Double-blind, Randomized, Multi-Center Placebo-Controlled Trial of Varenicline in the Treatment of SCA-3 (Achantia)

Theresa A. Zesiewicz, MD FAAN
Professor of Neurology
Director, Ataxia Research Center
University of South Florida
Tampa, Florida
Authors

- Susan L. Perlman, MD (UCLA, California)
- Penny Greenstein, MD (Beth Israel, Harvard University, Boston Massachusetts)
- Kelly L. Sullivan, Amber Miller,
- Israt Jahan, MD and University of South Florida team
Protocol Development

- Tetsuo Ashizawa
- Khalef Bushara
- Christopher Gomez
- S.H. Subramony
- George Wilmot, III
Varenicline (Chantix)

- Varenicline is a drug made by Pfizer Pharmaceuticals.
- Developed for the sole purpose of helping patients quit smoking.
- Other drugs used for this purpose include nicotine gum, nicotine patch.
- Drugs designer thought that agonist at nicotinic acetylcholine system would be beneficial.
Varenclline as a smoking aid

- Varenicline proved to be beneficial for the most part in assisting people with stopping their smoking habit
- However, its side effects marred it reputation to some degree
- There were reports of nausea, vivid dreams, and most importantly depression and suicidal ideation
- Not a drug to be taken lightly
Varenicline

- This would have been the last drug I would have chosen to test
- But in retrospect, hints about the cholinergic system and ataxia started many years ago with physostigmine
- There were also reports in the past about Wellbutrin, and its anecdotal reports about treatment of ataxia
Varenicline Reports

- In December 2007, a patient with FXTAS came to clinic and stated that he took his wife’s smoking drug, Varenicline (Chantix)
- This is a syndrome related to fragile X that causes ataxia and tremor, as well as parkinsonism
He told me that he hadn’t quite quit smoking, but that his balance and gait were much improved.

First: I doubted him.

Second, I took him off the drug and told him to come back in one month, for reevaluation.

Patient was taken off medication at USF, and came back January 30, 2008.
The patient’s balance and gait worsened off varenicline, although his tremor was better. The patient was prescribed varenicline again, with similar benefit within about 3 weeks time.
Reported the finding, using this patient as his own control

We decided to see if varenicline could improve some additional ataxias, including the ADCA’s and ARCA’s, like Friedreich’s ataxia

In March 2008, an SCA 3 patient and a patient with SCA 14 also took varenicline, got up to maximum dose of 1 mg BID

Both had marked improvements in the SARA scores

The SCA 3 patient used 2 crutch canes originally, but was able to ambulate without them.
Varenicline First Reports

- The titration up was a bit rocky
- The patients complained of nausea and very vivid dreams
- One patient took an antacid to help her, although some antacids may interfere with varenicline
- One patient had coronary artery disease and brain ischemia, even a myocardial infarction in the past
The SCA 3 patient estimated that it took about 3 weeks for her gait to improve. She noticed that she had better depth perception when she approached a curb to step onto it.

The SCA 14 patient also improved, but developed “muscle pain” in 2 months, and discontinued varenicline.
The patient with SCA type 3 had a 16-year history of imbalance, gait dysfunction, and dysarthria.

Her gait consisted of severe staggering and ataxia, and she required the constant use of a walker or the support of a cane to ambulate.

The patient could not stand in a natural position without falling, and she was unable to tandem walk even with support.
Varenicline

- Upon examination 1 month after starting varenicline, her gait dysfunction had improved markedly, and she was able to walk independently while only occasionally reaching for the wall for stability.

- The total SARA score prior to the patient taking varenicline 1 mg twice daily was 29, while the score one month after starting varenicline was 13. The patient has remained on varenicline for 5 months with continued improvement.
Varenicline

- She remains the patient with the most improvement
- Has taken varenicline for 3 years on and off
- She notes that everytime she stops it and then restarts the drug, it takes longer and longer for her to feel the effects (3 weeks, 6 weeks)
Study Rationale

- Varenicline is a highly selective partial agonist at the $\alpha 4\beta 2$ nicotinic acetylcholine receptor that aids smoking cessation by reducing nicotine withdrawal symptoms.
- Nicotinic acetylcholine receptors also have a possible role in cerebellar development.
- For example, nicotine has been shown to be harmful to developing cerebellum as evidenced by a loss of purkinje cells.
Study Rationale

- Nicotinic acetylcholine receptors are very numerous in the brain
- Cerebellar Purkinje cells express nicotinic acetylcholine receptors including the α4 and α7 subunits, and others
- Chronic exposure of the cerebellum to nicotine may also effect glutamate
Cerebellum and nicotinic receptor subunits

- Using immunohistochemical localization of nicotinic acetylcholine receptor subunits in human cerebellum samples from autopsy specimens, Graham et al found that most Purkinje cells were immunoreactive for \( \alpha_3, \alpha_4, \alpha_6, \alpha_7, \beta_2, \beta_4 \) subunits, or combinations of these.
Study Sponsored By:

- National Ataxia Foundation
- Bobby Allison Ataxia Research Alliance
Double blind, randomized, placebo controlled trial to study the preliminary safety and efficacy of varenicline in SCA-3
Study Purpose

- The purpose of the study was to test the efficacy and safety of varenicline (Chantix) in a controlled study in SCA - 3 patients
- This was a pilot trial to determine whether our preliminary observations were correct about varenicline in SCA - 3
Primary Objective

- To assess the effectiveness of varenicline on SARA symptoms and severity (as measured by clinical rating scales) at endpoint compared to baseline.

- To assess the frequency and severity of dose-limiting adverse events associated with varenicline treatment.
Secondary Endpoints

- Change in T25-FW
- Change in 9-hole peg test (9HPT)
- Change in SF-36 quality of life rating scale
- Change in Depression rating scale
- Change in Anxiety rating scale
- Change in clinical global impression of improvement (CGI)
- Change in activities of daily living scale
Inclusion Criteria

- Outpatients with SCA 3 diagnosed by a movement disorder specialist and confirmed by genetic testing (of the patient or in a first degree relative of the patient).
- Age 18 years to 80 years.
- Women of child-bearing potential must use a reliable method of contraception and must provide a negative pregnancy test at entry into the study.
- Serum creatine kinase, complete metabolic panel, complete blood count, liver function tests, renal function tests, platelets and EKG are within normal limits (results obtained from primary care physician and dated within the past 6 months)
Inclusion Criteria

- Stable doses of all medications for 30 days prior to study entry and for the duration of the study.
- Ability to ambulate with or without assistance.
- Score of 10 or higher (worse) on the SARA total score.
- Score of 3 or higher (worse) on the ‘gait’ subsection of the SARA rating scale.
Exclusion Criteria

- Any unstable illness or concomitant medical condition that, in the investigator’s opinion, precludes participation in this study. This includes other disorders that may affect gait or balance (stroke, arthritis, etc).
- Pregnancy or lactation.
- Concurrent participation in another clinical study.
- Patients with a history of substance abuse.
- Patients who currently smoke or have smoked within the past 12 months.
- Presence of psychosis, bipolar disorder, untreated depression (BDI greater than or equal to 21), or history of suicide attempt.
Exclusion Criteria

- Concurrent treatment with any MAOIs, Wellbutrin, or nicotine patches.
- Dementia or other psychiatric illness that prevents the patient from giving informed consent (Mini Mental Status Exam score less than 24).
- Presence of severe renal disease (BUN 50% greater than normal or creatinine clearance <60 mL/min) or hepatic disease.
- Abnormal creatine kinase and/or platelet count in the past 6 months (as determined by lab reports obtained from primary care physicians or conducted at baseline).
- Ataxia derived from any other cause than genetically-confirmed SCA (including but not limited to alcoholism, head injury, Multiple Sclerosis, olivo-ponto-cerebellar atrophy or multiple system atrophy).
Study

- Ended up enrolling with 3 sites (USF, UCLA, and Beth Israel, Harvard)
- 20 patients
- We saw some benefit with varenicline in other SCA types, and may work on these in the future
- Kept the type of ataxia uniform because we had so few patients
Study Design

- Subjects with genetically confirmed SCA 3 received a total of 2 mg of varenicline or placebo daily over a 5 week period.
- Stable dose maintained for an additional 4 weeks.
- The primary efficacy measure was the change in SARA scores from baseline to the end of the first arm (week 9).
RESULTS

- Nineteen subjects with SCA 3 were enrolled in the study (placebo n=10, varenicline n = 9). (Originally had 20 patients, one patient was given study drug, but the travel was too extensive and there were no scores.
- The mean age of patients was 51.7 ± 10.7 years.
- The mean total SARA score at baseline was 16.2 ± 4.6.
## RESULTS Phase I

<table>
<thead>
<tr>
<th>variable</th>
<th>baseline mean chantix</th>
<th>locf mean chantix</th>
<th>baseline mean placebo</th>
<th>locf mean placebo</th>
<th>p-value (wilcoxon)</th>
</tr>
</thead>
<tbody>
<tr>
<td>sara gait</td>
<td>4.1</td>
<td>3.4</td>
<td>5.2</td>
<td>4.9</td>
<td>0.0313</td>
</tr>
<tr>
<td>sara stance</td>
<td>2.2</td>
<td>2</td>
<td>3.4</td>
<td>2.8</td>
<td>0.0728</td>
</tr>
<tr>
<td>sara sitting</td>
<td>0.3</td>
<td>0.3</td>
<td>0.9</td>
<td>1.1</td>
<td>0.7539</td>
</tr>
<tr>
<td>sara speech</td>
<td>2.4</td>
<td>1.9</td>
<td>2.3</td>
<td>2.3</td>
<td>0.3213</td>
</tr>
<tr>
<td>sara finger chase</td>
<td>1.2</td>
<td>1.1</td>
<td>1.2</td>
<td>1.7</td>
<td>0.3159</td>
</tr>
<tr>
<td>sara finger nose</td>
<td>0.8</td>
<td>0.8</td>
<td>1</td>
<td>1.2</td>
<td>0.7102</td>
</tr>
<tr>
<td>sara rapid alternating movements</td>
<td>2</td>
<td>1.4</td>
<td>2.1</td>
<td>1.7</td>
<td>0.0034</td>
</tr>
<tr>
<td>sara heel shin</td>
<td>1.4</td>
<td>1.5</td>
<td>1.8</td>
<td>2</td>
<td>0.5976</td>
</tr>
<tr>
<td>sara total</td>
<td>14.4</td>
<td>12.5</td>
<td>17.8</td>
<td>17.5</td>
<td>0.1563</td>
</tr>
<tr>
<td>9hpt dominant average</td>
<td>41.3</td>
<td>36.5</td>
<td>57.7</td>
<td>57.9</td>
<td>0.3124</td>
</tr>
<tr>
<td>9hpt nondom average</td>
<td>43.7</td>
<td>39.3</td>
<td>66.5</td>
<td>65.5</td>
<td>0.1447</td>
</tr>
<tr>
<td>25' walk avg</td>
<td>15.7</td>
<td>12.2</td>
<td>31</td>
<td>21.3</td>
<td>0.0496</td>
</tr>
<tr>
<td>becks depression</td>
<td>7.4</td>
<td>3.7</td>
<td>8.6</td>
<td>6.2</td>
<td>0.0313</td>
</tr>
<tr>
<td>becks anxiety</td>
<td>11.8</td>
<td>7.7</td>
<td>16.8</td>
<td>12.1</td>
<td>0.1426</td>
</tr>
<tr>
<td>adl score</td>
<td>10.8</td>
<td>11.1</td>
<td>15.6</td>
<td>14.2</td>
<td>0.7715</td>
</tr>
</tbody>
</table>
Drop Outs

- 6 of 19 patients
- 4 of 19 patients took placebo, and dropped out in Phase I
- These adverse events included: urosepsis, muscle pain, 1 non-compliant patient and 1 patient with travelling issues
- 2 patients dropped out of 19 due to study drug complications (one from auditory hallucinations and one from “weakness”)
The patient with auditory hallucinations was a new father with a sleep disorder.

After dropping out of the study, he took varenicline and continues to take it with no problems thus far.

No patients complained of depression, nor dropped out due to depression.
<table>
<thead>
<tr>
<th>Event</th>
<th>Total #</th>
<th># Varenicline</th>
<th># Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GI-related</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>9</td>
<td>6[KL51]</td>
<td>3</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Sleep/energy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disturbed sleep</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Increased dreaming/vivid dreams</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Sleep restless</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Mood/Psych</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased depression</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Irritability</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Auditory hallucinations</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Neurologic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spasticity</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Increased stiffness, (LE)</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Increased tremor</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Tingling in legs</td>
<td>2</td>
<td>2[KL52]</td>
<td>0</td>
</tr>
<tr>
<td>Increased imbalance</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Increased dizziness</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Legs shaky</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Syndrome</td>
<td>2023-03</td>
<td>2023-04</td>
<td>2023-05</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>Right knee weakness</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Shoulder pain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hip pain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Urologic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine retention</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UTI/Urosepsis (SAE)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shivering</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blotchy feet</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cold feet</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL # EVENTS</strong></td>
<td>54</td>
<td>27</td>
<td>27</td>
</tr>
<tr>
<td><strong>Total # SAEs</strong></td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>
The idea that cholinergic drugs may be of therapeutic benefit for some types of ataxia is supported by studies conducted during the late 1970s using both physostigmine, a cholinesterase inhibitor that crosses the blood brain barrier and increases brain levels of acetylcholine, and choline, a precursor for acetylcholine and direct nicotinic receptor agonist.

Studies with physostigmine reported beneficial effects in patients with spinocerebellar degenerations and various inherited ataxias, but no benefit in patients with autosomal dominant and idiopathic cerebellar ataxia.

Unfortunately, optimal doses were not determined and further studies were not pursued.
Discussion

- It is likely that the ability of varenicline to improve ataxia is due to a combination of actions initiated at different subtypes of neuronal nicotinic receptors.
- Although varenicline was developed as a partial agonist at α4β2 receptors, it has differential actions at different nicotinic receptors in the brain.
- In addition to its action at α4β2 receptors, varenicline has full agonist activity at homomeric α7 receptors, and weak partial agonist activity at α3β2 and α6-containing receptors.
The affinity of varenicline for $\alpha_4\beta_2$ receptors relative to $\alpha_7$ receptors is about the same as that for nicotine.

Activation of $\alpha_7$ and $\alpha_4\beta_2$ receptors may be involved, as stimulation of both of these receptor subtypes protects glutamate-induced motor neuron death in rat spinal cord cultures.
Next step is continue towards an FDA orphan drug program
To test varenicline on a larger scale, possibly demonstrate efficacy so the FDA will approve for orphan drug status
Open the door to the effect of nicotinic activation (or is it antagonism?) in ataxia
Cholinergic effects, or downstream mechanisms that have little to do with how we think varenicline improves gait.
Lessons Learned

- There is a very large placebo effect in these clinical trials (twice as many placebo patients dropped out of the study as varenicline patients)
- The clinical rating scales can be subjective, and it is strongly urged that a gait rite computerized walking system be validated quickly to test patients
Lessons Learned

- Anecdotally, patients who were tremulous, or who had very advanced disease, did not appear to benefit as much, OR had the problematic side effect of weakness (1 patient, most severely affected)
- FA: very early patients often developed that "weakness": due to spasiticity?
- While varenicline gets a bad reputation for depression in smokers, it improved depression in this population
Crossover studies may not be a great idea in SCA

Once you treat a patient with a drug, there are changes induced that may not reverse in the time period that you think

There were so many placebo dropouts in Phase I, that there were too few patients to go on to Phase II and study varenicline

Spasticity and Dystonia may interfere with study results
“Weakness” may be due to change or loss of spasticity, causing patients to feel like “wet noodle”

- Upper limit to the SARA scale for patients
- Take Ashworth Spasticity Scale and dystonia scale scores
Authors

- Susan L. Perlman, MD (UCLA, California)
- Penny Greenstein, MD (Beth Israel, Harvard University, Boston Massachusetts)
- Kelly L. Sullivan, Amber Miller,
- Israt Jahan, MD
Protocol Development

- Tetsuo Ashizawa
- Khalef Bushara
- Christopher Gomez
- S.H. Subramony
- George Wilmot, III
- Special thanks to Mike Parent from the NAF and Mark Allison from BAARC
Thank You

- Patients
- NAF
- BAARC