J Exp Clin Med 2012;4(2):92–97

Contents lists available at SciVerse ScienceDirect

Journal of Experimental and Clinical Medicine

journal homepage: http://www.jecm-online.com

REVIEW ARTICLE

Overview of the Diagnosis and Treatment of Stuttering

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ARTICLE INFO

Article history:
Received: Jan 3, 2012
Revised: Feb 1, 2012
Accepted: Feb 1, 2012

KEY WORDS:
dopamine hypothesis of stuttering;
medication;
stuttering

Stuttering is a speech disorder defined by frequent prolongations, repetitions, or blocks of spoken sounds and/or syllables, as well as anxiety and cognitive avoidance. Stuttering is a very common disorder, and research now indicates that it is likely a multifactorial process with a physiologic etiology. Recent advances in the field of stuttering now provide insight into novel treatment strategies to help guide the practicing clinician. In addition to considering the upcoming revision to the *Diagnostic and Statistical Manual of Mental Disorders* criteria, comprehensive treatment should address all aspects of this disorder, as the optimal treatment of stuttering involves a multidisciplinary approach.

1. Introduction

Stuttering is a multifactorial speech disorder defined by frequent prolongations, repetitions, or blocks of spoken sounds and/or syllables. It is a common disorder affecting about 1% of the adult population[1] and is classified in the *Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition* as an Axis I disorder (Table 1). Characteristics of stuttering include repetition of sounds or syllables, sound prolongations, interjection, broken words, blocking of sounds, word substitutions, or excessive physical tension during speech production.[2] Other coexistent symptoms may include facial grimacing, tremors of muscles involved in speech, and eye blinks as well as avoidance of words or situations which exacerbate stuttering episodes.[3,4]

The most common form of stuttering is developmental stuttering, which begins in childhood. A total of 80–90% of developmental stuttering begins by 6 years of age and affects about 5% of children.[5,6] Spontaneous recovery occurs in about 75% of individuals.[7] Rare cases of acquired stuttering do occur and begin in adulthood, but are related to secondary causes such as medications, brain trauma, or stroke.[8] In about 60% of children who stutter, the symptoms will remit by 16 years of age. But many cases persist into adulthood, and given the importance of communication in the development of a child, treatment of stuttering in children requires early intervention.[9]

The American Psychiatric Association is currently in the process of modifying the classification and description of stuttering for *Diagnostic and Statistical Manual of Mental Disorders—Fifth Edition (Proposed Revision): Childhood Onset Fluency Disorder*, due for publication in May 2013.[10] Several proposals include changing the diagnostic label of "Stuttering" to "Child Onset Fluency Disorder," deletion of criterion of interjections, inclusion of avoidance and/or anxiety around speaking situations related to stuttering, and improved distinction between childhood-onset fluency disorder or stuttering from other adult-onset forms (Table 2). Such changes are proposed while recent advances in the knowledge of stuttering lead toward a neurophysiologic basis. Improved clarification of the *DSM* criteria will allow individuals who stutter to have greater access to comprehensive care including speech and cognitive therapies, and emerging pharmacologic treatments.[10]

2. Etiology

For centuries, stuttering was believed to involve abnormalities in the tongue or larynx. But treatments that focused on the tongue or larynx have not demonstrated consistent efficacy in improving stuttering symptoms. It was the pioneering work of Orton[11] and Travis,[12] who postulated that stuttering may arise from abnormal cerebral activity, which signaled a change in the understanding of stuttering. Research now indicates that stuttering is likely a multifactorial process with a physiologic etiology.

Genetic factors are thought to be involved in many cases of stuttering, accounting for about 50–80% of stuttering cases based on twin and family studies.[13] Pairwise concordance for monozygotic same-sex twins is significantly greater than in fraternal

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1878-3317/$ – see front matter
doi:10.1016/j.jecm.2012.02.001

Table 1 *DSM-IV-TR* diagnostic criteria for stuttering

Stuttering
A. Disturbance in the normal fluency and time patterning of speech (inappropriate for the individual's age), characterized by frequent occurrences of one or more of the following: 1. Sound and syllable repetitions 2. Sound prolongations 3. Interjections 4. Broken words (e.g., pauses within a word) 5. Audible or silent blocking (filled or unfilled pauses in speech) 6. Circumlocutions (word substitutions to avoid problematic words) 7. Words produced with an excess of physical tension 8. Monosyllabic whole-word repetitions (e.g., "I-I-I-I see him")
B. The disturbance in fluency interferes with academic or occupational achievement or with social communication.
C. If a speech–motor or sensory deficit is present, the speech difficulties are in excess of those usually associated with these problems.
Coding note: If a speech-motor or sensory deficit or a neurological condition is present, code the condition on Axis III.

DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition (Text Revision).

pairs (63% vs. 19%, respectively).[14] Stuttering also has a male/female ratio of about 4:1, with female stutterers much more likely to have spontaneous remission with age.[13] This sex discrepancy results in up to 80% of adult stutterers being male.[15]

Acquired stuttering also occurs, but is much less common and is often the result of brain trauma or medication.[3] Adults who stutter are also at an increased risk for both mood[16] and anxiety disorders.[17,18]

Several recent studies have focused on finding a genetic basis for stuttering. In a study of 112 individuals, the presence of the C allele at *rs6277* in the dopaminergic *DRD2* gene was associated with increased susceptibility to the disorder.[19] Similarly, a report on a case with a complex set of speech and language difficulties including stuttering by Petrin et al[20] found that deletions and disruptions in genes are involved in the cause of language and speech disorders. More recently, stuttering has been associated with mutations in genes involved in lysosomal metabolism in certain individuals. Mutations in three genes on chromosome 12 that disrupt the lysosomal targeting pathway which generates the mannose 6-phosphate signal have been identified. Although the mutations can only be identified in less than 10% of cases of familial stuttering, their identification provides new insight and direction for future studies.[21]

Table 2 *DSM-5* proposed revision of diagnostic criteria for childhood onset fluency disorder (stuttering)

Childhood Onset Fluency Disorder
A. Childhood onset Fluency Disorder, also referred to as stuttering, is diagnosed when disturbances in the normal fluency and time patterning of speech are inappropriate for the individual's age and language skills, persist over time (in most cases), and are characterized by frequent and marked occurrences of one or more of the following: 1. Sound and syllable repetitions 2. Sound prolongations of consonants as well as vowels 3. Broken words (e.g., pauses within a word) 4. Audible or silent blocking (filled or unfilled pauses in speech) 5. Circumlocutions (word substitutions to avoid problematic words) 6. Words produced with an excess of physical tension 7. Monosyllabic whole-word repetitions (e.g., "I-I-I-I see him") 8. Anxiety about symptoms 1–8 leading to avoidance associated with speaking situations.
B. The difficulties with speech fluency result in functional limitations in effective communication, social participation, academic performance, or occupational performance, alone or in any combination.
C. Exclude dysfluency associated with neurological insult (e.g., stroke, tumor, trauma) or conversion reaction and malingering. A fluency disorder may occur as primary or coexist with other communication disorders or any other disorder not excluded.
D. Symptoms must be present in early childhood (but may not become fully manifest until speech, language, communication, or social demands exceed limited capacities).

DSM-V: Diagnostic and Statistical Manual of Mental Disorders—Fifth Edition (Proposed Revision, Updated December 9, 2010). Retrieved December 20, 2011.

One recent case report suggests stuttering as a pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections (PANDAS),[22] which has been described in Tourette syndrome to share many clinical symptoms with stuttering. The hypothesis is that the antibodies created to fight the streptococcal infection cross-react with the developing basal ganglia, the region of the brain implicated in stuttering etiology.[23–25] While the recovery in this case may have been spontaneous and unrelated to antibiotic therapy, further research are indicated into this possible etiology.[22,26]

3. Brain imaging studies

Imaging studies have implicated a number of brain regions involved in the process of stuttering. While no single region of the brain has been identified as the source of developmental stuttering, imaging studies have implicated brain asymmetry, extra sulci, or reduced white matter changes involved in areas involved in speech or articulation.[27]

The first positron emission tomography (PET) study in stuttering (using [18F]deoxyglucose) reported abnormal glucose metabolism in speech cortical areas and the striatum in stuttering individuals. The speech cortical areas normalized under induced fluency, but the basal ganglia remained low.[28] Studies using PET scans of individuals with moderate to severe developmental stuttering also showed significantly higher 6-fluorodopa uptake in the medial prefrontal cortex, deep orbital cortex, insular cortex, extended amygdala, auditory cortex, and caudate tail compared to controls.[29]

Sommer et al[30] found structural abnormalities in the left hemispheric speech areas to be implicated in stutterers. Their findings also suggest that persistent developmental stuttering results from disturbed timing of activation in speech-relevant brain areas, meaning that right hemisphere overactivation may reflect a compensatory mechanism analogous to right hemisphere activation in aphasia.[30]

One study comparing cortical activation sequences in 10 fluent speakers and nine developmental stutterers showed clear differences in cortical activation patterns, both in the evoked responses, time-locked to word presentation and mouth movement onset, and in task-related suppression of 20-Hz oscillations. Several of the findings included differences in sequence of activation of articulatory programming and motor preparation, activation and silence of the right motor/premotor cortex during speech production, hemisphere dominance in suppression of motor cortical rhythms, and activity level of the right frontal cortex during speech production. The authors suggested that the findings may reflect imprecise functional connectivity within the right frontal cortex and incomplete segregation between the adjacent hand and mouth motor representations in stutterers during speech production.[31]

In another study using both structural and functional imaging of 12 patients with developmental stuttering, Watkins et al[27] in 2008 found bilateral structural abnormalities of the ventral premotor cortex, along with underlying reduced functional white matter integrity, which the authors argue are critical regions involved in the integration of motor planning and sensory feedback to produce fluent speech. In this study, patients also displayed marked overactivity in the midbrain, most likely involving the basal ganglia, lending further support for the central role of the dopaminergic system in the development of stuttering.[25]

Brown et al[32] conducted an activation likelihood estimation meta-analysis of imaging studies compared stuttered and fluent speech production in adults. They found that motor areas to be overactivated in stuttering include primary motor cortex, supplementary motor area, cingulate motor area and cerebellar vermis. Additionally, stutterers showed anomalous right-laterality in the frontal operculum, Rolandic operculum, and anterior insula. The authors further proposed the phenomenon of efference copy as a unifying account of the pattern activation revealed within their analysis, arguing that it provides the basis for a stuttering system model that is testable and should help advance the understanding and treatment of this disorder.[32]

Recent functional magnetic resonance imaging (fMRI) studies have looked at neural circuits involved in atypical planning and disrupted execution of speech commonly involved in patients who stutter. Lu et al[33] found that atypical planning occur in the bilateral inferior frontal gyrus and right putamen, and that their atypical execution of speech is evident in their activations in the right cerebellum and insula, left premotor area, and angular gyrus.

Transcranial magnetic stimulation has also been used to study the physiologic basis of stuttering. One recent study found that in persistent stuttering, intracortical excitability of the primary motor tongue representation is altered with a deviant time course for inhibitory activity in the right hemisphere and reduced paired-pulse facilitation. The results raise the possibility that changes in intracortical networks mediated by altered GABAergic regulations may be associated with persistent stuttering.[34]

4. The dopamine hypothesis of stuttering

Stuttering is likely related to abnormal elevations of cerebral dopamine activity. Studies with stimulant medications which increase dopamine activity have shown that they increase stuttering symptoms.[35] In addition, the striatal hypometabolism in stuttering seen in PET imaging may be the result of a hyperdopaminergic state. Wu et al[29] investigated the dopamine hypothesis of stuttering by measuring the presynaptic dopamine levels in individuals who stutter, and showed that these individuals have 50–200% higher levels of dopamine activity than controls. As dopamine is an inhibitor of striatal metabolism, elevated dopamine provides an explanation for the striatal hypometabolism seen in stuttering.[28]

An increasing amount of research has implicated stuttering as a disorder of the central nervous system, specifically systems involved in regulating dopamine levels within the brain.[25] The dopamine hypothesis is also supported by research in which patients with developmental stuttering experience worsened stuttering when given dopamine agonists such as levodopa.[36] Clinical trials investigating dopamine antagonists as a treatment for stuttering have provided findings supporting the central role of dopamine in the etiology of stuttering. Dopamine antagonists haloperidol,[37] tiapride,[38] risperidone,[39] and olanzapine[40] have all been shown to induce significant improvement of stuttering compared to placebo.

The dopamine hypothesis is also supported by pharmacologic studies of tic disorders. Given the well-documented association between stuttering and tic disorders, it has been proposed that both share a common pathology.[41] Studies using the anti-dopaminergic medication aripiprazole have shown effectiveness in reducing motor tics in both patients with developmental stuttering[42] and children and adolescents with a primary tic disorder.[43]

Lan et al[19] recently found evidence supporting a correlation between dopaminergic genes and stuttering among Han Chinese. Their case-control study showed the C allele at *rs6277* in *DRD2* gene is associated with increased susceptibility to the disorder, while the T allele is protective. They also found the haplotype 939 T/957 T to be protective factor.[19]

Alm's[23] 2004 review of possible relations between stuttering and the basal ganglia circuits examined pharmacologic trials, lesion studies, brain imaging, genetics, and developmental changes of the nervous system, which supported the proposed role of the basal ganglia–thalamocortical motor circuits through the putamen in stuttering.

Giraud et al[44] reported a correlation between severity of stuttering and activity in the basal ganglia and showed that this activity is modified by fluency shaping therapy through long-term therapy effects that reflect speech production improvement. The model of dysfunction in stuttering and possible repair modes further implicates the neural connections between the motor cortex and basal ganglia in speech motor functions.[44]

Recent studies with Pagoclone sheds new light on the dopamine hypothesis. It is currently unclear how Pagoclone, a selective gamma-aminobutyric acid A ($GABA_A$) partial agonist, benefits stutterers, but may be related to dopamine/GABA interactions in the basal ganglia[15] or to changes in intracortical networks mediated by altered GABAergic regulations.[34]

5. Historical approaches to treatment

In the past, approaches to treatment of stuttering reflected various competing theories on the etiology of stuttering. For many centuries, treatment modalities focused on stuttering as an abnormality of the tongue or larynx. More recent treatment modalities are based on behavioral principles intended to allow patients to produce more fluent speech while alleviating anxiety associated with disturbed speech production. Examples include fluency shaping and stuttering modification, where patients attempt to reduce tension. But research on intensive therapeutic modification therapy has failed to produce robust results, as therapeutic benefits have been reported to be limited and temporary.[45]

6. Pharmacologic treatments

Many medications have been tried in the treatment of stuttering, although at the time of this review, none have been approved by the U.S. Food and Drug Administration (FDA) specifically for the treatment of stuttering. The most promising medications thus far have been antidopaminergic agents.[46] Pagoclone, a $GABA_A$ partial agonist, has also shown favorable results.[15]

Research from imaging studies suggests that people who stutter exhibit hypometabolism of the striatum and increased dopamine activity.[29] This evidence provides a plausible mechanism as to how dopamine antagonists decrease stuttering by increasing striatal metabolism by blocking D_2 receptors in the striatum.[47] Pharmacological trials on medications that lower dopamine activity have consistently shown replicated efficacy in improving stuttering. Although they also exhibit sedating qualities, it is likely that their demonstrated efficacy in stuttering is related to their effects on dopamine and not to merely an antianxiety or sedating effect.[46]

Other agents have been tried with limited efficacy. Limited research with calcium-channel blocking medications such as verapamil, have shown limited efficacy in stuttering.[48,49] But such calcium-channel blocking medications may exert a mild antidopamine effect. Trials of serotonin-selective reuptake inhibitors[50] and benzodiazepines[46] have not yielded positive results. Benzodiazepines and barbiturates, which are anxiolytics that are also highly sedating, have been found to have no beneficial effects over placebo in the treatment of stuttering.[46] Histamine blocking agents have also not shown efficacy in stuttering in previous studies.[51]

6.1. Haloperidol

Many studies with haloperidol, a conventional dopamine antagonist and antipsychotic, showed that this medication can improve fluency in individuals who stutter. But long-term compliance with haloperidol in stutterers is poor given its drawbacks: dysphoric side effects, sexual dysfunction, extrapyramidal concerns, and risks of tardive dyskinesia.[46] Early hypotheses surrounding the potentially beneficial effects of haloperidol in the treatment of stuttering were based on its effect on the dopaminergic system and studies showing the efficacy in haloperidol in the treatment of Tourette's syndrome.[37]

In Rosenberger et al's early double-blind crossover study on the use of haloperidol in the treatment of stuttering,[8] patients show clinical improvement in percentage of time dysfluent. But this improvement is significant only for patients who have been greater than 30% dysfluent at baseline.[37]

Murray et al[52] performed another double-blind crossover study of 26 adults with haloperidol, and showed that almost all patients improved significantly in terms of number of dysfluencies, speed of speaking, and reduced secondary "struggle" while speaking. Nevertheless, only one out of out 26 patients decided to continue taking the medication after a year, and nearly one-third did not complete the 3-month trial due to the medication's adverse side effects.[52]

6.2. Risperidone

A newer generation dopamine antagonist with a side effect profile more favorable than haloperidol, risperidone, has been shown to improve stuttering symptoms (0.5–2 mg/day) in a double-blind, placebo-controlled study. This second-generation (atypical) antipsychotic (SGA) drug was generally well tolerated, but long-term compliance is hindered by prolactin-related side effects such as sexual dysfunction, galactorrhea, amenorrhea, and dysphoria.[39,53] Dysphoria with risperidone has also been reported to occur with its use in Tourette's syndrome, which shares many similarities to stuttering.[54]

In a double-blind, placebo-controlled study in the treatment of developmental stuttering in 16 adults, those in the treatment arm had a significant decrease in percentage of syllables stuttered, time stuttering as a percentage of total time speaking, and overall stuttering severity.[39] According to a recent case report, treatment with risperidone also has the added benefit of reducing tic-like motor behaviors in a patient with severe persistent developmental stuttering.[55]

6.3. Olanzapine

Olanzapine is another newer SGA psychotropic medication that has dopamine blocking properties with fewer prolactin-related side effects. Olanzapine acts as a D_2 receptor antagonist with additional antagonist activity at serotonergic receptors. Olanzapine possesses a different side-effect profile than risperidone, with a lower incidence of extrapyramidal side effects and hyperprolactinemia, but greater effects on weight gain and triglyceride elevation.[56]

In Maguire et al's[40] double-blind, placebo-controlled trial of 24 adults with developmental stuttering, olanzapine (2.5–5 mg) significantly reduces stuttering symptoms compared to placebo. The degree of improvement was deemed "clinically significant" on active medication by both the patient and the clinician as rated by the Clinical Global Improvement scale. Positive effects of the medication extended to natural speaking situations as measured by the Subjective Screening of Stuttering and Clinical Global Improvement scale. The medication is well tolerated with some degree of weight gain, without prolactin-associated side effects. Compliance is also high, with all participants electing to enter the open-label phase of the protocol. Of note, for many participants in the open-label extension, stuttering symptoms continued to improve over 6 months to 1 year (or maybe longer), suggesting that an adequate "treatment trial" should be measured in months instead of days or weeks.[40]

Case reports suggest that olanzapine may also be equally effective and tolerated in the child and adolescent population[57] and in cases of acquired neurogenic stuttering.[58]

6.4. Asenapine

Asenapine is a new SGA associated with less weight gain than other atypical antipsychotic medications.[59] Maguire et al[60] reported three cases of adults with stuttering who responded well to asenapine (5–10 mg) with good tolerability. Each case resulted in improved fluency, but no formal measures of fluency were taken. A common side effect in each case was sedation. One patient reported a 4.5-kg (10 lb) weight increase, while the other two experienced none. Theses case reports suggest that asenapine may be an effective and well-tolerated medication for the treatment of stuttering, warranting further investigation.[60]

6.5. Aripiprazole

Aripiprazole is a combined D_2 and 5-HT_{1A} receptor partial agonist and 5-HT_{2A} receptor antagonist. One case report published by Tran et al[42] described its use (5–15 mg) in treating an adult with developmental stuttering, but further research is required.

6.6. Pagoclone

Pagoclone is a selective $GABA_A$ partial agonist being developed through the U.S. FDA specifically for the treatment of stuttering. In an 8-week, multicenter, double-blind, placebo-controlled study of 132 patients aged 18–65 years, Maguire et al found that treatment with pagoclone (0.15–0.30 mg, given twice daily) resulted in a 19.4% reduction in percentage of syllables stuttered, with a 40% reduction after a subsequent 1-year open-label treatment. Furthermore, Pagoclone is well tolerated by patients in the study. The most commonly reported side effect, headache, was reported in 12.5% of treated patients. Nearly 90% of patients electively chose to continue taking the medication during the 1-year, open-label extension portion of the study. Furthermore, patients in the treatment group reported a greater sense of control over their stuttering and verbal fluidity without an effect in the reported naturalness of speech. Patients also reported reduced social anxiety, likely due to the medication's effect on GABA, an anxiety neurochemical, which is not readily observed with the dopamine-blocking agents. The exact mechanism of $GABA_A$ partial agonism benefitting speech is unclear, but may be related to dopamine/GABA interactions in the basal ganglia. In light of its favorable tolerability profile, as well as consistency of effects across multiple efficacy variables, pagoclone may have potential as a pharmacological treatment of stuttering.[15]

7. Conclusions

Stuttering involves abnormalities in fluency as well as anxiety and cognitive avoidance. In addition to considering the upcoming revision to the *DSM* criteria, comprehensive treatment should address all aspects of this disorder, including not only the fluency enhancement, but also improvement of social avoidance, anxiety, and cognitive restructuring. The optimal treatment of stuttering involves a multidisciplinary approach.[61]

We suggest that all children, at the age of onset, should be evaluated by a qualified speech-language pathologist. In patients 2–8 years of age, the primary treatment modality should be speech therapy, with possible workup of PANDAS[22] in relevant clinical cases. At 8–12 years of age, speech therapy should be continued and further research on the potential risks and benefits of pharmacological treatment in this age group are warranted. At the time this review was written, no pharmacological agent has been approved by the U.S. FDA specifically for the treatment of stuttering.

From adolescence through to adulthood, speech therapy utilizing behavioral[62] and cognitive methods[63] should be continued, and a trial of medications is warranted. Stuttering onset after 9 years of age should be worked up for possible "acquired" causes. An adequate trial of medication is at least 3 months, as studies have suggested that the medication needs to be continued to maintain its efficacy.

We further suggest that a physician should collaborate with a speech-language pathologist to help assess the patient's progress in treatment and to assist the patient through speech therapy. A clinician should enquire as to the patient's fluency of speech during different social situations (i.e., at work, during introductions, speaking in front of audience, with family) as the level of stuttering can vary depending on the particular speaking environment. The clinician should also be aware that stuttering waxes and wanes over time and should expect to see some "dips" in efficacy during the course of therapy. A longitudinal assessment over a period of months is needed to determine if the stuttering treatment is efficacious. Additionally, stuttering treatment should also address the level of social and cognitive avoidance that often accompanies this disorder.[64]

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