Botulinum Toxin: Update on Emerging Therapeutic Uses and Potential Safety Considerations

A podcast educational activity based on a live program conducted on December 7, 2008 in Orlando, Florida
Botulinum Toxin: Update on Emerging Therapeutic Uses and Potential Safety Considerations

PROGRAM AGENDA

Pharmacology of Botulinum Toxin and Characteristics of Available Products
Evelyn Hermes DeSantis, Pharm.D., BCPS

Current and Emerging Therapeutic Uses of Botulinum Toxin
David M. Simpson, M.D.

Pharmacy Considerations Related to the Use of Biosimilars in Health Systems
Richard G. Wenzel, Pharm.D.

PROGRAM FACULTY

Evelyn Hermes DeSantis, Pharm.D., BCPS
Clinical Associate Professor
Ernest Mario School of Pharmacy
Rutgers University
Director, Drug Information Center
Robert Wood Johnson University Hospital
Piscataway, New Jersey

David M. Simpson, M.D.
Professor of Neurology
Director, Clinical Neurophysiology Laboratories
Director, Neuro-AIDS Program
Mount Sinai Medical Center
New York, New York

Richard G. Wenzel, Pharm.D.
Diamond Headache Clinic Inpatient Unit
St. Joseph’s Hospital
Chicago, Illinois
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**Evelyn Hermes DeSantis, Pharm.D., BCPS**

Dr. DeSantis declares that he has no relationships pertinent to this activity.

**David M. Simpson, M.D.**

Dr. Simpson declares that he has no relationships pertinent to this activity.

**Richard G. Wenzel, Pharm.D.**

Dr. Page declares that he has no relationships pertinent to this activity.

**Benjamin I. Dickinson, Pharm.D.**

Dr. Dickinson declares that he has no relationships pertinent to this activity.
Botulinum Toxin: Update on Emerging Therapeutic Uses and Potential Safety Considerations

PROGRAM OVERVIEW

Botulinum toxin is well known for its cosmetic uses, but the current clinical literature is also replete with studies of the therapeutic use of botulinum toxins type A and type B for a variety of indications, usually characterized by excessive neuromuscular activity or chronic pain, only some of which are FDA approved. It has been challenging for health professionals to draw conclusions from the accumulated studies because of small sample sizes and limitations in study design. Further, since botulinum toxin products are not interchangeable, it is difficult to compare study results. Recently published evidence-based clinical guidelines from the American Academy of Neurology (AAN) provide much needed evidence-based reviews of the efficacy and safety of botulinum neurotoxin for spasticity, movement disorders, and autonomic disorders and pain. As the medication-use experts in health systems, pharmacists have the responsibility of ensuring the safe and effective use of botulinum toxin. In order to fulfill this responsibility, pharmacists must keep abreast of current clinical guidelines, evolving clinical evidence, and medication safety issues. This program will provide an overview of current and emerging therapeutic uses of botulinum toxin in light of evidence-based guidelines, after first reviewing the pharmacology of botulinum toxin and comparing characteristics of botulinum toxin products that are currently available. Safety considerations related to botulinum toxin will be reviewed, as well as the need to educate patients, their caregivers, and follow-up health care providers about potential systemic effects of botulinum toxin and instructions for seeking immediate medical care, if necessary.

Reimbursement issues related to biosimilars and the status of policy and regulatory initiatives related to follow-on biologics that may influence formulary decisions in the future will also be described.

The faculty will use an audience response system so that the audience can participate in the program through interactive questions.

PROGRAM OBJECTIVES

At the conclusion of this educational activity, participants should be able to

- Explain the mechanism of action and pharmacologic effects of botulinum toxin.
- Compare characteristics of botulinum toxin type A and type B products currently available.
- Identify at least one FDA-approved therapeutic indication for botulinum toxin type A and type B.
- Characterize the new and emerging evidence supporting or refuting the use of botulinum toxin for at least two other indications, such as autonomic disorders and pain, movement disorders, and spasticity.
- Identify at least three issues affecting the FDA’s governance, clinical monitoring, and interchangeability of biosimilar products.
CONTINUING EDUCATION ACCREDITATION

The American Society of Health-System Pharmacists is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This program provides 2 hours (0.2 CEUs) of continuing education credit (program number 204-000-08-473-H01P).

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This is an online activity consisting of audio for three presentations, a post-test, and an activity evaluation tool. Participants must listen to all presentations, take the activity post-test, and complete the course evaluation to receive continuing education credit. A minimum score of 70% is required on the test for credit to be awarded, and participants may print their official statements of continuing education credit immediately. The estimated time to complete this activity is two hours. This activity is provided free of charge.
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4. Click on the radio button next to the correct answer for each question. Once you are satisfied with your selections, click “Grade Test” to process your test and complete the remaining steps to complete the program evaluation and print your CE statement.

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Botulinum Toxin: Update on Emerging Therapeutic Uses and Potential Safety Considerations

Evelyn Hermes DeSantis, Pharm.D., BCPS
Clinical Associate Professor
Ernest Mario School of Pharmacy
Rutgers University
Director, Drug Information Center
Robert Wood Johnson University Hospital
Piscataway, New Jersey

Evelyn Hermes DeSantis is Clinical Associate Professor at the Ernest Mario School of Pharmacy at Rutgers, the State University of New Jersey and also is the Director of Drug Information Services at Robert Wood Johnson University Hospital. Dr. Hermes DeSantis received her undergraduate and graduate degrees from Rutgers University. After completing a specialized residency in drug information practice at the Medical College of Virginia Hospital in Richmond, Virginia, she practiced at the Drug Information Center at the University of Utah Hospital in Salt Lake City, Utah. Dr. Hermes DeSantis returned to the east coast in 1995 to assume a faculty position at Rutgers. She is also a board-certified pharmacotherapy specialist.

Dr. Hermes DeSantis has published numerous articles and a book chapter, and lectures in a variety of areas including: gastrointestinal disorders, glaucoma, drug-induced diseases and medication errors, dietary supplements, and patient counseling. In addition to these areas, her research focuses in the area of provision of drug information services and the relationship between hospital and industrial pharmacy practice.
Pharmacology of Botulinum Toxin and Characteristics of Available Products

Evelyn R. Hermes DeSantis, Pharm.D., BCPS
Clinical Associate Professor
Ernest Mario School of Pharmacy
Rutgers, The State University of New Jersey

Overview

Timeline of development
*Clostridium botulinum*
Mechanism of action
Product differences

Botulinum Toxin Timeline

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
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</thead>
<tbody>
<tr>
<td>1700-1800s</td>
<td>C. botulinum</td>
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<tr>
<td>1968</td>
<td>BoNT/A (BOTOX® Cosmetic) Allergan</td>
</tr>
<tr>
<td>1989</td>
<td>BoNT/A (DYSPORT®) Ipsen Solstice Neurosciences</td>
</tr>
<tr>
<td>1991</td>
<td>BoNT/B (MYOBLOC®) Merz</td>
</tr>
<tr>
<td>2000</td>
<td>BoNT/A (XEOMIN®) Merz</td>
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</tbody>
</table>

BoNT/A (BOTOX®) Allergan
BoNT/A (BOTOX® Cosmetic) Allergan
BoNT/B (MYOBLOC®) Ipsen Solstice Neurosciences
BoNT/A (XEOMIN®) Merz
History – Sausage Poisoning

• Justinus Kerner – suspected biological poisoning
• 1817 first report of botulism poisoning
• Proposed use of toxin for therapeutic uses

Clostridium botulinum

• A gram (+) anaerobic rod bacteria
• Typically found in water and soil
• Produces seven serologically distinct neurotoxins
  – A, B, C1, D, E, F, and G
• Botulinum neurotoxin is the most potent toxin known

Botulinum Toxin (BoNT)

• Macromolecular complexes
• BoNT A - first utilized clinically
• BoNT A and B - commercially available
• Toxin range from 300 kDa – 900 kDa
  – Exotoxin molecule 150 kDa
  – Non-toxin proteins
• Produce temporary chemical denervation and relaxation of striated muscle
• Each toxin’s molecular structure and intracellular target differs, resulting in the toxins’ dissimilar pharmacological properties and effects
**Clostridia** produce different size progenitor toxin complexes

![Diagram showing different sizes of toxin complexes for A, B, and E strains of Clostridia.]

Example: 900 kD Complex (Type A)

**Botulinum Toxin**

*Structural complex*

- Seven serotypes
  - A, B, C1, D, E, F, G
- Neurotoxin Complex
  - Di-chain 150kD neurotoxin component
  - Di-sulfide bond
  - Zn+ (metalloprotease)
  - +/- non-hemagglutinin (NTNH) protein

Example: 900 kD Complex (Type A)

**Botulinum Neurotoxin Serotypes**

- Neurotoxin Complex
- Neurotoxin

![Diagram illustrating the structure of neurotoxin serotypes with heavy and light chains.]

- COOH
- NH₂
- Light Chain
- Heavy Chain
- NICKED
- COOH
Neurotoxin Structural Homology

| Type A | Type B |

Efficacy and Safety Due To Specificity and Selectivity

- **Injection Specificity**
  - Low required dose
  - Focal delivery of therapeutic action
- **BoNT Selectivity**
  - Local neuronal uptake
  - Discrete mechanism of action
- **Extensive Clinical Literature**
  - Supports safe and effective use of botulinum toxin
  - Number and rigor of citations differs by brand of botulinum toxin
  - BoNT/A (BOTOX®) is the most frequently referenced product

Normal Neuromuscular Function

- **Normal Neurotransmitter Release**
  - Synaptic vesicle fusion
  - Acetylcholine release
  - Muscle cell contraction

- **Sympathetic Neurons**
  - SNP-25
  - SNAP-25
  - SNARE complex

- **Vesicle and Terminal Membranes Fuse**


Botulinum Toxin Mechanism of Action

SNARE* Protein Target Sites for Botulinum Toxin Serotypes

SNARE: Conserved Throughout the PNS

*SNARE: Soluble N-ethylmaleimide sensitive factor attachment protein receptor.
A Look at the SNARE Complex

Soluble NSF Attachment protein REceptor
Synaptobrevin (VAMP)
- On vesicle
- Anchors to membrane
SNAP25
- Within membrane
- Anchors vesicle
- BoNT-B cleaves VAMP
  - Also BoNT-D, F and G
- BoNT-A cleaves SNAP/25
  - Also BoNT-C, and E

Botulinum Neurotoxin Serotypes

- Therapeutic profiles are different
- Biochemical differences
  - Intracellular target
  - Acceptor affinities
  - Complex size
  - % nicking
  - Formulation
- Yield therapeutic differences
  - Dose
  - Efficacy
  - Duration
  - Safety

Vesicle-Mediated Exocytosis:

- Vesicle-mediated exocytosis is mediated by the SNARE complex throughout body:
  - Multiple types of neurotransmitters/neuropeptides are released from vesicles
- Cleaves SNAP-25, inhibiting exocytosis
- Inhibits Ach release
- Inhibits vesicular release of other mediators

The common link underlying toxins multiple biochemical effects
Beyond a Muscle Effect

Repetitive muscle contraction $\Rightarrow$ Abnormal posture $\Rightarrow$ Pain

- Clinical observations following botulinum toxin injections for Cervical Dystonia
  - Pain returns prior to postural symptoms
- Botulinum toxin A may have direct anti-nociceptive effect

Neurological Basis of Pain Response

Peripheral stimulation $\Rightarrow$ Release of glutamate and peptides $\Rightarrow$ Antidromic activation $\Rightarrow$ Additional activation $\Rightarrow$ CNS

Peripheral sensitization
- TRPV1 expression
- Increase afferent signals

Central sensitization

Effects on Painful Cervical Dystonia

<table>
<thead>
<tr>
<th>Biochemical</th>
<th>Neurotransmitter Inhibited</th>
<th>Clinical Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cleavage of SNAP25 blocks exocytosis</td>
<td>Ach in motor nerves</td>
<td>Reduction of neck pain</td>
</tr>
<tr>
<td>Neuropeptides (SP, CGRP, etc) in nociceptive nerves</td>
<td>Reduction of chronic pain</td>
<td></td>
</tr>
</tbody>
</table>
Spasticity: Effects Beyond the NMJ

Sensory (primary afferents)
- Ia- spindle, Ib-golgi II-joint
- Sensory signal to CNS
- Modulate muscle fiber state
- CNS modulates both
- Motor (Gamma efferent)
- Excitatory input (Ach)
- Contraction
- Agonist
- Antagonist
- Muscles

Sensory signal to CNS
- Modulate muscle fiber state
- CNS modulates both

CNS Input
- BoNT-A Induces atrophy in extrafusal/intrafusal Muscle
- Intrafusal (muscle spindle) atrophy may modify afferent discharge to the CNS

Botulinum Toxins:
**Single Target, Multiple Effects**

Highly Specific Cleavage of Target Protein (SNAP-25)

- Muscle (NMJ, Spindle)
- Autonomic (Glands)
- Sensory (Nociceptor)

Reversible blockade of acetylcholine release
- Inhibits local release of pain mediators from sensory nerves
- Changes in muscle function alters sensory input
- Decrease peripheral pain signals (peripheral sensitization)
- Inhibits local release of pain
- Mediates from sensory nerves

Muscle relaxation (posture, spasm)
- Reduction in excitability (neural, sensitization)
- Reduction in the perception of pain
Manufacturing Method Determines Molecular Size

- Type A strains produce 3 sizes of progenitor toxins
  - 300 kD (M)
  - 500 kD (L)
  - 900 kD (LL)
- Purification determines homogeneity of the formulation
- **BOTOX**
  - Crystallization
  - Homogeneous 900 kD complexes
- **DYSPORT**
  - Column chromatography
  - Heterogeneous mixture
  - Risk of contamination by enzymes, resins, and solvents

Manufacturing and Formulation Comparison

<table>
<thead>
<tr>
<th>BOTOX®</th>
<th>DYSPORT®</th>
<th>MYOBLOC®</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FIRST APPROVAL</strong></td>
<td>1989 (US)</td>
<td>1991 (EU)</td>
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<tr>
<td><strong>SEROTYPE</strong></td>
<td>A</td>
<td>A</td>
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<tr>
<td><strong>STRAIN</strong></td>
<td>Hall</td>
<td>NCTC 2916</td>
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<tr>
<td><strong>RECEPTOR/TARGET</strong></td>
<td>SV2/SNAP-25</td>
<td>SV2/SNAP-25</td>
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<tr>
<td><strong>PROCESS</strong></td>
<td>Crystallization</td>
<td>Chromatography</td>
</tr>
<tr>
<td><strong>COMPLEX SIZE UNIFORMITY</strong></td>
<td>900 kD* Homogeneous</td>
<td>&gt; 500 kD+ Heterogeneous</td>
</tr>
<tr>
<td><strong>EXCIPIENTS</strong></td>
<td>HSA</td>
<td>Sodium chloride</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>STABILIZATION SOLUBILIZATION</strong></td>
<td>Vacuum drying</td>
<td>Lyophilization</td>
</tr>
<tr>
<td>pH</td>
<td>~7</td>
<td>~7</td>
</tr>
<tr>
<td><strong>VIAJAGE (mG/IQhl)</strong></td>
<td>100</td>
<td>500</td>
</tr>
<tr>
<td><strong>PROTEIN (ng/VIAL)</strong></td>
<td>&gt;5</td>
<td>&lt;12.5</td>
</tr>
</tbody>
</table>


Non-Interchangeable

"Units of biological activity of BOTOX® cannot be compared to nor converted into units of any other botulinum toxin…"

"Units of Dysport® are specific to the preparation and are not interchangeable with other preparations of botulinum toxin."

"Units of biological activity of MYOBLOC® cannot be compared to or converted into units of any other botulinum toxin…"
Dose Conversion Assumes Bioequivalence

- Bioequivalence is usually based on standardized pharmacokinetic criteria
  - Not relevant or measurable for biological molecules

- Biosimilars
  - Biopharmaceuticals that are similar
  - May have difference in efficacy and safety

Botulinum Toxin A vs. Toxin B

There is NO generic equivalence between botulinum toxin A and botulinum toxin B

- Receptor targets
  - Botulinum toxin A – SNAP-25
  - Botulinum toxin B – VAMP

- Proteolytic activity
  - Botulinum toxin A – 4-6 months
  - Botulinum toxin B – 10 days

Botulinum Toxin A Products

- Various differences in botulinum toxin A
- Not interchangeable
- Protein exposure difference
  - May result in differences in antibody development
Protein Exposure

- Total doses per treatment cycle (units)
  - Total dose (unit) x ng/unit = ng BoNT
- Botulinum toxin A
  - Least amount of protein of any serotype
  - BOTOX (5 ng) < DYSPORT (12.5 ng)
- Important for long-term efficacy

Neutralizing Antibodies

- 10-18% patients develop antibodies
- Immune response to foreign protein
- Protein load and injection frequency determine response
- Lead to loss of efficacy
  
  Use lowest dose with longest interval between doses

Conclusions

- Botulinum toxin blocks release of neurotransmitters
- Neuromuscular and anti-nociceptive effect
- Not interchangeable
  - Botulinum toxin A and B
  - Botulinum toxin A products
SELECTED REFERENCES


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David M. Simpson, M.D.
Professor of Neurology
Director, Clinical Neurophysiology Laboratories
Director, Neuro-AIDS Program
Mount Sinai Medical Center
New York, New York

David M. Simpson, M.D., is Professor of Neurology at Mount Sinai School of Medicine in New York, New York. In addition, he is Director of the Clinical Neurophysiology Laboratories and Director of the Neuro-AIDS Program at Mount Sinai Hospital.

Dr. Simpson received his medical degree from State University of New York (SUNY) at Buffalo School of Medicine. He completed an internship in Internal Medicine at University Hospitals of Cleveland, Case Western Reserve University in Cleveland, Ohio, and a residency in neurology at Cornell University Medical Center in New York. Dr. Simpson completed a fellowship in Clinical Neurophysiology at Massachusetts General Hospital, Harvard Medical School, in Boston, Massachusetts. Dr. Simpson is a member of the American Neurological Association and the American Pain Society. He is a fellow of the American Academy of Neurology and the American Academy of Neuromuscular and Electrodiagnostic Medicine. Dr. Simpson serves on the editorial board of Clinical Journal of Pain, AIDS Patient Care, Neurology and Clinical Neurophysiology, and Current HIV/AIDS Reports, and he is an ad-hoc reviewer for Annals of Internal Medicine, Annals of Neurology, Archives of Internal Medicine, and American Journal of Medicine. An author of over 325 publications, Dr. Simpson is the principal investigator for numerous studies, including the treatment of neuropathic pain in patients with painful HIV-associated neuropathy and treatment of spasticity with botulinum toxin.
Current and Emerging Therapeutic Uses of Botulinum Toxin

David M. Simpson, M.D.
Professor of Neurology
Director, Clinical Neurophysiology Laboratories
Director, Neuro-AIDS Program
Mount Sinai Medical Center
New York, New York

Objectives

• Development of BoNT therapy
• What is standard of evidence?
• Clinical indications
• Safety issues
• Unmet challenges in BoNT practice/research

BoNT: Non-traditional Pharmaceutical Development

• Initial clinical research in ocular disorders (strabismus, facial spasm)
• Evidence ≠ experience ≠ regulatory approval ≠ reimbursement
• Spasticity
  − Numerous positive placebo-controlled studies
  − Accepted as safe and effective (AAN TTA Committee-2008)
  − Insurers reimburse (USA)
  − Lack of US FDA-approval
• Headache
  − BoNT for facial wrinkles ↓ HA (Binder 2000)
  − Numerous open label studies positive
  − Conflicting results in placebo-controlled studies negative
• Many uses driven by clinicians and serendipity
• Skepticism among academicians/regulators/payors
Clinical Applications of Botulinum Toxin
"If it moves, BoNT can stop it"

<table>
<thead>
<tr>
<th>Focal Dystonia</th>
<th>Other Inappropriate Contractions</th>
</tr>
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<tbody>
<tr>
<td>Blepharospasm*</td>
<td>Strabismus, Nystagmus</td>
</tr>
<tr>
<td>Oromandibular-facial-lingual dystonia</td>
<td>Myokymia, Bruxism (TMJ)</td>
</tr>
<tr>
<td>Cervical dystonia (torticollis)</td>
<td>Stuttering, Painful rigidity</td>
</tr>
<tr>
<td>Laryngeal dystonia (spasmodic dysphonia)</td>
<td>Tension &amp; Migraine headaches</td>
</tr>
<tr>
<td>Task-specific dystonia (occupational cramps)</td>
<td>Neck/low back pain</td>
</tr>
<tr>
<td>Other focal dystonias (idiopathic, secondary)</td>
<td>Myofacial pain</td>
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<tr>
<td>Other Involuntary Movements</td>
<td>Radiculopathy w/ secondary muscle spasm</td>
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<tr>
<td>Voice, head, and limb tremor</td>
<td>Spasticity, Spastic bladder</td>
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<td>Palatal myoclonus</td>
<td>Oculopalatal spasm</td>
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<td>Hemifacial spasm</td>
<td>Facial hyperglobusian</td>
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<td>Tics</td>
<td>Other spastic disorders</td>
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<td></td>
<td>Other Applications</td>
</tr>
<tr>
<td></td>
<td>Protective ptosis, essential hyperhidrosis</td>
</tr>
<tr>
<td></td>
<td>Cosmetic (wrinkles, facial asymmetry)</td>
</tr>
<tr>
<td></td>
<td>Hyperhidrosis, sialoreah</td>
</tr>
<tr>
<td></td>
<td>Neuropathic pain</td>
</tr>
</tbody>
</table>

*FDA-approved

Therapeutic Considerations:
Setting Priorities

- Efficacy
- Safety and tolerability
- Ease of use
- Cost and access

What is the Standard of Proof?

- The plural of anecdote is not data
  
  *(F Lublin via R Lisak via D Purpura)*

- Randomized, double-blind, placebo-controlled trials are the worst form of evidence...
  
  except for every other form of evidence

  *(adapted from Winston Churchill)*
Challenges in Clinical Trial Design

- Definition of disease
  - Spasticity: disease or syndrome
- Inclusion and exclusion criteria
  - Confounding disorders
  - Concomitant medications i.e., analgesics
  - Representativeness of population
- Outcome measures
  - Active vs. passive function
  - “Meaningfulness” of outcome to patient
- Placebo effects
  - Wide variation (20-70%)

Evidence-Based Review of BoNT
Therapeutics and Technology Assessment Committee
American Academy of Neurology

- Review of all BoNT/clinical trials literature
- Panel of clinical and research experts
- 2-3 reviewers per indication
- Clinical trials graded 1 (unbiased RCT) – 4 (uncontrolled)
- Selection of highest quality literature and indication
- Based on the strength of the evidence:
  - Conclusions: Effectiveness (established/prob/poss/not)
  - Recommendations: Offer as Rx (should/consider/not)
  - Clinical context: Limitations of controlled trials


Evidence-Based Review of BoNT
TTA Committee of AAN
Reviewed Indications

- Spasticity: adult, pediatric
- Dystonia: Bleph, HFS, CD, laryngeal, focal limb
- Motor tics
- Essential tremor
- Hyperhidrosis
- Bladder: detrusor overactivity
- Headache: migraine, tension-type, chronic daily
- Low back pain

BoNT: Treatment of Blepharospasm

Photographs courtesy of Dr. J. Jankovic

BoNT: Potential Blepharospasm Injection Sites

- Medial and lateral aspects of upper lid
- Pretarsally, in region of orbicularis oculi muscle
- Lateral aspect of lower lid

Facial Spasm Disorders

- **Blepharospasm**
  - Probably effective (2 class II studies)
  - Should be considered (Level B)
- **Hemifacial spasm**
  - Possibly effective (1 Class II and 1 Class III study)
  - May be considered (Level C)
- **Clinical Context**
  - Suboptimal evidence
  - Large effects in early studies → minimum follow-up studies
- **Botox® FDA-approved**

Cervical Dystonia

Involuntary contractions of neck and shoulder muscles cause head and neck to twist into abnormal positions.

Botox® Dose Ranges in Phase III Cervical Dystonia Study

- Splenius capitis, 60-100 U
- Levator scapulae, 25-60 U
- Trapezius, 35-100 U
- Sternocleidomastoid, 40-70 U
- Scalen complex, 15-55 U

Range of doses indicative of individual patient differences.

Cervical Dystonia Patient Before and After BOTOX® Injection

Photographs courtesy of Dr. M. Brin.
Cervical Dystonia

- AAN TTA Review
- Established as safe and effective
  (7 class I studies)
- Should be offered (Level A)
- Botox® and Myobloc® FDA-approved for cervical dystonia


Spasticity: Upper Limb

- The Adducted/Internaly Rotated Shoulder
- The Flexed Wrist
- The Pronated Forearm
- The Clenched Fist
- The Flexed Elbow
- The Thumb-in-Palm Deformity

Spasticity: Lower Limbs

- Equinovarus
- Striatal Toe
- Extended Knee
- Flexed Knee
- Adducted Thighs
Consequences of Spasticity

Spasticity can lead to:
• Development of contractures
• Chronic, disabling pain
• A reduction in quality of life:
  – mobility
  – hygiene
  – self-care
  – sleeping patterns
  – mobility
  – hygiene
  – self-care
  – sleeping patterns
  – cosmesis
  – self-esteem
  – affect and mood
  – sexual function

Passive: Personal Care Problems

Before treatment
Long and ring fingers are clenched into palm; poor access to malodorous, macerated palm

After treatment
Greater access after chemodenervation of FDS

Active: Limb Use Problems

Upper limb
• Reach
• Grasp
• Transport
• Release
Active: Mobility Problems

- Weight borne painfully on lateral border of right foot with equinorvarus
- Weight borne on right pantigrade foot after neurolysis

Spasticity: Oral Therapy

- Baclofen, diazepam, sodium dantrolene, clonidine, tizanidine
- Limitations:
  - Nonselective
  - High dosages often required
  - Often result in intolerable side effects, especially with rapid titration

BoNT for Adult Spasticity: TTA Committee of AAN

Based on the strength of the evidence:
BoNT is established as safe and effective, and should be offered as a treatment option, in the treatment of adult spasticity in reducing muscle tone and improving passive function (Level A), and is probably effective and should be considered to improve active function (Level B).
Spastic Dynamic Equinus in CP
Boyd, Graham, 2000

Pediatric Spasticity
AAN TTA Report

- Spastic equinus
  - Established as safe and effective (4 class I studies)
  - Should be offered (Level A)

- Thigh adductor and upper extremity spasticity
  - Probably effective (1 Class I study in each)
  - Should be considered (Level B)


Ten years following positive placebo-controlled trials of BoNT in spasticity...
Why isn’t BoNT FDA-approved for this indication?
Terminology of Spasticity

- “Spasticity” too restrictive a term
- Expand terminology to encompass deficits
  - Upper motor neuron syndrome
  - Spastic dystonia
  - Disabling muscle overactivity

What is Meaningful Function?

- “In addressing the question of whether botulinum toxin can improve function, one must first define function”
- Botox currently under review at FDA for adult spasticity

Spasticity: Treatment Options

When to Use What?

- Rehabilitation
- Oral medication
- Intrathecal baclofen
- Chemodenervation
- Neurosurgery
- Orthopedic surgery
- Mix and match
  - How to control in clinical trials?
BoNT (Botox®) vs Oral Tizanidine in the Treatment of Upper Limb Spasticity: A Double-Blind, Placebo-Controlled Study

DM Simpson, JM Gracies, SA Yablon, R Barbano and A Brashear for the BoNT/Tizanidine Study Team


BoNT vs. Tizanidine in Upper Limb Spasticity Conclusions

• BoNT results in greater reduction in muscle tone than tizanidine or placebo
• BoNT has a lower AE profile than tizanidine
• Tizanidine dosing was limited by adverse effects in most patients
• BoNT resulted in improved cosmesis
• Analysis of active functional scales underway (i.e., Frenchay)
• Reconsider first line medication(s) in adult spasticity


BoNT in Migraine Headache: Early Studies

• Early open-label study
• Migraine (N=77)
• Variable dose
• Variable duration
• Outcome measure:
  – Complete response (elimination of symptoms)
  – Partial response (≥ 50% ↓ in frequency and severity)
  – No response (< 50% reduction in frequency and severity)

Botulinum Toxin Type A: Migraine Headache

BoNT in Migraine Headache: Summary
- AAN TTA: 2 Class I and 2 Class II studies
- Subjects: 2-8 episodic migraines per month
- Injection schema: all used fixed sites
- Class I\textsuperscript{1,2}: BoNT vs. placebo, no diff 1-4 mo. post-injection
- Class II\textsuperscript{3,4}: No diff in primary outcome
  - Some diff between groups on secondary outcomes
- TTA conclusion: Probably ineffective (Level B)
- Subgroup: Imploding (+) vs. exploding (-)\textsuperscript{5}


BoNTA* Studies: Injections Paradigms
Fixed-site-fixed-dose and modified follow-the-pain

*Allergan, Botox®, USA
**BoNT in Migraine Headache: AAN TTA Summary**

- AAN TTA: 2 Class I and 2 Class II studies
- Subjects: 2-8 episodic migraines per month
- Injection schema: all used fixed sites
- Class I\(^1,2\): BoNT vs. placebo, no diff 1-4 mo. post-injection
- Class II\(^3,4\): No diff in primary outcome
  - Some diff between groups on secondary outcomes
- TTA conclusion: Probably ineffective (Level B)
- Subgroup response: Imploding (+) vs. exploding (-)\(^5\)
- Recent 2 Phase 3 studies positive (press release)

---


**BoNT: Adverse Effects**

- Discomfort at injection site\(^1\)
- Transient weakness of muscles\(^1\)
  - Usually localized at injection site
  - Rare systemic weakness
  - Rare death from respiratory failure (high dose injection in CP)

---


**Botulinum Toxin Therapy Open Questions**

- Serotype and brand differences
- Immunogenicity and clinical relevance
- Ceiling dose and frequency of injection
- Safety issues (esp. CP; perception vs. reality)
- Injection technique
  - Surface anatomy, EMG, electrical stimulation
- Optimal dose, volume, dilution
- # and location of injection sites
- Patient access (cost, regulatory approval)
SELECTED REFERENCES


Richard G. Wenzel, Pharm.D.
Diamond Headache Clinic Inpatient Unit
St. Joseph's Hospital
Chicago, Illinois

Since 1999, Richard Wenzel has been the pharmacist at the Diamond Headache Clinic Inpatient Unit in Chicago, Illinois, where he is responsible for patient education, staff development, and drug information services. After completing his Bachelor of Science degree at the University of Iowa, Dr. Wenzel earned his Doctor of Pharmacy degree from the University of Illinois-Chicago.

Dr. Wenzel is recognized as an accomplished practitioner, author, and presenter in the area of headache. He has written or co-written numerous headache articles for peer-reviewed journals including *Pharmacotherapy*, *Annals of Pharmacotherapy*, *American Journal of Health-System Pharmacy*, *Journal of the American Pharmacists Association*, and *Expert Review of Neurotherapeutics*. He is also a contributing author to the textbooks *Migraine in Women* and the National Headache Foundation’s *Therapeutic Guide for Treatment of Headache*. In addition, he has delivered numerous headache-related presentations nationwide. In 2005, Dr. Wenzel was one of five pharmacists to receive the *Pharmacy Today, One-to-One Patient Counseling Award* from the American Pharmacists Association.

Dr. Wenzel is a member of the National Headache Foundation and the American Headache Society. He has faculty appointments at the University of Illinois-Chicago, Midwestern University, Drake University, and the University of Iowa Colleges of Pharmacy.
Pharmacy Considerations Related to the Use of Biosimilars in Health Systems

Richard Wenzel, Pharm.D.
Diamond Headache Clinic Inpatient Unit
St. Joseph Hospital
Adjunct Professor, Chicago College of Pharmacy
Chicago, Illinois

Brand versus Generic

Issues of brand medications versus generic medications were common approximately two decades ago.

Today, generic drugs are:
- widely prescribed
- well accepted by the public as safe and effective
- generally viewed as a clinical and economic success
- preferentially reimbursed by managed care organizations

Hatch-Waxman Act of 1984

- A genuine compromise: patent term restoration for innovators coupled with rapid approval of generic products on patent expiration.
- Main approval procedure designed for small-molecule, chemically-synthesized drugs
  - Active ingredients must be “the same”
  - No clinical trials except for bioequivalence studies in healthy subjects, based on pre-existing FDA regulations and long-established scientific principles
  - No requirement for therapeutic equivalence evaluation
FDA Bioequivalence Standards

1. Same chemical composition as determined by nuclear magnetic resonance and mass spectroscopy
2. Similar bioavailability as determined by pharmacokinetic rate and extent of absorption studies

Ease of Demonstrating “Bioequivalence”

- To date, “generic” drugs are molecularly small, chemically (and relatively easily) synthesized compounds
- Furthermore, their pharmacological action typically only targets one (perhaps a few) receptors or body sites
- Examples – famotidine, simvastatin, propranolol

Traditional Drug

- Few molecular ingredients
- Molecules are mirror images
- Can be completely described
Future of drug therapy?

• Fewer chemically synthesized, small compounds will be brought to market

http://www.phrma.org/files/Biotech%202006.pdf

The future of drug therapy is “Biopharmaceuticals”

• Medicinal agents that contains proteins derived from a biological (living) source
• In 2006, a total of 418 biopharmaceutical agents in development
• In 2006, sales of biopharmaceuticals = $40 billion
• By 2010, an estimated 50% of newly FDA approved pharmaceutical agents will be biopharmaceuticals
• In 2010, sales of biopharmaceuticals = $?


Benefits of Biotechnology

• Provides new approaches to discovery, design, and production of drugs
• Biotechnology makes possible:
  • Prevention, cure, and treatment of more diseases
  • Targeted, more effective, less toxic medicines
  • Proactive vs. reactive approach
  • Production of replacement human proteins
  • Production of “pure” drugs - (no contamination by infectious pathogens from human/animal sources)
### Development Technologies

- Recombinant DNA (rDNA) technology
  - Transgenic animal production (pig / goat milk)
  - Fusion proteins (anticytokines [Enbrel®], immunotoxins [Botox®])
  - Nucleic acid modulation
    - Antisense nucleotides (block gene expression: HIV, CMV, multiple myeloma)
  - DNA vaccines
- Monoclonal antibody production
- Gene therapy
- Enabling technology
  - High throughput technology (bacterial cell surface display screening)
  - Pegylation / ligand technology
  - Glycosylation

### Some Marketed MoAb Products

**1986—Muromonab-CD3 (OKT3)**

First marketed MoAb for acute allograft rejection

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abciximab</td>
<td>ReoPro®</td>
<td>Cardiovascular</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>Herceptin®</td>
<td>Her2Neu cancers</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Rituxan®</td>
<td>Lymphomas, NHL</td>
</tr>
<tr>
<td>Gemtuzumab</td>
<td>Mylotarg®</td>
<td>Relapsed ALL</td>
</tr>
<tr>
<td>In 111+</td>
<td>Zevalin®</td>
<td>B-NHL</td>
</tr>
<tr>
<td>Anti-CD52</td>
<td>Remicade®</td>
<td>Crohn’s, GVHD</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>Erbitux®</td>
<td>EGFR expressing cancers</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>Avastin®</td>
<td>CDS2 antigen B-CLL</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>Campath®</td>
<td>Multiple Myeloma</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>Velcade®</td>
<td>Multiple Myeloma</td>
</tr>
</tbody>
</table>

### Some Marketed rDNA Technology

<table>
<thead>
<tr>
<th>Indication</th>
<th>Brand</th>
<th>Interferons: α, β, γ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>Several</td>
<td>Several</td>
</tr>
<tr>
<td>Anemia</td>
<td>Procrit® , Epogen® , Aranesp®</td>
<td>Several</td>
</tr>
<tr>
<td>Acute MI</td>
<td>Activase®</td>
<td>Several</td>
</tr>
<tr>
<td>Febrile Neutropenia</td>
<td>Neupogen® , Neulasta® , Leukine®</td>
<td>Febrile Neutropenia</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Neumega®</td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td>Kineret®</td>
<td>Rheumatoid Arthritis</td>
</tr>
<tr>
<td>Various</td>
<td>Pipeline</td>
<td>Various</td>
</tr>
</tbody>
</table>
Gene Therapy

- Introduction of genetic material into cells of the body to manipulate genes
- Human Genome Project is essential
- Estimated 100,000 human genes
  - 3 billion amino acid pairs (Nuclear DNA)
  - 3 million amino acid pairs (Mitochondrial DNA)
  - 500 genes currently associated with a disease
  - 20,000 gene patents / 25,000 pending
- Effects/response may vary among people
- Ethical issues
- Licensing, patents, and exclusivity

“Generic” Biopharmaceuticals?

- The majority of biopharmaceuticals approved by the FDA in the late 1980s & early 1990s are now nearing their patent expiration
- Historically, patent expiration offers opportunities for generic manufacturers

Equivalence of Biotech Drugs

- New products, chemically similar to the originator, could infringe upon one or more of the originator’s patents
- New products may not be therapeutically equivalent to the originator (per FDA)
- The “real world” considers drugs in similar therapeutic category, with equivalent outcomes to be “therapeutically equivalent”
Hatch-Waxman and Biopharmaceuticals

- Hatch-Waxman is irrelevant to biopharmaceuticals
- FDA has consistently maintained that there are no "generic" biopharmaceuticals

Classification of Biologicals

- Biotech drugs are FDA classified as biologicals but may be regulated as drugs:
  - Center for Biologics Evaluation & Research or
  - Center for Drug Evaluation & Research
- Legal standards for approval different
- Federal Food, Drug, and Cosmetic Act
  - Section 505 (and 505B2)
  - New drug application (NDA)
- Public Health Service Act (PHSA)
  - Section 351
  - Biologics license application (BLA)

Terms?

- "Generic biopharmaceutical" is considered inappropriate:
  - Implies an exact copy of the original product, with the exact pharmaceutical actions
  - Currently impossible to demonstrate due to technology limitations
- “Follow-on biological” (FOB) is currently the literature’s most common term
- “Biosimilar”, “biogeneric”, “comparable biologics”
Equivalency?

- How to demonstrate equivalency of follow-on biological versions of original compounds?
- To date, little guidance from FDA, although guidance is (hopefully) forthcoming

Special FOB Issues

- Molecularly large, heterogeneous protein structures
- Manufactured in living systems, with consequent potential for variability
- Complex modes and multiple targets of action
- Small differences in starting materials and manufacturing processes can alter clinical effects
- Assays are difficult to perform and may yield ambiguous results
- Potential for rare, but serious, immunogenic effects that cannot always be detected in pre-approval testing

Production changes

- The physiologic and clinical properties of biopharmaceuticals are highly dependent upon the method of production
  - Can alter the ratio of impurities
  - Can alter the composition of production related substances
  - Most importantly, can alter overall clinical effects
Typical Protein Production Process:
Standard process but sensitive to change

1. Design the gene sequence
2. Put gene sequence inside vector
3. Put vector inside a specific kind of cell
4. Fermentation – cells produce the protein defined by the vector
5. Purification: removing all the impurities

Typical Protein Production Process:
Standard process but sensitive to change

- Highly complex protein with 3 or 4 levels of structure

Purification:
removing all the impurities

Typical Protein Production Process:
Standard process but sensitive to change

European Union guidelines

- EU has addressed the biosimilar issue to a greater extent than the FDA
- FDA will likely use EU methods as a model to develop guidelines for the USA

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EU highlights

"… the company will have to demonstrate or justify that the 'new' and 'original/reference' products have similar profiles in terms of Quality, Safety, and Efficacy."

"…these data will have to be judged on a case by case basis."

* Immunogenicity must always be addressed by clinical data, unless clinically relevant immunogenicity can be excluded by other means ….. The issue of immunogenicity must always be considered when a claim of comparability is made, especially when repeated administration is proposed.*


Key Elements of Current EU System

- Includes 10 to 11 years of protection against follow-on products

- Basic provisions took effect in 2003
  - Govern “similar biological medicinal products” (“biosimilars”)
  - Generic applications ordinarily deemed insufficient

Key Elements of Current EU System

- Includes combination of primary and secondary legislation and guidance
  - Participation by expert committees, national authorities, scientific community, and industry
  - Detailed, product-specific requirements established
  - Preclinical and clinical testing required for all products
  - Special attention to immunogenicity and post-market testing and surveillance
  - Biosimilars are not regarded as “generics” of reference products
Basic Political Facts

- A FOBs pathway will provide important financial savings to patients, although not as much as estimated by some proponents.
- Creating a FOBs pathway is an important public health goal—legislation in the near future seems assured, probably after 2008.
- Legislation needs to balance public health protection, consumer welfare and cost savings, and incentives to innovation.

Why Do Biologics Have Risk of Immunogenicity?

- Biologics are manufactured in living cells:
  - Hamster cells, rabbit cells, bacteria (E. coli), etc.
- Proteins bypass many of the body’s natural defenses (injected into veins, or under skin).
- The body is good at detecting foreign proteins and attacking them, developing neutralizing antibodies.
- The more similar a therapeutic protein is to the human protein, the less the chance there is of immunogenicity.
- There are scientific tools for detecting immunogenicity but they are, in some cases, undeveloped:
  - In many cases, clinical data (switching studies) will be required.

Potential Impact of Immunogenicity

- Due to the comparatively short time periods of clinical trials (a few months, perhaps a couple of years), differences in immunogenicity rates may not be fully apparent at this time.
- Continued monitoring of immunogenicity issues within clinical settings will be essential in the future.
- Ultimately, a favorable immunogenicity profile may distinguish one product from another.
“Safety-Related Regulatory Actions for Biologicals Approved in the United States and the European Union”

“The nature of safety problems identified after approval for biologicals is often related to the immunomodulatory effect (infections)……close monitoring is recommended.”


Immunogenicity = opportunity for pharmacists

- Continuum of care
- Compilation of databases
- Analysis of data
- Patient education
- Dosing guidelines
- Formulary issues
- Others?

Pharmacy Considerations

- Proteins degrade when given orally
- Usually parenteral (liquid or lyophilized)
- Frequently unpreserved due to potential degradation by preservatives
- Fairly unstable
  - Sensitive to temperature “extremes”
  - Requires refrigeration, avoid freezing
  - Avoid vigorous agitation
- May need to store/handle as “hazardous material” (viral vectors)
Pharmacy Considerations

- Specific diluents (preservative free)
- Specific IV infusion solutions
- IV infusion containers may become an issue (polyvinyl chloride, glass, or plastic)
- IV preparation safety issues / environment (hazardous materials?)
- Special “training” for drug preparation?
- Unique reconstitution techniques

Pharmacy Considerations

- Drug compatibility data is limited
- Special infusion pumps
- Filtration may be a problem
- Patient teaching for self-administration
- Monitoring patients for hypersensitivity reactions during administration is essential

_Clostridium botulinum_

- Produces seven serologically distinct neurotoxins
  - A, B, C1, D, E, F, and G
- All toxins produce temporary chemical denervation and relaxation of striated muscle
- Toxin A was the first used clinically and for which the most clinical experience exists

Botulinum Toxin Type A Products

- Botox® consider the “brand” or originator product
- Dysport® meets “follow-on biologic” definition, thus calling Dysport® “generic” is inappropriate
- Dysport® undergoing FDA new drug approval process (currently approved in Europe)
  - Added time and expense compared with traditional “generic” approval process
  - Creates additional cost issues once FDA approved

Evaluating Biosimilars

- Interested parties will need to address the relative merits of different biosimilars
  
  *How to do this?*
  
  - One economical method is to compare the products based on their Summary of Product Characteristics (SmPC)

Comparing Two Botulinum Toxin Type A Formulations Using Manufacturers’ Product Summaries

Objective of Study

- To examine the similarities and differences between two botulinum toxin type A products based upon their worldwide Summary of Product Characteristics (SmPC) information
  - Botox®
  - Dysport®

Physical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Dysport®</th>
<th>Botox®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complex molecular weight (kDa)</td>
<td>500-900</td>
<td>900</td>
</tr>
<tr>
<td>Units/package</td>
<td>500</td>
<td>100</td>
</tr>
<tr>
<td>Neurotoxin protein content (ng/vial)</td>
<td>12.5</td>
<td>~5</td>
</tr>
<tr>
<td>Formulation</td>
<td>Lyophilized</td>
<td>Vacuum dried</td>
</tr>
<tr>
<td>pH</td>
<td>~7</td>
<td>~7</td>
</tr>
<tr>
<td>Excipients</td>
<td>Human albumin with lactose</td>
<td>Human albumin with 0.9% NaCl</td>
</tr>
</tbody>
</table>

Units Not Interchangeable

- The majority of SmPCs for both products clearly state that units of biologic activity are unique to each botulinum neurotoxin preparation and cannot be compared to nor converted into units of another
“...Units of biological activity of Botox® cannot be compared to nor converted into units of any other botulinum toxin or any toxin assessed with any other specific assay method.”

Prescribing Information for Botox® 2006

Product Description

<table>
<thead>
<tr>
<th>Dysport®</th>
<th>Botox®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strain of C. botulinum</td>
<td>NCTC 2916</td>
</tr>
<tr>
<td>Serotype</td>
<td>A</td>
</tr>
<tr>
<td>Isolation methods</td>
<td>Acid precipitation, column chromatography</td>
</tr>
</tbody>
</table>

Approved Indications

<table>
<thead>
<tr>
<th>Common approvals</th>
<th>Approvals unique to Botox®</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Blepharospasm</em></td>
<td><em>Palate myoclonia</em></td>
</tr>
<tr>
<td><em>Hemifacial spasm</em></td>
<td><em>Bruxism</em></td>
</tr>
<tr>
<td><em>Torticollis or cervical dystonia</em></td>
<td><em>Bladder hyperactivity</em></td>
</tr>
<tr>
<td><em>Focal spasticity</em></td>
<td><em>Anal fissure</em></td>
</tr>
<tr>
<td><em>Hyperhidrosis</em></td>
<td><em>Headache</em></td>
</tr>
<tr>
<td><em>Spastic cerebral palsy</em></td>
<td><em>Dysphonia</em></td>
</tr>
</tbody>
</table>

- Botox®: all 6 approved in 18 countries
- Dysport®: all 6 approved in 2 countries
- Botox®: all 6 approved in 18 countries
- Dysport®: all 6 approved in 2 countries
**Dose Comparisons**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Dysport®</th>
<th>Botox®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blepharospasm</td>
<td>120 units/eye; reduce to 60-80 units as needed</td>
<td>12.5-20 units/eye; 100 units max</td>
</tr>
<tr>
<td>Cervical dystonia</td>
<td>500 units, 250-1000 units; 1000 units max</td>
<td>Individual dosing; 200 units max</td>
</tr>
<tr>
<td>Spasticity²</td>
<td>Arm: 75-1000 units; Leg: 1500 units¹</td>
<td>Individual dosing; 360 units max</td>
</tr>
<tr>
<td>Hyperhidrosis²</td>
<td>Doses not listed</td>
<td>50 units/axilla</td>
</tr>
<tr>
<td>Cerebral palsy²</td>
<td>20-30 units/kg initial, 1000 units max</td>
<td>4 units/kg, 200 units max (Brazil only)</td>
</tr>
</tbody>
</table>

¹Countries included: France, Italy, The Netherlands, Spain, UK, Brazil
²Dysport® not approved for these indications in all 5 countries listed
³Some countries do not specify arm and leg

**Dose-Recommendation Ratios**

<table>
<thead>
<tr>
<th>CD</th>
<th>HH</th>
<th>CP</th>
<th>BP</th>
<th>FS</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.6</td>
<td>4.0</td>
<td>5.9</td>
<td>4.8</td>
<td>3.3</td>
</tr>
</tbody>
</table>

CD=cervical dystonia, HH=hyperhidrosis, CP=cerebral palsy, BP=blepharospasm, FS=focal spasticity

**Duration and Treatment Intervals**

*Top number=duration, bottom number=treatment interval*

<table>
<thead>
<tr>
<th>Condition</th>
<th>Dysport®</th>
<th>Botox®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blepharospasm</td>
<td>8-12 weeks</td>
<td>Up to 12 weeks</td>
</tr>
<tr>
<td></td>
<td>8-12 weeks</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Cervical dystonia</td>
<td>8-12 weeks</td>
<td>12-16 weeks</td>
</tr>
<tr>
<td></td>
<td>8-12 weeks</td>
<td>&gt; 10 weeks</td>
</tr>
<tr>
<td>Spasticity</td>
<td>12 weeks</td>
<td>12-16 weeks</td>
</tr>
<tr>
<td></td>
<td>8-16 weeks</td>
<td>12-16 weeks</td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td>Up to 48-52 weeks</td>
<td>16-52 weeks</td>
</tr>
<tr>
<td></td>
<td>≥ 12 or 16 weeks</td>
<td>≥ 16 weeks</td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td>8-24 weeks</td>
<td>12-24 weeks</td>
</tr>
<tr>
<td></td>
<td>≥ 8 weeks</td>
<td></td>
</tr>
</tbody>
</table>
Adverse Events

- Majority of SmPCs indicated that adverse events with both products are mild to moderate in severity, transient, and wax and wane with therapeutic effects.
- Most SmPCs categorize adverse events by incidence ranges:
  - For example: Common is >1% but < 10%
  - Difficult to compare between products

Most Frequent Adverse Events by Overall Incidence throughout the SmPCs Analyzed

<table>
<thead>
<tr>
<th></th>
<th>Dysport®</th>
<th>Botox®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blepharospasm Ptosis</td>
<td>&gt;10%</td>
<td>11%</td>
</tr>
<tr>
<td>Cervical dystonia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysphagia</td>
<td>26-39%</td>
<td>12.2-13%</td>
</tr>
<tr>
<td>Focal pain</td>
<td>11%</td>
<td>32%</td>
</tr>
<tr>
<td>Focal weakness</td>
<td>18%</td>
<td>17%</td>
</tr>
<tr>
<td>Cerebral palsy Falls</td>
<td>7-8%</td>
<td>9.3%</td>
</tr>
<tr>
<td>Leg pain</td>
<td>8%</td>
<td>2.3%</td>
</tr>
<tr>
<td>Axillary HH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compensatory sweating</td>
<td>1-10%</td>
<td>4.5%</td>
</tr>
</tbody>
</table>

Comparison Summary

- Botox® and Dysport® are not bioequivalent, based on available data:
  - Differ in physiochemical properties, doses, duration, and adverse events
  - Administration technique?
- Dose conversion ratio has not been established
- This analysis is one method for comparing biologic products with the same active ingredient
- Additional analytical techniques are needed
Erythropoietin

- Stimulates growth and maturation of erythrocyte precursors in bone marrow
- Lack of erythrocytes contributes to anemia (renal disease, chemotherapy, others)
- Glycoprotein hormone with large carbohydrate chains
- Several different commercial isoforms, based upon glycosylation
- Isoforms influenced by cell lines of production, culture conditions, and purification procedures
- Different isoforms have different biological activity


Products Currently FDA Approved

- **Epoetin alfa**: Epogen®, Procrit®
  - Differ in regard to manufacturing process, resulting in subtle molecular changes but retaining the basic 165 amino acid-protein sequence and carbohydrate chains, as well as "closely" identical pharmacology and pharmacokinetics
- **Darbepoetin alfa**: Aranesp®
  - Two additional glycosylation chains, providing longer plasma half-life and once-weekly or bi-weekly dosing


<table>
<thead>
<tr>
<th>Epoetin Alfa</th>
<th>Darbepoetin Alfa</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA-approved indications</td>
<td>CIA, HIV/AIDS, renal, surgery</td>
</tr>
<tr>
<td>FDA-approved dose</td>
<td>CIA, renal</td>
</tr>
<tr>
<td>150 units/kg three times weekly</td>
<td>2.25 mcg/kg weekly</td>
</tr>
<tr>
<td>weekly (10,000 units)</td>
<td></td>
</tr>
<tr>
<td>Alternating dosing</td>
<td>40,000 units weekly</td>
</tr>
<tr>
<td></td>
<td>200 mcg every 2 weeks</td>
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<tr>
<td>FDA-approved dose adjustment for nonresponse</td>
<td>300 units/kg three times weekly (for oncology)</td>
</tr>
<tr>
<td></td>
<td>4.5 mcg/kg weekly (for oncology)</td>
</tr>
<tr>
<td>Alternating dose adjustment for nonresponse</td>
<td>60,000 units/kg weekly</td>
</tr>
<tr>
<td></td>
<td>300 mcg every 2 weeks</td>
</tr>
<tr>
<td>Compendia-approved and Medicare-reimbursable indications</td>
<td>CIA, ACC, HIV/AIDS, surgery, MM, MDS, renal</td>
</tr>
</tbody>
</table>

Availability

- 10,000 and 20,000 units/mL single-dose vials; 200, 3000, 4000, 10,000, and 40,000 units/mL single-use vials
- 25, 40, 60, 100, 150, 200, 300, and 500 mcg single-dose vials and prefilled syringes

CIA = chemotherapy-induced anemia, ACC = anemia of cancer, MM = multiple myeloma, MDS = myelodysplastic syndrome
Patent Protection

- Key patents for epoetin alfa expire in 2013
- At least eight biosimilar erythropoietic agents are marketed or in development in countries outside of the United States
- Additional products are likely to seek FDA approval by 2013

Multiple Efficacy Measures

- Timely Hb increase
- Maintenance of target Hb
- Hematopoietic response
- Increased Hb levels over baseline
- Reduction of transfusion frequency
- Combinations

*Which will the FDA require for equivalency?*
"[the manufacturer] has indicated that it will ask the Court for a permanent injunction prohibiting sales...until the last of the infringed patents expire (which will not occur before 2017)"


Conclusion

• These two cases highlight
  – The clinical challenges of comparing and contrasting the “equivalence” of biosimilar and originator products
  – Some of the barriers toward realizing economic benefits from biosimilar agents
  – The need, as well as opportunities, for pharmacists to help resolve biosimilar issues
SELECTED REFERENCES


