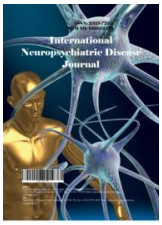

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Speech Fluency Disorders: A Review of Studies Conducted Over the Past Five Decades (1970-2020)

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Authors' contribution

This work was carried out in collaboration among all authors. Author NAQ designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors AMD, NAQ and AAH managed the analyses of the study and the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Background: Speech fluency disorder(SFD), a common disorder is reported in all age groups of people but most commonly in children around the world.
Objective: This study aimed to review critically several aspects of SFD, specifically epidemiological parameters, etiological foundations, clinical and treatment perspectives.
Methods: Electronic searches of relevant data published (1970-2020) in PubMed, MEDLINE, Google Scholar, and Science Direct databases were made using the Boolean operators and keywords and following iterative process 194 papers selected for this review.
Results: Speech fluency disorder presents in a variety of forms including acquired neurogenic and psychogenic stuttering is a complex, challenging neurological disorder. SFD is determined by diverse biopsychosocial and cultural etiologies, commonly afflicts male children at age 2-3 years compared to their counterparts (4:1 ratio). SFD manifests a variety of signs and symptoms, and up to 85% children who stutter improves spontaneously with or without intervention. Childhood developmental stuttering (CDS) persists in 1-2% of adults and persistent developmental stuttering (PDS) is again male-gender condition. Persons who stutter (PWS) are managed by non-pharmacological especially speech therapy and pharmacological interventions in particular

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dopamine antagonists. Gender, early intervention, chronicity, severity, language skills, and comorbid conditions mainly determine the prognosis and outcome of stuttering.
Conclusion: Extensive data concerning different perspectives of SFD is published globally, and projected better understanding of most speech disfluencies. Nonetheless, research need to be conducted to develop and provide better quality services to all PWS and to reduce the discrimination against PWS around the world.

Keywords: Speech fluency disorder; epidemiology; etiology; clinical manifestations; pharmacotherapy; non-drug interventions and comorbidity.

ABBREVIATIONS

Childhood fluency disorder (CFD); Diagnostic and Statistical Manual (DSM-IV); Adults who stutter (AWS); Children Who Stutter (CWS); Childhood developmental stuttering (CDS); Basal ganglia (BG); People/persons who stutter (PWS); People/persons who not stutter (PWNS); Persistent developmental stuttering (PDS); Adults fluency disorders (AFD) Acquired psychogenic and neurogenic stuttering (ANS & APS); cognitive behavior therapy (CBT); US Centers for Disease Control and Prevention (CDC); Supplementary motor area (SMA); Internal timing cues (ITC); Endosomal-lysosomal system (ELS); Hypoxic-ischemic injury (HII); traumatic brain injuries(TBI); Tourette syndrome (TS); Obsessive–compulsive disorder (OCD); Gamma-aminobutyric acid (GABA); Acquired factitious stuttering (AFS); Generalized anxiety disorder (GAD); Post-traumatic stress disorder (PTSD); Attention deficit hyperactivity disorder (ADHD); childhood persistent stuttering (CPS); Persistent Adult stuttering (PAS); Strength of Recommendation Taxonomy (SORT); Delayed auditory feedback (DAF); Repeated transcranial magnetic stimulation (rTMS); Transcranial direct current stimulation (TDCS); Deep brain stimulation (DBS); electromyography (EMG); Frequency altered auditory feedback (FAF); Delayed auditor feedback (DAF); Masking auditory feedback (MAF); Vesicular monoamine transporter-2 (VMAT-2); Randomized clinical trials (RCT).

1. INTRODUCTION

Childhood fluency disorder (CFD) is an idiopathic speech disorder that involves problems with fluency, flow, and the time pattern of speech that is inappropriate for the individual's age and persists over time [1-3]. Diagnostic and Statistical Manual (DSM-IV,2013) recognized it as Axis-1 disorder and comprehensively described its several perspectives [3]. The fluent speech is a highly complex dynamic process involving a combination of word selection with the motor activities that allow the coordination between articulation of those words with the respiratory, laryngeal, and articulatory muscles [4]. Furthermore, speech, a defining feature of human cognition is one of the principal developmental tasks for preschool children [5,6]. Using novel approach, Tichenor and Yaruss integrated the experiences and behaviors of PWS with listener's reactions in defining the term stuttering. Adult stutters defined the term stuttering as a constellation of experiences and behaviors outside the observable speech disfluency behaviors considered as stuttering by listeners. Further study participants (n=430) expressed that beginning of stuttering mostly linked to a sensation of anticipation, feeling stuck, or losing control that may cause PWS to react in affective, behavioral, and cognitive ways. These reactions, also affected by environmental factors, overtime tend to deeply ingrain among adults who stutter (AWS). Consequently, AWS have difficulties in saying what they want to say with adverse impact on their lives [7].

CFD is the most common neurodevelopmental disability disorder and affects 5% to 10% of preschoolers [4]. Stuttering is classified into developmental and acquired stuttering, and the latter is further categorized into psychogenic and neurogenic stuttering. Childhood developmental stuttering [CDS] has its onset at 2-3 years of age, and most frequently observed in males during speech and language developmental period through 2-6 years of age. CDS spontaneously remits through the age of 3-7 years in about 65% (boys) to 87.5% (girls) stutters with or without any intervention and predicted by associated language abilities [1,8,9]. CFD rarely starts after age 7 [10], and persistent childhood stuttering (PCS) continues beyond age 7 years linked with slow rate of attaining normal fluency [5]. The underlying factors concerning PCS may include the reduced cortical gray matter of the left inferior frontal region with a secondary basal ganglia

(BG) dysfunction independent from recovery, dopamine D2 receptors and dopamine neurotransmission significantly peaking in the developing BG at age 2.5-3 years, and finally slow neuronal reorganization or neuroplasticity [1,6,11-13]. Interestingly, at clinical level people who stutter (PWS) know what they want to say, but have trouble saying it, and repeat or prolong a word, a syllable, or a consonant or vowel sound. In addition, while speaking, PWS pause as they reach a problematic word. Most children outgrow CDS when their speech and language abilities are completely developed compatible with what they want to speak [14,15].However, PCS takes chronic course in1% of adults, called persistent developmental stuttering (PDS), who develop low self-esteem, poor interactions with people, lower quality of life, reduced employment opportunities and other adversaries. In addition, PWS chronically develop social anxiety disorder, depression, impaired social skills, maladaptive compensatory behaviors, and negative attitudes toward communication [4,7,16].

Childhood fluency disorder (CFD) is a complex, neurological disorder and disabling condition. Developmental, acquired psychogenic and neurogenic stuttering (ANS & APS) have diverse causes including genetic, biopsychosocial, drugs, and environment also plays an important role in its etiopathogenesis [2,5,17-30]. Children and adults who stutter benefit from several non-pharmacological and pharmacological treatments including speech therapy, cognitive behavior therapy (CBT), invasive and noninvasive neurostimulation devices and medications [1,4,27,31]. Overall, CDS begins in early childhood and rarely continues to persist in adulthood, especially among males but APS and ANS may occur at any age, and all types of stuttering are multifactorial in origin and respond variably to pharmacological and non-pharmacological interventions and their combinations.

1.1 Aim of the Study

This descriptive study aimed to appraise published English language literature of the past five decades (1970-2020) on stuttering and focus on its epidemiological trends and multiple clinical perspectives. The relevance of this narrative review is that this critical review addresses multiple clinical domains of stuttering, unlike other published studies from Arabian Gulf countries [32-37]. The significance of this inclusive review is that it will update the most relevant clinical knowledge of healthcare professionals who provide care to PWS around the world.

2. METHODS

2.1 Search Strategy

The most relevant literature published in English (1970 to 2020) was searched in PubMed, Google Scholar, and ScienceDirect databases to retrieve most influential and freely accessible articles on stuttering. The Boolean operators and keywords used in multiple e-searches were “stuttering OR stammering OR speech fluency disorder OR acquired neurogenic stuttering OR acquired psychogenic stuttering AND epidemiological trends OR etiologies OR risk factors OR clinical manifestations OR diagnostic tools OR assessment rating scales OR comorbid conditions AND drug treatments OR psychotherapies OR neurostimulation devices OR speech therapy. The search strategy and the keywords were modified as appropriate according to the searched databases, for example stuttering and SFD were used in PubMed search and stammering/ stuttering was used in Google Scholar. In addition, references included in full text articles including editorials, reviews and meta-analysis that focused mainly on details of stuttering and its related narratives were reviewed for inclusion in this critical review. Although there were numerous books on stuttering, we considered most relevant influential freely accessible books’ chapters for this article.

2.2 Search Results

Numerous articles concerning various types of stuttering were retrieved and reviewed by two independent researchers. Our focus was on full articles describing stuttering along with its concise narratives including epidemiology, biopsychosocial and cultural risk factors, diagnostic and assessment scales, management strategies in terms of medications, speech therapy, electronic devices and key behavior psychotherapies and educational counselling. These articles were reviewed extensively and the brief sketches of relevant contents were incorporated in this narrative review. The additional inclusion criteria were free access to

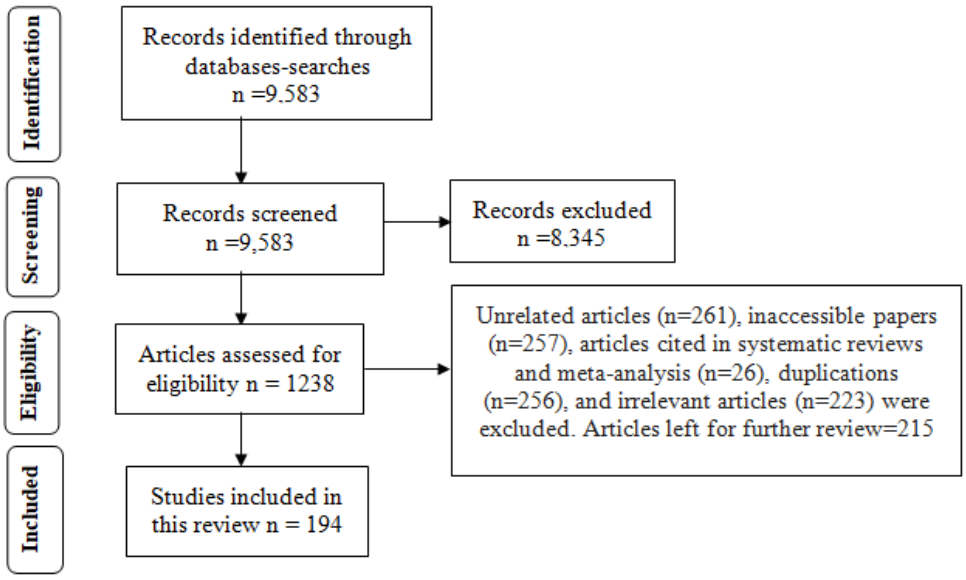

Fig. 1. Prisma chart summarizing the flow of search results

full articles, papers containing salient features of types of stuttering along with details of epidemiological data, clinical manifestations, etiologies including neurophysiology and risk factors, comorbid conditions and various treatment interventions. All types of related studies such as case series and single case reports, descriptive studies, systematic reviews, meta-analyses, randomized clinical trials (RCT), observational studies, editorials and short communications were included for further review. Screening of retrieved relevant records excluded more than three thousand papers. More than one thousand records were reviewed for eligibility purpose. After removing duplications, unrelated articles, some articles cited in systematic reviews and meta-analysis, full articles not accessible, abstracts not available and irrelevant unrelated information, 215 articles were left for further review. Finally, two independent reviewers included 194 published studies for this comprehensive review (Fig. 1).Overall, relevant data concerning all forms of stuttering is in fact based on single case reports, case series, small observational studies, limited RCT, a number of reviews and meta-analyses.

3. RESULTS

3.1 Epidemiology of Stuttering

Epidemiology of different types of stuttering varies globally. CDS is known to affect 5% of children with a higher rate in males than females. Fassetti and colleagues (2019) reported stuttering afflicts nearly 5% of the population including 2.5% of children under the age of 5 years [38]. Other study reported that CDS affects 5% to 10% of preschoolers [4], notably variable epidemiological data consistent with age. Several research found that CDS persists in 1-2 % of adults, PDS) [4,16,39].The PDS is more frequently observed among males than their female counterparts [40].According to a Danish study, the reported 2-year incidence of CDS was 5.2% and 71.4% children improved without any interventions over two-year period [41].The stuttering is mostly observed in male children compared to females in a ratio of 4:1[1].The reported average age of CFD onset is between 2.5 and 3yearswith 80–90% of affected individuals showing symptoms by age 6, and followed by a high rate of self-remission within the first ~12 months. The self-recovery in stuttering continues to the end of the preschool years [12].Stuttering affects5% of children with a lifetime incidence upward of 10%, and most incidents crop up in children [12]. Few longitudinal research evidenced that 65–85% of children recover from dysfluency by age 16, with a prevalence of less than 1% in adult population [42,43]. Severe stuttering affects over 70 million *or more* people worldwide and can limit their social and occupational opportunities and quality of life [44], two unmet challenges till now. Furthermore, stuttering affects about 1% of the

general population and from 8 to 11% of children, and about 8% of people experience the onset of stuttering during their lifetime that is called cumulative incidence rate [12]. In a cohort study of 1,619 Australian children recruited at 8 months of age, the cumulative incidence of stuttering onset by 3 years of age was 8.5%. Stuttering onset was characterized by sudden occurrence over 1–3days and determining factors were male gender, twin birth status, higher vocabulary scores at 2 years of age, and high maternal education that collectively accounted for 3.7% of the total variance [45].The cumulative incidence of stuttering onset rose to11.2%after 1-year follow-up [46].In context to race and color, a survey of the parents and guardians of 119,367 children ages 3-17 years from the US Centers for Disease Control and Prevention (CDC) reported higher prevalence rate of stuttering in non-Hispanic black children (2.63%) compared to non-Hispanic whites (1.27%) and in general intermediate (1.96%) for Hispanic groups[47]. Overall, it is almost difficult to make a conclusion about the epidemiology of stuttering that varies globally attributable to research methodological differences and types of speech disfluencies.

3.2 Biopsychosocial Correlates of Stuttering

3.2.1 Genetics of childhood fluency disorder (CFS)

Evidently, there are multiple underlying causes of speech disfluencies including CFD and AFD which can be broadly categorized into biological, psychological, social, cultural and environmental [17,40] and collectively called biopsychosocial model. Biological underpinnings of PWS are important from multiple perspectives including brain developmental differences compared to people who do not stutter. Molecular and genomic studies have reported substantial genetic contribution to the causation of CDS [40,48]. Most studies on twins reported high prevalence of stuttering among male children and monozygotic twins compared to dizygotic pairs [18,19,49]. Genetics play an important role in the causation of stuttering as it runs in families and various researches including twin researches have revealed inherited/genetic abnormalities, i.e., the heritability coefficient for stuttering in monozygotic twins averages at about .80 across studies. This means there is a strong genetic component to stuttering. However, because this coefficient is less than a perfect 1, genes are not the sole causal agent in stuttering and, hence, gene-environment interaction needs to be researched is also crucial for stuttering [18,19,48,49]. Different genes involved partially (20% cases with PDS) in the incidence of PDS are GNPTAB, GNPTG, NAGPA, and AP4E1. These genes encode several cellular enzymes and proteins identified in PWS, nonetheless more genes need to be explored in PDS [48].Yairi and Ambrose (2013) suggested that genetics account for 50–80% of stuttering, while fraternal studies estimated 19% genetic correlation with stuttering [12]. Notably, monozygotic twins consistently displayed higher concordance for stuttering than dizygotic twins [18,19].Several genetic studies further identified a single process of intracellular trafficking as the cellular defect for stuttering that is linked to genes on chromosomes 9, 10, 12, 13, and 18, and specific gene (s) yet to be found within the larger population [50-55]. Large association studies have identified 9 genes on aforesaid chromosomes associated with stuttering [56]. Dopamine is involved in stuttering as evidenced by a linkage between SLC6A3 and DRD2 [57-61].Genetic analysis of the DRD2 gene found in BG showed increased frequency of a specific allele in PWS [51] but this report was not corroborated by other study [59].Based on a review, Perez and Stoeckle highlighted the possible mechanistic functions of the identified genes in stuttering which are neurometabolism, cell-cell interaction, embryonic transcription regulation, and behavior modification[40], and till now specific mechanisms underlying stuttering evade researchers, a challenging task to be pursued in future by genetic researchers. Overall, genetic of stuttering is a highly complex research avenue and needs further genomic studies globally using highly advanced digital technologies.

3.2.2 Neuroanatomical and functional differences in Stuttering

Stuttering is a neurological disease or a troubling symptom with social adverse consequences that drew the attention of researchers to explore precisely the neuroanatomical and functional differences between PWS and PWNS. Several studies that used neuroimaging techniques have explored brain functional and anatomical differences among children and adults with or without stuttering and found changes in speech areas concerning grey and white matter volumes of cortical and subcortical in the left hemisphere (Broca's and Wernicke's Areas) in PWS attributable to the slow process of

neuroplasticity[62,63].Ingham et al (2018) further suggested that certain therapies produce changes in timing and speech motor patterns are most effective treatments for PWS, and attributed to significant *neural reorganization*. The implication of this research is that the new methods need to be identified to directly intervene at neural circuits and behavioral techniques to stimulate neuroplasticity required to enhance recovery from stuttering [62]. In addition, dopamine neurotransmitter networks and direct and indirect BG pathways projecting to prefrontal cortex, subcortical areas, and supplementary motor area (SMA) addressed by Alm's circle have been found to be malfunctioning in PWS [13, 64-67]. Chang et al. (2015) reported about cortical white matter tract differences reflecting "*deficits* in long-range neuronal connectivity that supports efficient sensorimotor integration and cortical-subcortical interaction with the BG for skill movement control" [67]. According to Alm, one of the core dysfunction concerning stuttering is an impairment of the basal ganglia to produce internal timing cues (ITC) during speech [13], which means normally functioning BG driven ITC help in the prevention of dysfluency of speech. Falk and colleagues (2015)also reported sensorimotor deficits especially nonverbal both in children and adolescents who stutter[68].Functional and anatomical abnormalities have been reported in speech motor control system in terms of timing and sensory and motor coordination in the brain [17].Tourville and Guenther (2011)suggested concerning DIVA (Directions into Velocities of articulators) model that a cortical region in the SMA is a point of gating to release articulator motor commands from neurons in the primary motor cortex in order to enable speech movement, and ITC of the BG mediate this gating mechanism [69].Further, several studies have concluded that difficulties with producing ITC by BG and reduced dopamine, i.e., D1 and D2 receptor ratio that affects speech sequence for rhythm could be a core deficit in stuttering[13,66].Conversely, as mentioned up the D1:D2 receptor ratio increases during 2-3 years of age when spontaneous recovery occurs in CDS. Alm (2004) proposed "a vicious cycle" comprised of various neuroanatomical and functional circuits where negative experiences of stuttering *may* lead to increased stuttering [13], Fig. 2. Alm (2004) explained that a child experiences stuttering due to poor ITC, perceives speaking to be less rewarding than predicted, and develops a negative emotional reaction to the experience. Negative emotions/experiences are associated with reduction of dopamine (reward neurotransmitter) release in the striatum of the BG; all above factors collectively cause a weakening of speech motor behavior leading to increased stuttering [13]. In a nutshell, despite advanced technological methods to directly study neuroanatomical circuits and metabolism of the brain and their functions, yet the game to elucidate specific neurophysiological mechanisms underlying stuttering is not over.

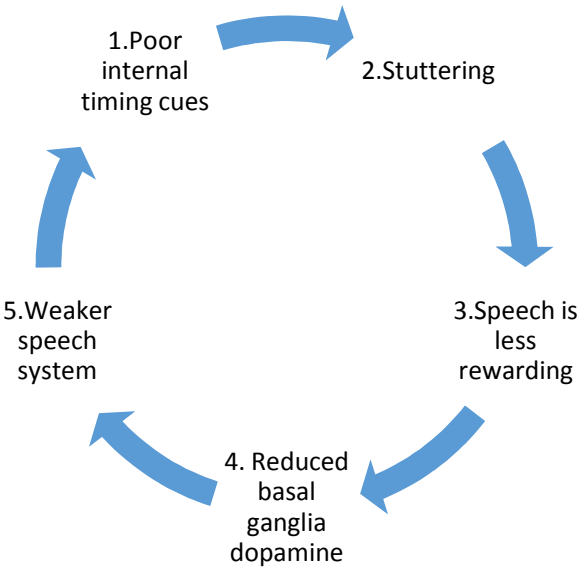

Fig. 2. Alm's vicious cycle [13]

3.2.3 Stuttering and inflammation

Inflammation may also cause stuttering. In this context, CDS may be caused by complete blood count (CBC) values as indicators of a systemic inflammatory response and processes. In a retrospective, case-control study of DS patients (n=54 PWS, n=54 PWNS), three CBC parameters in terms of basophil count, percentage of basophil, and platelet count were significantly higher in PWS. Mean platelet volume was significantly lower in PWS. A significant correlation was found between basophil count and platelet count ($p<0.05$), basophil count and mean platelet volume ($p<0.05$), basophil count and percentage of basophil ($p<0.05$). Basophil count correlated with disease duration ($p=<0.05$). Furthermore, low mean platelet volume predicted DS, basophil count correlated with PD duration, and these factors may be potential markers for and predictors of CDS [70], which means cryptic inflammation of prefrontal, superior and temporal cortex and sub-cortical regions and BG may be one of the main underlying causes during early stages of CDS. Inflammatory biomarkers are taking leading role in the development of DS, though DS is multifactorial. This important emerging avenue needs further global research.

3.2.4 Stuttering and endosomal-lysosomal system

The endosomal-lysosomal system (ELS) performs a variety of roles necessary for the normal cellular functions in the body. Hu et al. (2015) reported ELS maintains cellular homeostasis by sorting out plasma membrane proteins, receptors and possibly other proteins necessary for normal cellular function. The ELS is known to transport essential proteins or degrading unwanted proteins or receptors concerning cellular dynamics. Endosomes sort molecular cellular traffic for recycling or degradation and aid with the genesis of storage vesicles for the transportation of those molecules to their final destinations [71]. However, lysosomes are the final site of molecular degradation [71].Endosomes and Lysosomes work in close collaboration to perform the complex processes in terms of sorting out, transportation, production of storage vesicles and degradation required for normal cellular functioning. Hue et al (2015) hypothesized that mutations of multiple genes (5 to 9 genes) already discussed aforesaid *might* encode for a dysfunctional ELS in specific neurons of BG and left-hemisphere white matter axon tracts, leading to the functional and neuroanatomical deficits in PWS [71].Notably, the BG produces ITC during speech and left-hemisphere white matter axon tracts integrate auditory-sensory feedback for on-line adjustments during speech. The deficits in these areas lead to reduced dopamine (reward-neurotransmitter) levels in the BG when speech is experienced less rewarding leading to further difficulties in producing fluent speech [13,17]. Notably, one consistent finding has been abnormal auditory-sensory feedback systems in PWS [72]. The elevated dopamine levels in BG are associated with stuttering and lower activity of the striatum as shown significantly higher 6-FDOPA uptake in the ventral limbic cortical and subcortical regions that lead to an overactive presynaptic dopamine system [73]. The implication of these findings is that unlike dopamine antagonists, dopamine agonists aggravate the stuttering as evidenced in cases of Parkinson's disease [1,29,31,73].

3.2.5 Other theoretical foundations of stuttering

The theories of stuttering are diverse and attempt to explain its heterogeneous nature. Despite advanced researches, stuttering evades any specific uniform hypothesis and needs continuing research to find out the specific etiological pathways underlying this disability. Several studies have reviewed comprehensively various hypotheses concerning stuttering [74,75]. According to Alm (2014), stuttering is ingrained in temperament, personality traits including anxiety and timidity of PWS [75]. Another hypothesis of stuttering relates to stutters' awareness when they are about to develop stuttering leading to its occurrence, and, interestingly, driving them to consult speech therapist and/or physicians [76,77]. Other theories of stuttering discussed in details in the aforesaid section include BG networks defect concerning ITC [78], dopamine D1 and D2 receptors involvement [13,66], and dysfunctional auditory (sensory) and motor system [67, 79, 80] and mutations of GNPTAB, GNPTG and NAGPA genes involved in lysosomal enzyme processes observed in (<10%) of unrelated stutters having positive family history of stuttering [81]. Notably, the GNPTAB and GNPTG genes are reported to cause several diseases including mucolipidosis types II and III-autosomal recessive lysosomal storage disorders-linked with motor disabilities and delayed speech and abnormalities of bone, connective tissue, liver, spleen, and brain

[82].Smith and Weber (2017) proposed the multifactorial dynamics pathway theory involving genetics, sensory motor system, BG circuits and neuronal projections to other brain areas and medications in AWS [5]. According to Mawson and colleagues (2016), a theory related to acquired stuttering and/or PDS should note these observations including adverse perinatal outcomes and birth injury, recurrence or development of new onset of speech disfluency at any age due to brain injury or diseases, structural and functional abnormalities in the brain regions and spontaneous remission in most CWS and boys tend to persist with stuttering into adulthood [74].Based on these observations and review of pertinent literature, Mawson and colleagues (2016) proposed a hypothesis concerning CDS that focused on an early hypoxic-ischemic injury (HII) to anatomical areas and multiple neurological pathways in the brain related to speech motor control [74], Fig. 3.

3.2.6 Acquired neurogenic stuttering

In contrast to CDS, ANS in adults is a rare condition and develops typically after brain damage due to stroke or traumatic injuries [83-85]. ANS is characterized by speech fluency disruptions such as slowness, pauses and repeated sounds. ANS afflicts more frequently males than females, and its incidences vary between 2:1 and 10:1 [85].ANS occurs in individuals without previous stuttering (or cryptic stuttering) and attributed to multiple factors including traumatic brain injuries(TBI) from external sources, Parkinson's disease, epilepsy, multiple sclerosis, corticobasal ganglionic degeneration, dialysis dementia, hypoxic ischemic encephalopathy and other dementias [83-92].Genetic and various medications are additional risk factors in ANS [93]. Nonetheless, strokes and TBI are the leading causes of ANS [22]. A recent review (4 of 28 studies) estimated that between30% and 60% of PWS with ANS had a positive family history compared with less than 10% of controls [85]. Notably, ANS could be caused by pediatric autoimmune disorders associated with streptococcus infection (PANDAS) [94]. Evidently, PANDAS has etiologic contribution to Tourette syndrome (TS) and obsessive–compulsive disorder (OCD), and ANS/CDS shares several similarities to both conditions which begin in childhood, have male to female ratio of 4:1, a waxing and waning course, are made worse with anxiety, and associated with tic motions, have brain pathologies localized to the BG, have common etiological explications, respond to dopamine antagonists, and clinically worsen with dopamine agonists [1,95]. It is hypothesized that ANS (CDS) and OCD may develop when antibodies directed against streptococcal infection cross-react and attack the developing BG and its neuronal circuitries. After all, persons with developmental and neurogenic stuttering are reported to have neuroanatomical differences in both hemispheres (Table 1).ANS needs to be differentiated from several disfluencies in terms of aphasias such as amnestic aphasia, Broca's aphasia, conduction aphasia and Wernicke's aphasia and apraxias and CDS [2,96,97].For more details about ANS, see these resources [27,86,94,98,99].

Several pharmacological treatments (Table 2) are paradoxically associated with the causation of ANS and discontinuation of offending medication improves the speech disfluency [2,25-30,102,103]. Interestingly, these medications whose mechanisms of action relates to increase in dopamine and serotonin levels, reduction in gamma-aminobutyric acid (GABA) and acetylcholine, and these factors contribute to stuttering [27]. In sum, ANS is relatively an uncommon speech disorder of adults who have no prior stuttering, caused by diverse systemic diseases, TBI from external sources, and various medications, and managed mainly by speech therapy, standalone medications and combined pharmacological therapies with or without non-drug therapies including neurorehabilitation [83]in line with causative factors (see the treatment sections).

3.2.7 Acquired psychogenic stuttering (APS)

Acquired Psychogenic Stuttering (APS) is another type of stuttering associated with psychological and brain diseases and can comorbid with ANS [21,104,105]. APS is mostly reported in young females having histrionic personality and often characterized by sudden onset, precipitated by emotional trauma and severe stress and manifest speech disfluency features including muteness and psychotherapy is the key treatment associated with full recovery. The two conditions (ANS &APS) in fact need differentiation based on clinical features, etiologies and outcome as their treatment approaches and outcome vary widely [28,87,106]. A collaborative service between mental health expert, neurologist and speech-language pathologist and family physicians are imperative in the diagnosis and management of APS. Evidently, unlike CDS and ANS, males are

not at greater risk to develop APS than their counterparts. Overall, a psychological conflict or severe stress with sudden onset of stuttering and rapid recovery with psychological intervention and without any evidence of brain damage often guides the diagnosis of APS, a form of conversion reaction [28,83,85,106,107]. However, persons with APS manifesting pause in speech or muteness need exclusion of acquired factitious stuttering (AFS) linked with apparent clear motive [83,108].Children and adults with delayed brain development, other speech disorders and family history of stuttering are susceptible to develop stuttering with disruptions in flow of speech [17]. Evidently, dysfunctional families, high parental expectations, inter-parental violence and childhood adversities including emotional, physical and sexual abuse, severe excitement, exhaustion, high feeling of self-consciousness, and under pressure are other risk or aggravating factors not only of CDS but also of APS in children and adolescents[109-112].However, the most difficult stressful situations for a PWS (APS) have been identified as speaking in front of an audience or talking on the phone and this could be attributed to their anxiety traits and social anxiety [113]. Conversely, PWS when talk to self and sing in harmony with someone else do not show stuttering behavior may be because of protective milieu. Multiple causes and risk factors underpinning three types of stuttering are somewhat different, and in fact PWS need dissimilar, flexible personalized approach for their management [114,115]. Recently, a conceptualized working alliance concerning Bordin's model that collaborates and navigates agreement, goals and assigned tasks between speech and language therapists *or family physicians or mental health professionals (therapists)* and client is found to show good outcome in PWS. A strong therapeutic alliance between client and therapist and early intervention were other variables associated with better outcome. Accordingly, therapeutic alliance is a major contributor to the psychotherapeutic outcome in stuttering [116-119], though other differential factors associated with client and therapist are also responsible for good improvement in PWS. In sum, persons with APS which is a multifactorial neuropsychological disorder respond to a variety of individualized therapies including speech therapy, behavioral and somatic interventions, psychotropic medications and integrative modalities but psychotherapy is the key intervention.

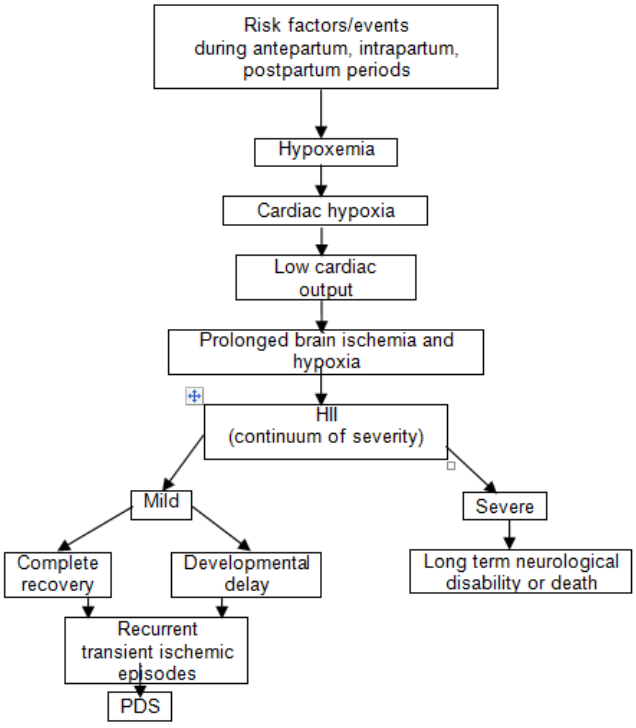

Fig. 3. Hypoxic-ischemic injury (HII) theory of CDS [74]

Table 1. Neuroanatomical structures involved CDS and ANS

DS	ANS	Remarks
• Right frontal operculum, • Right motor cortex, • Supplemental right motor cortex, • Right inferior temporal gyrus • Right superior temporal gyrus, • Right cerebellar hemisphere, • Left cingulate gyrus, • Left temporal lobe, • Left Rolandic operculum, • Left prefrontal cortex, • Left sensorimotor cortex, • Basal ganglia • Ventrolateral nucleus of thalamus, mesothalamus and left caudate nucleus • D1/D2 receptors proportion change. • Right frontal parafalcine region	• Inferior frontal cortex, • Superior temporal cortex, • Intraparietal cortex • BG with multiple interconnections. • The striatum and the pale globe	• Left hemisphere areas mainly involved in ANS and both right and left hemispheres in DS. • The dysfunctional circuit concerning intraparietal cortex and BG tends to cause ANS [100] • The involvement of left cerebral medial artery in most patients of stroke [100] will not inform about other brain regions involved in the pathophysiology of ANS, a weakness of this research. • Hypothesized that many brain areas overlap in DS and ANS and this avenue needs research in future [100]. • Delayed neural activation in neuroanatomical areas in stuttering [101] • Hyperdopaminergic activity in BG (D1/D2)

Table 2. Prescribed medications associated with ANS

Medications	Class	Remarks
Haloperidol, chlorpromazine &thioridazine	TA	Evidence based on case reports. Paradoxical effect
Clozapine, olanzapine, quetiapine, ziprasidone, lurasidone, aripiprazole & risperidone	AA	Evidence based on case reports and case series. Paradoxical effect
Carbamazepine, gabapentin, topiramate, phenytoin, valproate, Levetiracetam and lamotrigine	Antiepileptic	Drugs used in seizure disorders, mood disorders as mood stabilizers and other conditions. Gabapentin and lamotrigine have abuse potentials
Citalopram, Escitalopram, paroxetine, sertraline and fluoxetine	SSRI	Used in depression, OCD, anxiety disorders, panic attacks and other disorders including PTSD
Venlafaxine, duloxetine	SNRI	Used mainly in mood disorders
Mirtazapine	TCA	Used in depression and insomnias
Bupropion (aminoketone class)	NDRI	Used in depression, anxiety, and SAD and for quitting smoking
Alprazolam and clonazepam	BZD	Used in anxiety disorders and insomnia have potential for abuse
Propranolol	Beta blocker	Used in anxiety with palpitations and hypertension
Theophylline	Bronchodilator	Used in asthma
Methylphenidate & Pemoline	Neurostimulants	Used in ADHD & have abuse potential

TA=Typical antipsychotics; AA=atypical antipsychotics; SSRI=Selective serotonin reuptake inhibitors; SNRI=Serotonin norepinephrine reuptake inhibitor; TCA=Tricyclic antidepressants; NDRI=Norepinephrine dopamine reuptake inhibitors; BZD=Benzodiazepines; SAD=Seasonal affective disorder

3.2.8 Clinical manifestations of stuttering

The children and adults with stuttering present with diverse signs and symptoms that help in diagnosing and measuring the treatment progress following various interventions. The individuals with stuttering (stuttering-like disfluencies) often have difficulty starting a word, phrase or sentence, and prolonging a word or sounds within a word [120].PWS tend to repeat sound, syllable or word and brief silence concerning syllables or words, or pauses within a word (broken word). PWS add extra words if difficulty moving to the next word is anticipated [4,14,120] Table 3. In preschool children, other disfluency features may emerge during normal speech development, and this is called normative stuttering [4,121]. PWS tend to show excess tension, tightness, or movement of the face (grimacing) or upper body to produce a word, anxiety about talking, and limited abilities to communicate effectively with people. While talking, PWS may also show rapid eye blinks, tremors of the lips or jaw, facial tics, head jerks and clenching fists, collective signs of increasing tension [1,4,27,40].In CDS, children may confuse between clinical symptoms and complications of stuttering and the latter include low self-esteem, social anxiety disorder about speaking, communication problems, avoidance of situations requiring speaking, loss of social, school, or work participation and success, and bullying and harassment [1,3,4,27,122]. AWS tend to have multiple psychiatric disorders, lower quality of life, occupation and educational barriers, and difficulties with finances and access to high-quality treatment plans [123-128]. Repetitions, prolongations, broken words, blocking, circumlocutions, and excess physical tension characterize the disturbances of SFD [3]. Further, motor movements including tremors, head jerking, breathing movements may accompany stuttering [1,4,27,95]. The extent of these disfluency disturbances varies in accordance to stressful situations, types of stuttering age, and can be related to fearful anticipation of stuttering. The resulting anxiety, embarrassment, insecurity, shame, and bullying can cause limitations in social participation and academic or occupational achievement. For many individuals, avoidance and social anxiety are often the disabling features of stuttering [1,3,4,27,40]. Overall, the key clinical features of stuttering include but not limited to blocks in speech, prolonging a word or sounds within a word, repetition of sounds, syllables and words, difficulty or inability to articulate certain syllables, or pauses within a word, and adding extra words if difficulty arises in speaking the next word. Speech difficulties are often accompanied by rapid eye blinks, tremors of the lips or jaw, facial tics, head jerks, clenched fists, facial grimacing and flushing, pallor, perspiration, and cardiovascular changes [14, 40,129] Table 3.

3.2.9 Comorbidity of stuttering

Comorbid conditions have diverse relationships with stuttering. CDS co-occurs with other non-speech, communication, phonological and language disorders [130,131] and co-morbid disorders are harbingers of poor outcome concerning all forms of stuttering [42]. PWS have been reported to have comorbidities which may be either mostly secondary or primary to stuttering or may not cause one another (Table 4). Co-occurring conditions of stuttering guide the healthcare providers to focus on the following perspectives: (1) to have a better understanding of the co-occurring speech disorders, language disorders, and non-speech disorders in CWS; (2) to identify the speech disorders, language disorders, and non-speech disorders with the highest frequency of occurrence in CWS; and (3) be aware of the subgroups of children with co-occurring disorders and their potential impact on assessment and treatment outcomes [131]. Co-occurring disorders and stuttering may share mutually etiological foundations, manifestations, response to treatment and outcome. Therefore, an individual with PDS, ANS and APS needs extensive evaluation by a multidisciplinary team, and the use of several rating scales such as Stuttering Severity Instrument, the Overall Assessment of the Speaker's Experience of Stuttering (OASES), Clinical Global Impression–Severity scale (CGI-S), Clinical Global Impression–Improvement scale(CGI-I),Subjective Screening of Stuttering (SSS), the Modified Erickson Scale of Communication Attitudes (MESCA, S-24), the Perceptions of Stuttering Inventory (PSI), the Self-Efficacy Scale for Adult Stutterers (SESAS), the Locus of Control (LOC),and the Tentative Assessment Procedure (TAP) for Stuttering [15,45,89,83,90,106,108, 122,132] in order to assess the severity, make a correct diagnosis, and decide about proper drug and nondrug interventions and monitor the improvement in stuttering behavior. Overall, comorbid conditions which are diverse complicate the outcome of stuttering and need joint treatment approach for better outcome and quality of life of stutter.

Table 3. Clinical differences between childhood fluency disorder and other disfluencies

Stutter-like disfluencies*	Examples	Other disfluencies**	Examples
1. Dysthymic phonations			
-Blocks	Unable to articulate	1. Interjections	"Um"
-Broken words	"O pen"		
-Prolongations	"Mmmmy"		
2. Part word repetition	"B-but"	2. Multisyllable repetitions	"I want I want to go"
3. Single word repetition	"You-you-you"	3. Revised/abandoned utterances	"I want/hey look at that"

Characteristic of childhood-onset fluency disorder;Transient and observed during learning phase of speaking in most preschoolers [4,121]*

Table 4. Comorbid conditions of stuttering

Comorbid condition	Remarks
1.Anxiety disorder (separation anxiety disorder and overanxious disorder)	Adolescents with stuttering develop social anxiety and continue to manifest later in adult life. Six- to sevenfold increased odds of having an anxiety disorder
2.Social phobia,	16- to 34-fold increased odds of meeting criteria for DSM IV
3.Generalized anxiety disorder (GAD)	Fourfold increased odds of meeting criteria for DSM IV
4.Post-traumatic stress disorder (PTSD)	Relatively unexplored area but in veterans this co-morbidity exists[27,133,134]
5.Panic disorder	Six -fold increased odds of meeting criteria for ICD-10
6.Mood disorders	Stutters have two fold increases in mood disorders compared to normal.
7.Personality disorders	Stutters have threefold increase in personality disorders compared to normal. Also linked with psychopathic traits, violent crimes and nonviolent crimes [135]
4. Alcohol and other substance abuse	Tendency to abuse different substances including marijuana
5. Sound system disorders	Phonological disorders (13%); articulation (34%), phonology, and language disorders;62.8% had other co-occurring speech disorders, language disorders, or non-speech–language disorders; reduced phonological skills may contribute to a greater risk of developing persistent stuttering [130, 136-138].
6. Tourette's syndrome	Both conditions have multiple overlapping manifestations
7. Insomnia, headache, & pain	Veterans Iraq &Afghanistan Veterans [27]
Hay fever, asthma, eczema and psoriasis	Stuttering associated with Psychosocial adversities and atopic diseases[112].
ADHD, Autism, cerebral palsy, Down syndrome, arthritis, muscular dystrophy, cystic fibrosis, Congenital Heart disease, Diabetes, Sickle cell anemia,	These comorbid conditions of stuttering reported by Choo and colleagues [139]. Comorbid conditions may be primary or secondary or may not cause one another and poor outcome may be due to multiple reasons including untrained therapists [138, 140]

3.2.10 Indicators for seeking help from healthcare professionals

Early recognition, diagnosis and referral to a speech therapist are critical in the management of stuttering. Most of the children with stuttering improve completely without any intervention prior to age 5-6 years[11].CDS may persist in about 2% of cases, and such persons must consult a family doctor or speech therapist for the early management of CPS [1,119].Early identification of stuttering and intervention help minimize the chances of developing social anxiety, impaired social skills, maladaptive compensatory behaviors, and negative attitudes toward speech disfluency[4,114].The other indications for seeking help from a speech therapist are; if stuttering lasts more than six months, and comorbid with other speech or language or phonation disorders [129,134].Furthermore, when stuttering becomes more frequent or continues as the child grows older need referral to speech therapist for early intervention, a critical step in the management of CPS[40].When PWS become tense or anxious that affects their ability to effectively communicate at different places or in social interactions need liaison services from speech therapist [40]. In addition, referral to a health provider should be considered when persistent adult stuttering (PAS) causes avoidance of situations where speaking is required [16]. The CPS predicted by late age of onset, chronicity, family history of persistent stuttering, and lower language abilities and nonverbal skills need a comprehensive evaluation by an experienced speech-language pathologist[141,142]. Speech therapists use several strategies including observing the adult or child speak in different types of situations, ask parental concerns and explore adults using guide with relevant questions concerning stuttering and details about the past treatment interventions, relationship concerns and career are other important issues of interest to interventionist [14]. Speech-pathologist-therapist may use rating scale to diagnose stuttering and measure its severity [122,143,144] and to rule out other neurological conditions by various laboratory and radiological investigations [38].Overall, there are several clinical recommendations (Table 5) based on various dynamic factors that drive PWS to seek early help from related healthcare providers in order to achieve nearly full recovery from speech disfluencies.

3.2.11 Treatment of stuttering

3.2.11.1 Non-pharmacological treatment

Persons who stutter (PWS) need a comprehensive evaluation by a speech-language pathologist. Then in coordination with multidisciplinary team and stutter, the therapist decides collective informed decision about the

Table 5. Clinical recommendations with evidence for seeking help

Clinical Practice Recommendations	E*	Comments
Referral to a speech-language pathologist should be considered for any child who exhibits stutter-like disfluencies, especially if there are parental concerns or the disfluency has remained unchanged for 12 months or is worsening in severity or frequency [5,40,145,146]	C	Expert opinion and limited data from systematic review
Therapy for persistent stuttering should be individualized and focused on developing effective compensatory techniques and eliminating ineffective secondary behaviors[147].	C	Systematic review of low-quality studies
Families should be reassured that stuttering is primarily the result of brain abnormalities and is not the fault of the patient or family[5,6,66,119, 148, 149].	C	Meta-analysis, review, case-control observational studies
Patients with stuttering should be evaluated for secondary psychosocial effects and offered appropriate treatment [5,128,148,150-154].		Multiple studies show risk of psychosocial effects; qualitative studies show benefits of treatment

**E=Evidence; A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. The SORT—Strength of Recommendation Taxonomy which suggested;1. Stuttering can be distinguished from typical disfluency of childhood by the occasional prolongation of sounds and increased learned secondary behaviors, including closing the eyes or tensing facial muscles while stuttering (C) [51]2.Stuttering is associated with psychosocial morbidity and worsened quality of life in adults (B) [155-158];3.Medications, including atypical antipsychotics, might serve as an adjunctive treatment option for adults who stutter, but evidence is limited to smaller trials[159];4.Early intervention and referral to speech therapy in children who stutter is critical(C) [141];Speech therapy is the mainstay of treatment for stuttering in children and adults [160]*

best personalized treatment approach for PWS [114,147,161]. Several different approaches are available to treat children and adults who stutter persistently. PWS often have different needs, and, therefore, require a method or a combination of several approaches that best help to improve their disfluencies. Evidently, PWS can learn pertinent skills that help to improve speech fluency with the development of effective communication and, consequently, PWS could participate fully in school, work and social activities. Various non-drug therapies used effectively in PWS are but not limited to speech therapy, electronic devices/AI machines, CBT, intensive behavior modifications therapy, supportive therapy, counselling, self-control models and LOC, and parent-child interaction exercise [38,162-165] Table 6. Speech therapist teaches a PWS to slow down flow of speech and to identify clues when stuttering is occurring. As a result, initially stutter speaks slowly and deliberately but over time, works up to a more natural speech pattern [165]. Briefly, several electronic devices to deliver various therapies are available to enhance systematically flow of speech [38]. Notably, delayed auditory feedback (DAF) technique informs a stutter to slow speech fluency. Another mechanism of machine to slow down the speech is to distort the speech. Additionally, electronic device like DIVA may mimic speech of the stutter as if stutter is talking in unison with someone else. Some studies suggested wearing small electronic devices to harmonize flow of speech during daily activities [38]. CBT with limited one-to-one or in family group sessions (five to twenty sessions) helps PWS learn to identify negative thoughts (cognitive triads-past, present and future negative cognitions), distressful feelings and troubling situations, and change ways of thinking and emotions that might make stuttering worse [162-165]. CBT is also used in several comorbid psychiatric disorders including depression with no or little risk to PWS. In addition, CBT uses various techniques such as relaxation, coping skills, resilience, stress management, assertiveness and interpersonal therapy. Furthermore, CBT uses goal-directed approach to help PWS resolve stress, anxiety or self-esteem problems related to dysfluency. CBT combined with other therapies or medications provides greater improvement, though complete recovery may not take place [166]. Multiple factors in terms of co-morbidity, gender, language abilities, severity and chronicity of stuttering impede good outcome including educational attainment [167]. Adults with chronic, persistent stuttering show a little improvement with given treatments and tend to relapse [122,168]. Parental involvement in practicing certain techniques at home (home exercises/assignments) is a key part of helping a child cope with stuttering. Overall, speech-language pathologist, cognitive behavior therapist and physician determine the diagnosis of stuttering and use the best possible approach to treat PWS. Other psychological and behavioral programs used in PWS include the Lidcombe program based on the principles of operant conditioning, intensive smooth speech therapy and its various home based speech programs which are effective in PWS [157,169-172]. Currently, somatic brain stimulation treatments including deep brain stimulation (DBS invasive), repeated transcranial magnetic stimulation (rTMS, noninvasive) and transcranial direct current stimulation (TDCS) have been used in PWS with variable outcomes and need continuing research [101,173,174]. Notably, most therapies assist mechanistically in restoring a left dominant network for speech production, this effect requires continued maintenance through refresher therapies [11,175].Overall, non-pharmacotherapies have been used effectively in all PWS, are better options than neurostimulation devices, though outcomes largely determined by types of stuttering, severity, co-morbidity and chronicity vary across the board.

3.2.12 Pharmacological treatment of stuttering

Pharmacological management of PWS is important from many perspectives. Although many psychotropic and other medications have been used off-label for the treatment of stuttering (Table 7), FDA has not approved any drug for the treatment of stuttering. Medications from different classes including first and second generation of antipsychotics (TA&AA), TCA, SSRI, BZD and barbiturates, GABA agonist (Pagoclone), D1 receptors antagonist (Ecopipam),vesicular monoamine transporter-2 (VMAT-2) inhibitors, alpha receptors agonists, and calcium channel blockers have been used in limited sample of PWS (single case reports, case series and very few double blind trials) and found to have variable outcomes, and most of these medications reported to have a variety of side-effects especially on long-term use and some of these medications also cause acquired neurogenic stuttering, a paradoxical effect [183-187].

Table 6. Non-pharmacological treatments of stuttering

Behavioral modalities	Benefits	+/- results	Remarks
1.Speech therapy	+++	Higher relapse rate and negative effects on speech naturalness	Most effective therapy for stuttering
2. Intensive smooth speech	++	Intensive smooth speech showed more immediate improvement	Decreased stuttering frequency of 85–90%, in children of 9-14 years of age.
Intensive electromyography (EMG) feedback,	Frequency altered auditory feedback FAF [171]	No statistically significant differences between the three treatment groups when measuring stuttering frequency across time [170]	Better long-term success with the EMG and home-based smooth speech one-year post-treatment. DAF controls the rhythm of articulation and dysfluency can be corrected by auditory feedback manipulation. Advice delivering AAF (SpeechEasy®) improved stuttering, a viable option for its treatment [172].
3. Homebased smooth speech	++		Better long-term success with the EMG and home-based smooth speech 1-year post-treatment
4.Combination of cycles and speech-rate reduction	+++	Combined therapy good in fluency and phonological disorder [176]	Efficacious throughout the literature [177].
5. Multiple fluency enhancing strategies; Singing and vocal control techniques &easy onset, delayed auditor feedback (DAF) and tension release techniques.	++Masking auditory feedback (MAF), DAF&FAF.	Are used in CDS and ANS. Techniques include; word facilitation, decreased speech rhythm, choral effect, non-automatic speech, change in vocal pitch, and white noise.	Results mostly based on single case reports are encouraging as well as discouraging because of inter-individual differences [83,,86,171].ANS is more resistant and present slower and less effective treatment response [83,178]
6.The Lidcombe Program for preschool children	+++(Operant Conditioning VS Indirect treatment)	Relatively effective program for preschool CWS	Verbal contingencies for stuttering administered by the parents, a direct approach. Indirect treatment means for reducing communicative pressures at home. [169]
7. Camperdown Program, the Lidcombe Program, and an integrated treatment approach	+++	Integrated treatment program gives better results in stuttering	Live-stream, video telepractice is a promising service-delivery method for the treatment of stuttering using the three programs (participants=80), and results from a systematic review [179]
8. Behavioral methods(bypass control from the medial to the lateral system consist of the lateral premotor cortex & cerebellum).	+++	Behavioral treatments for CWS and AWS reported better improvement results [164]	Metronome-timed speech, unison reading, accent imitation, and role-play are believed to produce attentional, controlled speech based on auditory and somatosensory feedback [13, 180]
9. Cognitive Behavior therapy	+++CBT explores triad-past, present and future negative thoughts and change by positive cognition	AWS having social anxiety disorder, CBT reduces social anxiety and avoidance behaviors	CBT had no impact on chronic stuttering frequency, but was associated with less anxiety and avoidance of daily speaking situations and good response in non-chronic stutters[128,140,165,167].Internet CBT added good improvements to stuttering severity and quality of life[181]
10. Parental counselling , Children-parent interaction	+++	These methods are effective in CWS	Parental counseling and interaction with CWS improves frequency and severity of stuttering [4, 182]
Brain Stimulation Devices (Somatic modalities)	**Doses Benefit***	**Side effects**	**Remarks**

Behavioral modalities	Benefits	+/- results	Remarks
Deep Brain stimulation (DBS)	Devices that govern brain stimulation ++ ----	Invasive technique	Used in essential tremors of Parkinson's diseases, OCD, acquired and developmental stuttering with improvement [173]
Repeated transcranial magnetic stimulation (rTMS)	Neurostimulation +++	Non-invasive	rTMS has been used to reconstruct timed neural integration in intracortical motor networks to further understanding of functional brain dynamics in PWS, with future possibility in clinical treatment [101]
Transcranial Direct Current stimulation (TDCS) VS sham stimulation	Daily application of 20 min of 1-mA anodal TDCS -/+	For 5-consecutive days showed a significant reduction in disfluency& at 1-week post-intervention, maintained in reading tasks at 6 weeks	TCDS paired to the left inferior frontal cortex, known to be underactive during speaking in PWS, in order to improve behavioral therapies including choral speech and metronome-timed speech [174].Conversation tasks returned to pre-intervention baseline levels

Table 7. Pharmacological treatment of stuttering

Medications	Doses & Benefit*	Side effects	Remarks
1. Haloperidol 2. chlorpromazine, 3.Trifluoperazine, 4. Thioridazine	2.5-5mg/d++ 100-600mg/day 15mg/day 400mg/day	EPS, TD, dysphoria and sexual dysfunctions [184]	D2 antagonists improve fluency by increasing brain activity in speech areas (B&W)[185] which like striatum have abnormal low activity [73].Typical antipsychotics are used with benefits in case reports [29,31,184,185]
Risperidone	6mg daily+++	Hyperprolactinemia, sexual dysfunction, galactorrhea, amenorrhea and dysphoria	Blocks D2 receptor linked with increased activity of the striatum and improves fluency and decreases severity of stuttering. Striatal hypometabolism reflects elevated dopamine.[143].
Olanzapine[188]	5mg/d+++ Olanzapine better than haloperidol in the treatment of stuttering [189].	Weight gain, fewer EPS, sexual dysfunction, and prolactin elevation [144].	Blocks D2 receptor linked with increased activity of the striatum improves fluency and decreases severity of stuttering, and induces down-regulation of postsynaptic GABA-A receptors, and directly acting as GABA-A agonists or partial agonists improve stuttering.[25,31,189].
Quetiapine	100-300mg/d ++	Weight gain +/- , Priapism	D2 blocker with some action on serotonin leading to decrease in depression and improving fluency[31]
Lurasidone**	20mg/day ++	Lesser weight gain, lipid elevations, & sedation	Lurasidone potent D2 antagonist improves stuttering [31, 190]
Ziprasidone	20mg/day ++	Well tolerated with mild weight loss	An effective medication for the treatment of stuttering and may be considered as an alternative atypical antipsychotic [191].
Aripiprazole	5-7.5mg/d ++	Akathisia is common side-effect	Partial dopamine agonist of D2 and 5HT1a receptors and used in TSOCD and stuttering with good response[192,193]
Amisulpiride	100-200mg/d	Weight gain	Clozapine-induced stuttering effectively treated by

Medications	Doses & Benefit*	Side effects	Remarks
			Amisulpiride[194]
Pimozide/Paroxetine and citalopram	Pimozide 4mg to 8mg /day ++; SSRIs have no effect on PWS+/-	Pimozide linked with EPS, TD, >Prolactin, dysphoria and cardiac arrhythmias, etc.	Unlike Pimozide, Paroxetine, a SSRI, found to have no effect on stuttering[195]. Pimozide may cause depression in PWS [196].
TCA, Desipramine &Clomipramine	25mg/150mg/day +	Linked with side-effects as dry mouth, tremors, and sexual dysfunctions, cardiovascular effects, etc. [197]	Clomipramine linked with better outcome (fluency) in stutters compared to other TCAs[198,199].
Benzodiazepines and barbiturates	Limited efficacy	Sedation and potential for abuse and addiction	GABA receptor agents reduce both anxiety and stuttering [197].
Pagoclone$	+/- Placebo response	No more info	Selective GABA-A partial agonist & limited info. Decreases stuttering by lowering social anxiety levels, which can make stuttering worse [200]
Ecopipam	++	Tolerable drug, no weight gain, no EPS, good quality of life	D1 receptor antagonist with little affinity to D2 receptors effective in stuttering and TS. Double blind studies needed[201]
VMAT-2 Inhibitors- Valbenazine and Deutetrabenazine.	Valbenazine 40mg/day and Deutetrabenazine 6mg/day +/-	Cause depression, VMAT2 inhibition is non-selective for monoamines and decrease in serotonin induces depression	Used in TS, TD and Huntington's disease. Decrease the synthesis of dopamine through inhibition of VMAT2, a transport protein that packages dopamine into synaptic vesicles for release within the CNS. Promising treatment in PWS[1].
Gabapentin	300mg/day +; Other antiepileptic drugs with +/- effects in PWS	Potential to develop addiction.	Useful in ANS [202].Carbamazepine and sodium divalproate showed equivocal effects but Levetiracetam was effective in CDS/ANS[30].
Clonidine	No effect in stuttering --	Causes adverse effects include hypotension, giddiness and fatigue and others	An alpha receptor agonist. Effective in TS [203].
Verapamil and amlodipine	Verapamil240mg//day and Amlodipine 5mg/day+	Adverse effects include giddiness, lightheadedness and nausea/vomiting and +weight gain	Calcium channel blockers partially effective in ANS[204].

*Striatal hypometabolism=elevated dopamine; Dopamine antagonists increase striatal metabolism; Dopamine activity elevated in PWS; Dopamine agonists worsen stuttering [29,31,73,184,185,205,206];EPS=extrapyramidal symptoms; TD= tardive dyskinesia; B&W=Broca's and Wernicke's areas; OC= operant conditioning;*Measured by various scales SSS=Subjective Stuttering Scale, SSI-3=Stuttering Severity Instrument, CGI=Clinical Global Impression and others*

4. DISCUSSION

This review with facts finding mission described epidemiological parameters, etiological risk factors and theories, clinical core manifestations, comorbid conditions, drivers of help seeking and clinical practice recommendations, diagnostic and measurement tools, differential diagnoses, and psychological and pharmacological treatments together with outcome of PWS.SFD or CDS is reported to develop at age 2-3 years [12] and most children up to 85% naturally recover at 6-7 years with or without treatment [1,8,9,12] attributed to the processes of neural reorganization or neuroplasticity of the brain. CFD rarely starts after age 7 and continues beyond this age with slow rate of normal fluency attainment [5,10]. CDS tends to persist in about 1% to 5% of children and continues in AWS. CDS and PAS are reported four times more in males compared to their counterparts [40] and chronicity, comorbidities, gender, early treatment interventions and severity determine their outcome [42,122,139-141,167,168]. By nature, PAS herald poor prognosis and invariably poor outcome in males compared to females [1,12]. Overall, the variability is a common denominator of epidemiological trends PWS attributed to diverse factors including complex, heterogeneous nature of stuttering, characteristics of individual stutter, and different research methods. More cohort observational studies are required to find out uniform epidemiological parameters of stuttering globally.

The causation and neurophysiology of CDS, PAS, ANS and APS are explored by a large number of studies that focused on biological means, brain injuries attributed to internal and external sources, psychological traits, social determinants and stress models, cultural upbringing and gene-environment interactions [2,5-68,83-95] yet stuttering is not fully understood. Further research especially genomics using most advanced technologies are needed in developmental stuttering. The treatment interventions of all forms of SFD are diverse but speech therapy, behavioral modification techniques especially CBT, speech-devices delivered programs are mainstay of management of PWS. Pharmacotherapeutic interventions, most are associated with various adverse effects in stuttering (2,25-30,102,103,207) are alternative or adjunctive choices in PWS especially in those having psychological comorbid conditions [75,113,133-138,166]. The most challenging task for researchers is to develop drugs effective in stuttering, with a safe clinical profile and minimal side-effects. Therapists need to know that various pharmacotherapies administered to PWS cause paradoxical stuttering [186]. In the treatment context, most studies have reported variable results but rarely complete recovery attributable largely to methodological differences. The implication of most intervention studies is that each PWS needs personalized treatment approach, as a fist does not fit in all sizes.

Acquired speech fluency disorder is mainly categorized into ANS and APS, which are relatively uncommon conditions and etiologically overlapping but these two speech disorders have better defined neurophysiological pathways in terms of TBIs and severe emotional traumas and need a detailed workup for differentiation from articulation, phonation and psychological disorders [2,5-68,83-95,104-106]. The results of most intervention studies using several approaches including neurorehabilitation programs concerning ANS demonstrated poor outcome and more morbidity and mortality compared to persons with APS [1,37]. Concerning APS, non-pharmacological approaches including CBT are most effective and associated with complete recovery with no adverse effects. For the assessment purpose, various rating scales for diagnosing, scaling severity and measuring treatment progress and quality of life of PWS are available in the published literature [38,122,143,144], and should be utilized especially in stuttering RCTs and other research designs.

This review has some limitations. The literature on stuttering is extensive and this introduced selection bias, beyond our control and publication bias as we did not manage unpublished papers on stuttering. Our team could not include all published papers due to many reasons including importantly freely inaccessible papers. However, we managed to contain most influential systematic reviews, meta-analysis and RCTs and other observational studies from around the world and found facts especially about epidemiology, clinical signs and symptoms, diagnosis and rating scales, and drug and non-drug treatments of stuttering. Nonetheless, several perspectives including genetic, social and cultural dimensions need continuous research in stuttering globally. Take away home messages to patients, parents, therapists, policy makers and public at large include the following; 1) stuttering is a

neurological disorder; 2) PWS should consult early related healthcare providers for diagnostic and treatment assessment; 3) early recognition and intervention herald better recovery and quality of life; 4) relevant strategies and awareness campaigns to reduce stigma and discrimination against PWS; 5) PWS should be given equal opportunities in civil rights; 6) healthcare services need scaling up with easy access to all patients with stuttering; and 7) parents at homes and employers at work places should build a milieu free of overwhelming stresses that induce stuttering.

5. CONCLUSION

Speech fluency disorder, a well-recognized Axis-1disorder in DSM-IV, is a complex neurological condition afflicts about 1% general population, reported in all age group of people but most frequently in male children of 2-3 years, improves spontaneously in 85% of PWS, determined by a wide variety of biopsychosocial factors, characterized by salient clinical features, and diagnosable and treatable disease with inconsistent outcomes attributed to research methods. Studies conducted worldwide projected better outlook for PWS who need equal opportunities in all parts of life. Despite many challenges and barriers, cohort studies and randomized clinical trials involving drugs and non-drug therapies are needed in all categories of stuttering in future.

CONSENT

It is not applicable**.**

ETHICAL APPROVAL

It is not applicable.

STUTTERING RESOURCES FOR PHYSICIANS, PARENTS, AND PATIENTS

- Erada Stuttering Foundation, Riyadh, Saudi Arabia
- American Board of Fluency and Fluency Disorders: http:// www.stutteringspecialists.org
- American Speech-Language-Hearing Association: https:// www.asha.org
- National Stuttering Association: https:// westutter.org
- The Stuttering Foundation: https:// www.stutteringhelp.org

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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