated in the expression of OCD (see below).

In the fall of 2012, the results of the single largest studies to date on the possible genetic underpinnings of both OCD and TS were published in the journal "Molecular psychiatry". The OCD study,[21] for example, examined 1465 persons with OCD and 5557 ancestry-matched controls. The TS study,[22] included 1285 clinical cases and 4964 ancestry-matched controls. Both, though, failed to find any single nucleotide polymorphisms (SNPs) that achieved a genome-wide threshold of significance.

Results of gene expression on neuroanatomy

In whatever fashion genetics contributes to the development of OC symptoms, it will undoubtedly do so by primarily impacting brain structure and function. The primary pathway proposed for obsessive compulsive behavior involves three brain regions: the orbital-frontal cortex, caudate nucleus, and the thalamus, also known as the cortico-striatal-thalamic circuit (CSTC).[15] Within this neural feedback loop, a series of dysfunctions within the circuits at both the cortical and subcortical levels are believed to be involved in the facilitation of repetitive thoughts and behaviors.[18] Mercadante *et al*.[15] found a number of functional neuroim-

aging studies that indicate abnormal metabolic activity within the orbitofrontal cortex, the anterior cingulate gyrus and the caudate nuclei of patients with OCD.

The CSTC, though, is not the only structure that has been implicated in OCD. Kalra and Swedo [18] found the basal ganglia, a group of nuclei that are interconnected with the cerebral cortex, thalamus, and brainstem, to be associated with OCD. According to Mercadante *et al.*[15] for individuals with OCD, the basal ganglia does not filter cortical impulses properly and, consequently, excitatory impulses will reach the orbitofrontal cortex and prohibit the individual from removing irrelevant worries from the focus of attention. This evidence supports Hollander *et al.*'s [20] view that OCD is characterized by hyperfrontality.

Other brain imaging studies have indicated structural abnormalities within patients of OCD as well.[16] These abnormalities include decreased volume and increased gray matter density with the cortico-striatal-thalamic circuits.[16] Additionally, Kalra and Swedo [18] found greater orbital frontal gray matter volume and a smaller globus pallidus in patients with childhood onset OCD. A smaller globus pallidus could arguably decrease thalamus inhibition, which would result in an increase in obsessions and compulsions that are present in individuals with OCD.

Bacterial infections and OCD

One area of potential OCD etiology that has received a large amount of attention and generated significant controversy in the past decade is the role of bacterial infections and antibodies. A number of longitudinal follow-up research studies examining children and adolescents diagnosed with OCD revealed that many participants suffered from episodic OCD symptoms that often occurred after a diagnosis of group A β-hemolytic streptococcal (GABHS) infection.[23-25] To support the hypothesis that "autoimmunity mediates the neuropsychiatric symptoms", Swedo *et al.*[26] proposed five criteria that clinicians should use to identify a particular group of children and adolescents with pediatric autoimmune neuropsychiatric disorders associated with streptococcal (PANDAS) infections. The first criterion proposed by Swedo *et al.*[26] is the diagnosis of OCD and/or a tic disorder as described in the DSM-III-R or DSM-IV. The second criterion proposed is an onset of symptoms occurring before the child or adolescent hits puberty. The third criterion proposed is an abrupt onset, dramatic symptom exacerbations, and/or episodic symptom severity. The fourth symptom proposed is a diagnosis of a GABHS infection made in association with OCD symptom exacerbation on at least two occasions. The fifth and final criterion proposed is neurological abnormalities such as motoric hyperactivity.

Using the PANDAS criteria, Swedo *et al.*[26] found that all 50 of the children and adolescents who participated in the study portrayed similar symptoms and clinical features to other non-PANDAS children diagnosed with childhood-onset OCD. However, the children in the PANDAS group also had many unique characteristics such as, an extraordinarily young age of onset (approximately 3 years younger than previously diagnosed non-PANDAS children), sudden worsening and dramatic symptoms associated with GABHS infections, frequent motoric hyperactivity, impulsivity, and distractibility, and a number of comorbid symptoms and disorders.

A key factor in PANDAS is that GABHS infections were directly linked to symptom exacerbations. Swedo *et al.*[26] and Giulino *et al.*[27] found that other fever or viral illnesses may have triggered some symptom exaggeration, however a single episode of non-GABHS symptom inducing infections does not rule out the diagnosis of PANDAS. It is also important to point out that Swedo *et al.*[26] insisted that two positive antistreptococcal titers that occur at the same time as symptom exacerbations is necessary but not sufficient to diagnose a child with PANDAS. The evidence found by Swedo *et al.*[26] cannot be used to provide information about the natural history of PANDAS or measure the number of children with the disorder,

however, based on their evidence, the researchers developed a model of pathogenesis: "Pathogen + Susceptible Host → Immune Response → Sydenham's chorea or PANDAS".

Other research provides evidence that children with OCD, TS, and/or chronic tic disorder, have a 2.5 higher risk of receiving a diagnosis of a streptococcal infection in the three months before neurological onset.[28] Interestingly, children diagnosed with OCD, TS, and tic disorders who received a diagnosis of a GABHS infection in the previous year have also been associated with higher rates of attention deficit/hyperactivity disorder (ADHD) and major depressive disorder (MDD).[29]

Although PANDAS patients are significantly more likely to suffer from GABHS infections and symptom exacerbations, only 25% of exacerbations were temporally associated and no relationship was found between the antistreptococcal antibody titers and clinical exacerbations in a study done by Kurlan, Johnson, Kaplan, and the Tourette syndrome study group.[30] These findings contradict the research by Swedo *et al.*[26] who found a temporal relationship between streptococcal infections and symptom exacerbations according to parental reports and medical records. Each of the 50 participants suffered from symptom exacerbations with in the six weeks prior to a GABHS infection. This is not the only area of controversy in PANDAS, although it is a major one.

One of the initially described neurological symptoms of PANDAS (as mentioned above) is hyperactive motor movements.[31] Restlessness and squirminess are two other symptoms frequently seen in patients with PANDAS.[31] One area of uncertainty is that these symptoms could be attributed to the fact that children diagnosed with PANDAS frequently have a comorbid diagnosis of ADHD.[26, 31] Murphy *et al.*[32] discovered that distal choreiform movements are significantly more frequent in children diagnosed with GAHBS infections, whereas upper-limb choreiform movements were not significantly more frequent. According to Swedo *et al.*[26] the most common symptom of children with PANDAS diagnosed OCD is washing and checking behaviors. Other research provides evidence that children with PANDAS often experience urinary urgency, impulsivity, hyperactivity, and deterioration in handwriting skills during the initial episode of PANDAS related illnesses.[33] A significantly high percentage of children with PANDAS also meet the criteria for separation anxiety when compared to children who do not have PANDAS during their episodes of neuropsychiatric illness.[33] Other frequently diagnosed comorbid disorders are oppositional defiant disorder, major depression, and generalized anxiety disorder.[31] Swedo *et al.*[26] noted that the symptoms for the comorbid diagnosis were in sync with the exacerbations of the OCD and/or tic disorder symptoms as well as an increase in antistreptococcal antibody titers. In addition, there is considerable uncertainty in how to best treat children who appear to be suffering from PANDAS, as will be reviewed shortly.

Controversies in conceptual issues

The two primary areas of controversy surrounding how we construct and conceive of pediatric OCD are: 1) under what class of disorders does it best fit? and 2) what is the underlying structure of OCD symptoms? Numerous studies, reports, editorials, and conferences have examined these issues, but there is a high amount of (understandable) dissent in the clinician and researcher communities. Below we will review both areas.

Anxiety disorder or not?

For years, the nosological status of OCD's categorization as an anxiety disorder has been debated vigorously. This became an increasingly important issue with the ongoing review of the DSM-IV psychiatric disorder classification [34] and resultant DSM-5 classifications. In fact, it is important to note that, despite the controversy as reviewed be-

low, in the DSM-5 OCD will *not* be included among the anxiety disorders, and will instead be categorized under "Obsessive-compulsive and related disorders" alongside body dysmorphic disorder, hoarding, trichotillomania, and others.

A reclassification of OCD into a broader spectrum of disorders known as obsessive-compulsive spectrum disorders (OCSD) is a topic that sparked considerable debate.[35] Throughout most of the twentieth century, this disorder has been viewed in the context of an anxiety disorder; however, the notion of obsessive-compulsivity as a spectrum of disorders has been gaining acceptance since the publication of the DSM-IV in 1994.[36] Clinical focus and research groups were formed to try and better investigate both the scientific and practical aspect of such a shift, and were successful in that the DSM-5 will not have OCD as an anxiety disorder. The challenge to OCD as an anxiety disorder has many sources [34] and these arguments led to the formation of work groups to determine whether or not there should be an obsessive-compulsive spectrum, or instead if obsessive-compulsive related disorders should be a separate subset within anxiety disorders. As mentioned above, this spectrum of disorders may also include body dysmorphic disorder, hypochondriasis, hoarding, trichotillomania and other grooming disorders, and other compulsive-impulsive disorders.

Several primary arguments have been introduced for reaching the conclusion that OCD lies more on a spectrum with other disorders, rather than solely as an anxiety disorder:[35]

1. symptoms of OCD and OCSDs share core features such as impulsivity and compulsivity;

2. phenotypical similarities include age of onset, comorbidity, and family loading;

3. these disorders share brain abnormalities in circuitry and neurotransmitter/peptides as well as family/genetic factors;

4. this spectrum of disorders share treatment response commonalities, in particular pharmacological interventions.

Firstly, although anxiety is a symptom of OCD, this is not the primary or central phenomenological characteristic; obsessions and compulsions are primary.[37] Proponents of this model believe OCD differs greatly from other anxiety disorders due to the repetitiveness of behaviors and their inability to resist impulses and urges.[38] This model of OCSD believes that these disorders rely on compulsivity and impulsivity. The compulsive anchor is characterized by harm avoidance and anxiety reduction, whereas impulsivity is characterized by pleasure seeking and gratification behaviors. Once more, these symptoms are shared by many other disorders.[35]

Lochner and Stein [39] hypothesize that several disorders are closely related to OCD. In one study, it was found that those who suffered from OCD were more likely to have multiple comorbid OCSDs than those who suffered from other anxiety disorders, specifically phobic disorders (PD) and social anxiety disorder (SAD), although some OCSDs were more comorbid with PD (hypochondriasis) and SAD (body dysmorphic disorder) than with OCD. Some OCSDs such as repetitive behaviors (trichotillomania) or impulse/reward (kleptomania, hypersexual disorder) were more common in OCD, and both OCD and other anxiety disorders had equally high rates of comorbidity. These findings introduce implications both for and against the OCSD category. As such, the authors concluded it may be beneficial to include OCD and other OCSDs in an enlarged categorization under anxiety disorders in the DSM-V.[39]

Secondly, proponents of OCD as an OCSD feel that these disorders are phenotypically similar to many of the other compulsive-impulsive disorders. Many studies have concluded that the course of these disorders is often chronic and the age of onset is similar to that of many other compulsive/impulsive disorders as well as many anxiety disorders. Stein *et al.*[40] point out that specific phobias, as well as OCD and certain OCSDs, often have an early onset of symptoms. They conclude that there is some overlap, but important distinctions, among anxiety disorders and OCD. Anoth-

er similarity is the high comorbidity rate of OCD and other anxiety disorders with other mood disorders, such as major depressive disorder. For example, one study [41] found that 13% of OCD patients also met criteria for generalized anxiety disorder, 20.8% met criteria for panic disorder, 16.7% for agoraphobia, 36% for social phobia, 30.7% for specific phobias, and 54.1% for recurrent major depression. As such, primary comorbids were anxiety and mood disorders, not the proposed OCSDs (a finding replicated in several other studies).

Phillips *et al*.[42] examined many of the disorders that are being considered for the OCSD, looking at comorbidity, course of illness, familial/genetic components, and treatment response, as well as many other factors. They found that BDD is similar to OCD and OCSD disorders in many ways, but information pertaining to brain abnormalities needs further researching. This is decidedly different from Tourette's disorder, which research indicates may share similar brain abnormalities with OCD. These disorders involve the frontostriatal circuits that are believed to serve as regulatory controllers. Extensive neuroimaging research shows that Tourette's disorder shares the same abnormalities in the frontostriatal circuits in children and adults. This circuit is known to play in mediating ritualized behaviors, negative cognitions, error detection, and implicit learning.[43, 44]

Other converging evidence suggests that the anterior cingulate cortex (ACC), orbitofrontal cortex (OFC), and the caudate nucleus all play a distinct role in OCD. Furthermore, when exposed to threat provoking stimuli, OCD appears to be hyporesponsive in the amygdala than other anxiety disorders. Neurologically speaking, some would say this shows that OCD differentiates itself from other anxiety disorders in respect to the hypersensitivity of the ACC, OFC, and caudate nucleus as well as the hyporesponsivity in the amygdale.[40]

There are some interesting similarities between OCD and the other proposed OCSDs pertaining to treatment response. Some disorders respond well to the same cognitive behavioral techniques used for the anxiety disorders, in particular exposure with response prevention (EX/RP), and some may be differentially affected by pharmacological interventions. For instance, Tourette's syndrome and other tic disorders respond to many of the techniques that are also effective with OCD. The most studied is habit reversal training (HRT), which helps those suffering to resist urges and replace them another behavior until the urge to perform a tic dissipates. Conceptually, this is very similar to EX/RP, and both are based on behavioral theory. Other disorders, BDD for instance, respond well to the same pharmacological interventions as OCD, primarily serotonin reuptake inhibitors (SRI; 42). Of course, SRIs are also front-line pharmacological treatment for most anxiety disorders (generalized anxiety, social anxiety, etc.), so this relationship is not unique.

As already discussed, the work group tasked with the placement of OCD in the DSM-5 has made its decision. The Anxiety, Obsessive-Compulsive Spectrum, Posttraumatic, and Dissociative Disorders workgroup has placed OCD with other purported OCSDs in a new diagnostic category. While this is considered to be a premature and not well-supported move by some, others feel that it is the right thing to do based on the available evidence. Only time and further research will tell if this is a permanent and a lasting change.

Subtypes and structure of OCD

There has been considerable debate in the literature over how to best subdivide patients presenting with OCD, and even if subdivisions based on presenting symptoms or etiological factors are more clinically useful. Interestingly, the symptom subtypes of OCD as identified in the research literature do not really match up with those that are being proposed for the DSM-5. As we will show, though, this may not be problematic.

Presently, OCD is most commonly divided into four or five subtypes that are characterized according to the primary symptoms displayed by the individual.[45] An early

study identified four subtypes: 1) obsessive thoughts with checking compulsions; 2) obsessions over symmetry with ordering, arranging, and counting compulsions; 3) contamination obsessions with cleaning compulsions; and 4) hoarding obsessions and compulsions.[46] A fifth clinician-identified subtype, known as "pure obsessions" has also been evidenced in some studies.[45] In contrast, empirically-derived symptoms clusters most often identify four clusters (contamination/cleaning, symmetry/ordering, forbidden thoughts, and hoarding) or five (the previous four plus over-responsibility).[47]

There have also been a number of specifiers proposed for inclusion in the DSM-5, including early onset OCD, tic-related OCD and PANDAS subtypes.[47] These are more etiologically-oriented than the above symptom clusters, and just as above there is considerable debate on their usefulness and soundness. Below we will review the controversy over these subtypes.

According to Mancuso, Faro, Joshi, and Geller [48] a higher prevalence of OCD within the pediatric population was not recognized until 20 years ago, when the first epidemiological study was conducted. Now, it is generally recognized that approximately 1% of the pediatric population has OCD.[49] Additionally, it is agreed that there are two peaks of incidence for OCD across the lifespan: during pre-adolescence in children and adulthood.[48] Of those, Packer [49] reports that approximately 1/3 to 1/2 of adults with OCD indicate an onset of symptoms before age 10. MacMaster, O'Neill, and Rosenburg [50] corroborate their findings with their report that as many as 80% of all cases begin during childhood or adolescence.

Those who support the inclusion of early onset OCD as a specific subtype argue that the juvenile form of OCD may differ in important ways from its adult counterpart, including a male predominance and higher levels of comorbidity with disruptive behavior disorders such as oppositional defiant disorder, and ADHD.[51] Geller *et al.*[51] also argue that children and adolescents with OCD exhibit higher rates of aggressive obsessions and hoarding behavior compared to adult counterparts. Anatomically, Leckman *et al.*[47] report that individuals between the ages of 10 and 17 show lower levels of brain activity and decreased blood flow in the right insula, putame, thalamus, left anterior cingulated cortex, dorsolateral prefrontal cortex and orbitofrontal cortex compared to individuals with a late onset (*i.e.*, after puberty). It is argued that these differences support a developmental discontinuity between juvenile and adult OCD. On the flip side, however, are those who call for a larger amount of research needed to support an early-onset type.[47] The common problems include the lack of clear-cut operational definitions of "early onset" (in terms of age) across studies, which damages generalizablity; confounds between early-onset and tic-related OCD (which often manifests prior to age 10); and a poor understanding of how subclinical symptoms in childhood may develop into full-fledged OCD in adults.

Tic-related OCD may account for as many as 10-40% of cases diagnosed in either childhood or adolescence.[52-54] Individuals who experience OCD related to tics are more likely to report experiencing antecedent sensory phenomenon such as perceptions associated with visual, tactile, auditory stimulations and feelings of incompleteness.[55] They also exhibit a higher rate of obsessions concerning symmetry and ordering compulsions and higher rates of disruptive behavior disorder.[56] Although no specific genes have been associated with a tic disorder or OCD (as mentioned above), individuals struggling with OCD and concurrent tics have been found to be highly familial. For example, Grados *et al.*[17] found that first degree relatives with OCD and tic disorder displayed an earlier age at onset of OC symptoms, which suggests an association between OCD at age of onset and the expression of tics. Additionally, Kalra and Swedo [18] report that nearly 67% of children with OCD were observed to have comorbid tics and between 20 and 80% of children with Tourette's express OCD symptoms. Based on these findings, 81% of 187 OCD

experts around the world endorsed the inclusion of a tic related subtype to be included in DSM-V.[57] The primary argument against such a subtype is a powerful one, though: those with and without tics do not differentially respond to cognitive-behavioral therapy, the most effective psychosocial treatment for OCD.[47] There is evidence, in comparison, that those with tics do show differential treatment effects with SRIs and neuroleptics.

As described previously, the PANDAS subtype of OCD is supposedly characterized by five clinical features that make it unique and distinct from other forms of OCD.[18] Given the uncertainty and inconsistency across studies, there is considerable debate over whether to include a PANDAS subtype in the DSM-5. This is reflected in the finding that only slightly over half of all OCD experts in a major survey thought there should be a PANDAS subtype in the DSM-5.[57] It appears as though it will be included in the next edition of the DSM, though, despite some doubting that it even actually exists.[58]

Controversies in treatment

A very large percentage of adults with diagnosed OCD reportedly developed the disorder as a child or adolescent.[59] This is one of many reasons why developing and disseminating effective treatments for children and adolescents is important and necessary. Increasing awareness of OCD symptoms and treatments may help to enhance the diagnosis rate and broaden the opportunities for treatment. Pediatric research provides evidence that OCD symptoms are reduced by 30-40% with pharmacotherapy,[60] while many consider CBT with exposure and response prevention (EX/RP) to be the treatment of choice for pediatric OCD.[61] Below, we will address the literature on whether pharmacology, psychotherapy, or a combination is the most effective means of treatment for various degrees and forms of pediatric OCD. After that, we will examine some issues surrounding the most effective means of getting effective treatments to the masses.

Medication, therapy, or both?

Multiple psychopharmacological avenues for the treatment of pediatric OCD exist. For example, ample research provides evidence for the use of selective serotonin reuptake inhibitors (SSRIs) as an effective treatment for pediatric OCD.[60, 62, 63] They may not, though, be the most effective medication, as Abramowitz, Whiteside, and Deacon [64] found contradictory results of the superiority of Clomipramine, a tricyclic antidepressant (TCA), over SSRIs. Gellner *et al.*[60] also found that clomipramine was significantly more effective than SSRIs at reducing pediatric OCD symptoms. Although it was more effective, their conclusions and recommendations were that clomipramine has more aversive and frequent side effects than SSRIs [18] and, therefore, should only be prescribed for children and adolescents with severe, treatment resistant symptoms.[60, 64]

Although SSRIs can reduce symptoms by approximately 50-75%, medication alone is rarely effective in removing OCD symptoms completely.[65] It also causes a fairly common set of negative side effects that include nausea, headaches, sleepiness, dizziness, sexual difficulties, constipation, dry mouth, insomnia, poor appetite.[66] There are also no strong guidelines about which SSRI will be most effective for whom, leading to guesswork on which SSRI to use for treatment.[60, 67]

In contrast to above findings that show multiple pharmacological agents are effective in alleviating OCD symptoms, the literature is clear that only one psychotherapy approach that works well. The most effective treatment by far is cognitive-behavioral therapy with an exposure and response prevention component.[63] The cognitive component involves using certain techniques to help the client recognize maladaptive thinking patterns and understand how to reframe those negative and anxiety producing thoughts. The exposure and response prevention component involves presenting the anxiety producing stimuli (obsessions)

and preventing the child from performing their anxiety reducing ritual (compulsions). EX/RP is superior to medications alone, with effect sizes ranging from 1.16-1.72.[68] There is a low relapse rate compared to medications, but it is important to note that up to 25% of patients will drop out prior to completion of treatment due to the nature of treatment.[69]

In a meta-analysis examining the effects of treatments for pediatric OCD, Abramowitz *et al.*[64] concluded that both SSRIs and EX/RP were effective in significantly reducing OCD symptoms. While both treatments are effective in reducing symptoms post-treatment, the use of EX/RP was associated with larger effect sizes on OCD measures and found to be superior in some treatments.[64] Keeley *et al.*[63] concluded that CBT alone or CBT with pharmacotherapy should be the first treatment option for children and adolescents because results of pharmacotherapy research are so modest. In the Pediatric OCD Treatment Study,[62] researchers found that both CBT and sertraline (an SSRI) were significantly effective in reducing OCD symptoms when compared to placebo treatment, however when CBT and sertaline were used in accordance, they proved to be significantly more effective than when used alone.

Although serotonin reuptake inhibitors have been proven efficacious, they have modest treatment effects in addition to the above detailed adverse effects. Given the limitations of SSRIs, other medical interventions have also been recently examined. Storch *et al.*[70] researched the effects of D-Cycloserine as a concomitant pharmacotherapy when treating children with OCD. They found that those children who were assigned to the D-Cycloserine group showed moderate treatment effects when compared to those who were assigned to the placebo control on many severity indices. Furthermore, they found that the participants tolerated the medication well with limited adverse effects. In another study, patients who were given D-Cycloserine appeared to benefit more from exposure-based therapy than those who did not.[71] As both studies were relatively small and have not been replicated, the routine usage of D-Cycloserine cannot be recommended.

Another area of study has examined the use of antibiotics and therapy to treat those children with OCD who are suspected to have it as a result of autoimmune problems. Research supporting the use of antibiotics to decrease the amount of PANDAS induced symptom exacerbation is contradicting. A longitudinal observation of patients with PANDAS found antibiotics effectively decreased the amount of GABHS infections and that OC symptoms disappeared all together.[72] A separate 8-month long study found that randomized penicillin or placebo treatment were not significantly different.[73] After correcting some limitations, researchers found that the number of GABHS infections along with symptom exacerbations significantly decreased when comparing baseline to end of study scores (12 months later) for individuals who received antibiotic medications penicillin or azthromycin on day 1 of the week and a placebo on the other six days.[74] Because of the amount of contradictory research, it is important that more research is done before concluding the effectiveness of antibiotics in reducing OCD symptoms.

Plasma exchange (PE) and intravenous immunoglobulin (IvIG) treatments have been hypothesized to interrupt the autoimmune process, which might aid in decreasing the number of exacerbations or lessening the severity of PANDAS-related OCD.[31] Plasma exchange is the removal of old plasma that may have diseased substances, in exchange for new red and white blood cells and new platelets are returned to the body. Many doctors use IvIG, a blood product also known as pooled human gamma globulin, in patients who lack the antibodies to fight off infections. Perlmutter *et al.*[75] found that OC symptoms significantly decreased one month after treatment by 45% for children who received PE and 58% for children who received IvIG. At the one-year follow-up, the symptoms had decreased even more. For children who received PE, their symptoms had decreased by 58% and by 70% for children who had received IvIG. It is important to note that

researchers have found that neither PE nor IvIG have been effective in reducing symptoms for children with non-PANDAS OCD.[31] While PE and IvIG seems to be effective, there are severe side effects and more research is needed to determine the extent of its effectiveness and safety.

Dissemination of treatments

Given that a combination of therapy and medications appears to be the most effective route to symptom remission for those suffering from pediatric OCD, it would be hoped that the estimated 1-3% of the population with OCD could gain effective access to evidence-based treatment. Effective treatment is even more important when the huge impact on the quality of life of patient and the patient's family is considered.[76] A relatively small number of therapists worldwide, though, are trained in effective therapeutic techniques for a number of reasons.[77] This has led to numerous avenues of research examining the best way to disseminate treatment, many of which are still relatively unresearched and potentially controversial.

The use of computers to supplement or completely replace a human therapist has a history dating back to the 1980s.[78] Although the research on the use of computers for both the treatment of OCD is small in terms of published literature but very promising in terms of outcome.[79] The decrease in symptoms and improvement in functioning across the treatment with the most potential, BT STEPS, is far superior to no treatment, and in some cases was found to be as effective as clinician-guided treatment.[80] Given that only phone access is needed to engage in BT STEPS, this could be a very important step to increasing availability of EX/RP.

Computers can also be leveraged to increase provider access in remote areas. Providing EX/RP through web-camera delivery may decrease a number of distribution problems. The cost of service is lower for both the therapist and the parents of the youth receiving treatment because it cuts down the cost of travel, time off work, and clinical resources. While using a web-camera, treatment is more accessible and helpful in treating obsessions in their natural habitat. Because clients can use web-camera to participate in therapy, it may be more effective in an adolescent population because they can participate in the comfortable, secure, and confidential space of their own. If a client has more access and comfort during therapy, it is possible that treatment will result in more frequent positive results. Results of the preliminary study show that EX/RP delivered via webcam is a promising treatment option for children and adolescents with OCD.[81] The results echoed other CBT trials in which the OCD symptoms decreased by at least 56%. Over half of the study participants in the active condition achieved remission status and even more maintained the symptom reduction at the three month follow-up.

Conclusions

As noted above, those of us who work in the area of pediatric OCD are no strangers to controversy. Because of the discrepant or uncertain nature of some areas of the literature, though, there exist numerous possibilities for advancement of our understanding. The finding of a lack of SNPs associated with OCD, for example, help point to the need for studies that examine allele combinations, as well as an increased focus on epigenetic contributions to OCD and related disorders. More functional and structural studies of the OCD brain may shed increased light on how biology results in the symptoms seen in children with OCD, as well as how those structures and functions change across time. More prospective and longitudinal studies need to be conducted to better understand PANDAS and the impact of autoimmune function on OC symptoms. Treatment outcome studies that compare traditionally-delivered therapies to newer medical and technologically-assisted therapies can help to understand both what should be disseminated and what may work

best for whom. More studies examining the proposed subdivisions of OCD in youth will undoubtedly occur with the publication of the DSM-5, and this will in turn drive forward potential revisions and changes in criteria in the future. With the continued persistence of established and new researchers, well-designed and conducted studies can help to improve our understanding of pediatric OCD over the next thirty years just as much as we have increased it over the past thirty.

Riassunto

Controversie nel disturbo ossessivo-compulsivo infantile

Sebbene il disturbo ossessivo-compulsivo (DOC) sia stato riconosciuto, descritto e studiato da diversi secoli, la ricerca su come il DOC si presenti nei bambini e negli adolescenti si è sviluppata solo negli ultimi tre decenni. Nonostante psichiatri, psicologi e altri ricercatori abbiano prodotto un'enorme mole di conoscenze in tale lasso di tempo, permangono tuttavia diverse aree di acceso dibattito negli ambiti in cui la letteratura è poco chiara, contraddittoria o semplicemente poco sviluppata. La presente *review* passerà in rassegna i principali punti di disaccordo e le aree di incertezza riguardo la nostra attuale comprensione basata sulle evidenze del disturbo ossessivo-compulsivo infantile. Si discuterà se il DOC debba essere classificato come disturbo d'ansia o se debba costituire invece il centro di una diversa classe di disturbi; discuteremo degli strumenti di trattamento ottimali e del ruolo delle terapie psicosociali e farmacologiche combinate, di come diffondere al meglio i trattamenti basati sulle evidenze e del potenziale ruolo dei disturbi autoimmuni da streptococco quali cause del DOC; discuteremo inoltre della struttura del disturbo ossessivo-compulsivo, incluso il numero di sottotipi del disturbo e dei relativi contributi della genetica *versus* dell'ambiente alle possibilità che un individuo sviluppi un DOC. L'articolo termina con alcune raccomandazioni sulle direzioni di ricerca da intraprendere per contribuire a risolvere alcune di queste controversie.

PAROLE CHIAVE: Disturbo ossessivo-compulsivo - Età pediatrica - Malattie neuropsichiatriche autoimmuni associate con infezioni da steptococco - Psicofarmaci - Terapia cognitivista.

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