The Neurophysiology and Pharmacologic Treatment of Stuttering

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- Consultant: Merck, Novartis
The History of Stuttering

- Stuttering has occurred throughout recorded history in every culture.
Every Language Has a Word for Stuttering

<table>
<thead>
<tr>
<th>Language</th>
<th>Word</th>
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</thead>
<tbody>
<tr>
<td>English</td>
<td>stuttering</td>
</tr>
<tr>
<td>French</td>
<td>begaiement</td>
</tr>
<tr>
<td>Spanish</td>
<td>tartamudez</td>
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<tr>
<td>Sanskrit</td>
<td>Jivha Jarata</td>
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<td>Chinese</td>
<td>hau hick</td>
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<td>Japanese</td>
<td>domori</td>
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<tr>
<td>Nigerian</td>
<td>nsu</td>
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<tr>
<td>Persian</td>
<td>locknatezaban</td>
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Diagnostic Criteria for Stuttering

DSM-IV-TR diagnostic criteria for stuttering
(Code = 307.00) Axis I

A. Disturbance in normal fluency and time patterning of speech (inappropriate for the individual’s age), characterized by frequent occurrences of 1 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 communications
C. If a speech-motor or sensory deficit is present, the speech difficulties are in excess of those usually associated with these problems
Revised Criteria for Stuttering in DSM-V—Childhood Onset Fluency Disorder

- Addition of Criterion Concerning Avoidance/Anxiety (captures “covert” stuttering)
- Removal of interjections
- Placement of “Developmental” Stuttering as Axis I condition with onset in childhood.
- “Psychogenic” stuttering (termed not used in medicine or psychiatry) placed as Axis I and termed under Malingering or Conversion Disorder based on presentation
- “Acquired” Stuttering placed as Axis III

www.psych.org
### Stuttering Statistics

- **1% of US adult population**: >2,000,000
- **4% of US child population**: >3,000,000
- **Total in the US (as of 2000)**: >5,000,000
- **Membership in National Stuttering Association**: 4,500

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**Source:** 2000 Census (numbers are rounded).  
Total US population: 281,421,906.  
Total US adult population: 200,948,643.  
Total US children (under age 19): 80,473,263.
Historical Stuttering Theories and Treatments

- Believed to be caused by abnormalities of the tongue or larynx
  - Cauterizing or cutting the tongue
  - Botulinum toxin injections into the larynx
  - Both without efficacy
Orton and Travis: A Brain Theory of Stuttering

- Stuttering may arise from abnormal cerebral activity/stuttering viewed as a brain disorder (cross dominance with handedness)

- Believed to be brought about by an incomplete dominance of the speech centers

Travis EE. Speech pathology; A dynamic neurological treatment of normal speech and speech deviations; 1931.
Psychoanalytic Theory

- Unconscious neurotic need fulfillment
- Unresolved oral conflict
- “Stuttering results from thoroughly unresolved pregenital oral sadistic conflict”
Stuttering Shows Many Similarities With Tourette’s Syndrome

- Both associated with tic motions
- Both follow a waxing and waning course
- Made worse under anxiety or stress
- 4:1 male to female ratio
- Begins in childhood
- Symptoms worsened by dopamine agonists and improved with dopamine antagonists
- Related to abnormalities in the basal ganglia
- Genetic linkage postulated

Etiology of Stuttering (Likely Multifactorial)

- Genetics

- Abnormal development of basal ganglia and/or white matter tracts (Maguire et al; Neumann et al; Sommer et al)

- Autoimmune Component (i.e. PANDAS) (Maguire et al. Annals of Clinical Psychiatry.)
PANDAS Stuttering

- Pediatric Autoimmune Disorder Associated with Streptococcus
- Antibodies directed against streptococcal infection cross-react and attack developing basal ganglia.
- Established etiologic mechanism in Tourette Syndrome and OCD.
- Now described in Stuttering
Famous Persons Who Stutter(ed)

- Alexander the Great
- Aristotle
- Winston Churchill
- Charles Darwin
- King George VI
- James Earl Jones
- Bo Jackson
- Somerset Maugham
- Marilyn Monroe
- Moses
- Carly Simon
- Bill Walton
- Bruce Willis
PET and SPECT Imaging

- Allow measurement of the metabolism of the living functioning brain
Wood, Stump 1980 investigated the effects of haloperidol on brain activity in stuttering utilizing SPECT.

- Stuttering symptoms improve with haloperidol with resulting improved fluency associated with increased brain activity in speech areas.
Pool, Devous, et al. in a large SPECT study showed stuttering to be associated with no abnormalities in brain structure (MRI), but associated with abnormally low brain activity in left-sided speech cortical areas.

Brain Imaging Studies of Stuttering (cont.)

- Left hemispheric speech areas less active than analogous areas of right hemisphere
- Now confirmed with structural (MRI) studies (Foundas et al; Sommer et al)
- Is the increase in right-sided structures a compensatory effect/therapy effect? May explain gender differences.

Wu, Maguire, Riley, et al. utilized FDG to measure glucose metabolism in stuttering

- Stuttering associated with abnormal low activity of speech cortical areas (Broca’s and Wernicke’s) and striatum
- During induced fluency, cortical speech areas increase to normal or high normal areas, but striatum remains low

"Increased Brain Regional Metabolism in Stutterers when Fluent" (n = 4, matched t-tests, pilot data)
Two “Loops” of Speech

- An inner or medial system
  - Abnormal in stuttering

- An outer or lateral system
  - Can be activated in stuttering through induced fluency

Possible Neurologic Pathway of Stuttering Involved in Pharmacologic Treatment

- Dopamine lowers activity of striatum
- Olanzapine/risperidone block dopamine, leading to increased activity of the striatum and improved fluency
- GABA can reduce dopamine function (Pagoclone)
Dopamine Theory of Stuttering

- Striatal hypometabolism = elevated dopamine
- Dopamine antagonists increase striatal metabolism
- Dopamine antagonists improve stuttering
- Dopamine activity elevated in persons who stutter
- Dopamine agonists worsen stuttering

Numerous medications have been studied but until recently, only those with dopamine blocking activity have shown confirmed efficacy.

Pagoclone, a GABA selective agonist, has shown efficacy as well in the largest pharmacologic trial of stuttering ever conducted.
Haloperidol

- First-Generation Dopamine Antagonist
- Associated with improved fluency
- However, poor long-term compliance secondary to disabling side effects (e.g., dysphoria, sexual dysfunction, extrapyramidal symptoms, tardive dyskinesia)

Pimozide/Paroxetine Study

- Positive clinical response in those on pimozide (dopamine antagonist)

- Paroxetine (serotonin reuptake inhibitor) exhibited no clinical response

- However, Pimozide associated with limiting side-effects such as EPS, TD, dysphoria, prolactin elevation and cardiac conduction concerns

New Generation Dopamine Blockers Studied in Stuttering

- Risperidone
- Olanzapine

These agents have a much lower risk of motor system side-effects (e.g. tardive dyskinesia) and are much better tolerated than first generation agents.
Risperidone Study

- n=16
- Double-blind, placebo-controlled
- 6-week duration

Risperidone Study (cont.)

- Ages 20-74 (mean 40.75)
- 12 males/4 females
- Dose 0.5-2.0 mg
- Ratings (% SS, duration, % TS, SSI-3)

Reductions in Severity Scores at best time-point in Subjects Receiving Risperidone or Placebo

% SS=syllables stuttered; % TS=time stuttering as a % of total time speaking.
SSI-3=Stuttering Severity Instrument, Third Edition (measured overall stuttering severity).
Subtraction: ON-OFF

Changes w/ Risperidone:
1. Caudate increase
2. Broca's area (speech production) increase
3. Putamen increase
PET Imaging of the Effects of Risperidone in Stuttering

- Risperidone is associated with increased activity in the striatum and cortical speech areas.
Olanzapine: An Atypical Dopamine Antagonist

- In studies of other disorders, olanzapine has different tolerability than risperidone (less EPS, TD, dysphoria, sexual dysfunction, and prolactin elevation). Propensity for greater weight gain, however.

Olanzapine vs Placebo: 3-Month Study

- 24 adult patients who stutter (ages 18-55)
- Multicenter, 3-month, double-blind, placebo-controlled trial
- Dose range 2.5→5 mg (starting dose 2.5 mg)

Reductions in Severity Scores on the SSI-3 Measures in Subjects Receiving Olanzapine or Placebo

% SS=syllables stuttered; % TS=time stuttering as a % of total time speaking.
SSI-3=Stuttering Severity Instrument, Third Edition (measured overall stuttering severity).

*p<.044 vs. placebo
Reduction in Subjective Stuttering Scale in Subjects Receiving Olanzapine

SSS = Subjective Stuttering Scale

% Reduction in SSS

-30
-25
-20
-15
-10
-5
0

Olanzapine
Placebo

22%*

<1%

* p < .01
Results

- Olanzapine more effective than placebo in reducing stuttering on all 3 ratings (SSI-3, CGI, and SSS)
- Olanzapine well tolerated with minimal side effects
- Efficacy continues long-term
  - Some subjects showed greater efficacy at higher doses
- At the conclusion of the study each subject requested to remain on olanzapine

Olanzapine vs. Placebo

Three-month study – Safety results

- No prolactin related side effects
- No changes of fasting blood glucose or development of diabetes in this study
- Weight gain/appetite increase 4.0 lbs on olanzapine vs. <1 lb placebo
- Mild sedation
- 1 subject discontinued study (subject was taking placebo)
- At the conclusion of the study, each subject requested to remain on olanzapine

Asenapine

- Not associated with significant weight gain or glucose/lipid increases
- Sublingual administration
- Associated with bitter taste but flavored available in US
- Double-blind Placebo-Controlled Trial ongoing
- Published data supporting utility in Stuttering ([Am. J Psychiatry—June 2011])
Quetiapine

- Not extensively studied in stuttering
- Relatively weak D2 antangonism--With Histamine blockade—causes sedation and this side-effect limits its use in stuttering
Aripiprazole

- Partial dopamine agonist—Lower dosages may work better?
- Akathisia can limit utility in stuttering
- Published report examining safety and effectiveness in stuttering

Tran NL, Maguire GA. Journal of Clinical Psychopharmacology
Ziprasidone

- Not adequately studied in stuttering but based on mechanism of action, promising agent
Iloperidone

- Requires a titration of dosage
- Associated with light-headedness
- Not adequately studied in stuttering but based on mechanism of action, promising agent
Lurasidone

- Well-tolerated except akathisia
- Low weight gain/metabolic risk
- Not adequately studied in stuttering but based on mechanism, may be promising
Pagocclone

- Pagocclone, is a selective GABA-A partial agonist

- The Largest Pharmacologic Trial of Stuttering Ever Conducted has now been Completed.

- Based on an unclear mechanism for stuttering treatment—GABA agonism.
Pagoclone Program in Stuttering

- 2 Cases identified in Panic Disorder trial
  - History of persistent developmental stuttering at entry
  - Stuttering improved while on active drug (along with anxiety symptoms)
  - Stuttering returned to baseline after trial

- Literature: GABA may have role in stuttering

- Consultant input on stuttering assessment

- Indevus decision to conduct pilot (Phase 2a) trial 039
Pagoclone Phase Ila Study 039

- Double-blind, placebo controlled, 8 weeks
  - Titration: 0.15 mg BID x 2 wk, then 0.30 mg BID x 6 wk
  - Primary endpoint: change in SSI-3 total score
    - Secondaries included subcomponents of SSI-3 (% SS), CGI-I, Liebowitz Social Anxiety Scale
- Open label extension
Pagocclone Phase IIa Study 039
Change from Pre-Treatment in Percentage Syllables Stuttered

P-values from ANOVA with effects for treatment and center.
Pagoclone Phase Ila Study 039
Percent of Patients with Improvement as Assessed by CGI-I Severity

On-Treatment
Week 2 Week 4 Week 8
CGI Severity Percent of Patients Improved from Pre-Treatment

Placebo Pagoclone

P<0.01 P<0.02

P-values from CMH controlling for center.
Pagoclone Phase IIa Study 039
LSAS Total Score – Subset of Patients with Baseline LSAS Total Score > 45

<table>
<thead>
<tr>
<th>On-Treatment Week</th>
<th>LSAS Total Score Change from Pre-Treatment</th>
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<tbody>
<tr>
<td>4</td>
<td>-20</td>
</tr>
<tr>
<td>8</td>
<td>-18</td>
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Placebo            Pagoclone

P<0.03            P<0.03
Pagoclone Phase IIa Study 039
Open Label Extension

➢ Over 90% of patients in the 8 week double blind phase entered the open label extension

➢ Some patients experienced life-changing benefits (e.g., employment, public speaking)

➢ Very Effective on Social Anxiety associated with Stuttering
Improvements in fluency seen in the double blind phase increased progressively over 4-6 months of treatment

- original placebo group showed expected lag in timecourse

Dosing was 0.6 mg once per day

Starting with second year of extension, added dose flexibility to 0.6 mg BID

Safety data revealed excellent tolerability
Pagocclone Phase IIa Study 039
Percentage Syllables Stuttered – DB + OL

P-values from ANOVA with effects for treatment and center.
Pagoclone Phase IIa Study 039

Percent of Patients with Improvement as Assessed by CGI-I Severity

P-values from CMH controlling for center.
Pagocclone Phase IIa Study 039
LSAS Total Score – Subset of Patients with Baseline LSAS Total Score > 45

Week 4
Week 8
Month 3
Open-Label Phase

Placebo DB
Placebo DB --> Pagocclone OL
Pagocclone DB
Pagocclone DB --> Pagocclone OL

N=27 for Placebo N=37 for Pagocclone
N=18             N=23
P<0.03
P<0.03
Pagoclone Phase IIa Study 039
Open Label Extension

➤ Improvements in fluency seen in the double blind phase increased progressively over 4-6 months of treatment
  • original placebo group showed expected lag in timecourse

➤ Dosing was 0.6 mg once per day

➤ Starting with second year of extension, added dose flexibility to 0.6 mg BID

➤ Safety data revealed excellent tolerability
Pagoclone Tolerability and Safety

- Pagoclone was very well tolerated and resulted in a “natural” speech
- Pagoclone Very Effective in Social Anxiety Associated with Stuttering

J. Clin. Psychopharm 2010
Protocol IP456-041

- Title of Study: A 3-arm, double-blind, placebo-controlled clinical trial to assess the efficacy, safety and tolerability of pagoclone for the treatment of adults with stuttering.

- Multi-center, randomized, 3-arm, placebo-controlled, parallel group Phase IIa study involving 24 weeks double-blind treatment followed by an 8-week double-blind Wash-out and then a long-term open-label extension phase.

- Approximately 60 investigational centers in the United States in around 330 patients.
Pagocclone

- Pagocclone Tolerated Very Well
- Higher dosages appear to result in higher efficacy
- Challenge of accurately measuring stuttering efficacy—natural variability of the disorder—accommodation to therapeutic setting
- Funding has currently ceased. No further development planned
Treatment of Comorbid Conditions

- Social Anxiety common stuttering. CBT may be useful
- Comorbid ADHD—stimulants may worsen stuttering. Perhaps trials of noradrenergic agents first-line
Deep Brain Stimulation (DBS)

- Approved for Treatment of Parkinson’s, Essential Tremor
- Cases in the literature of treatment of acquired stuttering
- First case published this month (Maguire et al, Am J. Psych) of treatment of developmental stuttering with DBS
- DBS case replicated in France
- Patent filed by Medtronic for DBS treatment of stuttering
Future Directions in Stuttering Pharmacologic Research

- Trials of Pagoclone at higher dosages?
- Trials of other dopamine antagonists
- Asenapine trial beginning—case series published
- How do we accurately assess changes in stuttering severity? Global scales consistent with treatment effect but what about more quantitative measures?
Future Directions (cont.)

- What about combining speech therapy with medication?
- What about medication treatment in adolescents?
- Lysosomal Storage Modified treatments?
- Psychiatrists should be the lead physicians, partnering with Speech/Language Pathology in the Treatment of Stuttering
“Professor Gallagher and his controversial technique of simultaneously confronting the fear of heights, snakes, and the dark.”  

Gary Larson
You don't know psychiatry.
I do.
Contact Me!

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- **(714)456-5794**
- **www.kirkupcenter.uci.edu**
- Without Hesitation: Speaking to the Silence and to the Science of Stuttering. **www.westutter.org**