Facing Depression: Can BOTOX® Give You A Lift?
Botulinum Toxin for the Treatment of Depression

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Learning Objectives

1. Describe the pathophysiology, clinical presentation, and treatment of major depressive disorder
2. Summarize the postulated mechanism of botulinum toxin in the treatment of major depressive disorder
3. Evaluate the literature regarding the use of botulinum toxin for major depressive disorder
4. Provide recommendations based on the current evidence for the use of botulinum toxin in major depressive disorder
Major Depressive Disorder (MDD)

I. Epidemiology\textsuperscript{1-3}

a. Prevalence in the United States (U.S)
   i. Annual \textasciitilde 6.6\%
   ii. Lifetime \textasciitilde 16.2\%
   iii. Patients with chronic medical illness: \textasciitilde 25\%
   iv. Prevalence in 18 to 29-year-old individuals is threefold higher than the prevalence in individuals age 60 years or older
   v. Lifetime prevalence for those aged 65 to 80 is 20.4\% in women and 9.6\% in men

b. Incidence appears to peak in the 20s

c. First-degree family members of individuals with MDD have a risk for MDD two to fourfold higher than that of the general population

II. Pathophysiology\textsuperscript{4-6}

a. Monoamine deficiency hypothesis: diminished neurotransmission of monoamines, particularly serotonin and norepinephrine

b. Hypothalamic-pituitary-cortisol system hypothesis: abnormalities in the cortisol response to stress may underlie depression

c. Dysregulation hypothesis: failure of homeostatic regulation of neurotransmitter systems

d. Cellular alterations: the number, density, and size of neurons are abnormal

e. Genetic predisposition

f. Anatomic changes

g. Polymorphism of the serotonin-transporter

III. Diagnosis\textsuperscript{2}

A. **Five (or more)** of the following symptoms have been present during the **same 2-week period**
and represent **a change from previous functioning**; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure

1. Depressed mood

2. Markedly diminished interest or pleasure

3. Significant weight loss or weight gain

4. Insomnia or hypersomnia

5. Psychomotor agitation or retardation

6. Fatigue or loss of energy

7. Feelings of worthlessness or excessive or inappropriate guilt

8. Diminished ability to think or concentrate

9. Recurrent thoughts of death (not just fear of dying)

B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning

C. The episode is not attributable to the physiological effects of a substance or to another medical condition

*Figure 1: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) of MDD*
IV. Treatment

a. Goals of Treatment
i. Should focus on alleviating functional impairments and improving quality of life in addition to achieving symptom resolution and episode remission
ii. Remission: achieving a full return to the patient’s baseline level of functioning

b. Treatment Guidelines

<table>
<thead>
<tr>
<th>Table 1. Treatment Guidelines</th>
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<tbody>
<tr>
<td><strong>Level of Intervention</strong></td>
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</table>

c. Treatment Resistant Depression<sup>9,10</sup>

i. At least two adequate trials of recommended therapy from different pharmacological classes fail to produce a significant clinical improvement

ii. APA and NICE guidelines recommend:
   1. Electroconvulsive therapy (ECT)
   2. Monoamine Oxidase Inhibitors (MAOIs)

iii. STAR*D trial suggests that patients with persistent depression can significantly improve after trying several treatment strategies, but the likelihood of sustained remission diminishes as additional treatment strategies are needed

d. STAR*D (Sequenced Treatment Alternatives to Relieve Depression) study<sup>10</sup> (Appendix A)

i. A seven-year randomized controlled trial

ii. Evaluated medication switching and augmentation in 3,671 patients with depression

iii. After the first level of treatment approximately 30% of patients achieved remission (two-thirds did not achieve remission) and 50% of patients experienced improvement in symptoms

iv. After two treatment steps, over 50% of patients will achieve remission if they stay in treatment, thereafter, the chances of subsequent remission are much lower

v. Poorer longer-term outcomes were found with participants who required more treatment steps
V. Clinical Rating Scales⁵ (Appendix B)
   a. Hamilton Depression Rating Scale (HAM-D)
   b. Montgomery-Åsberg Depression Rating Scale (MADRS)
   c. Beck Depression Inventory (BDI)
   d. Clinical Global Impression (CGI) Scale
   e. Quick Inventory of Depressive Symptoms (QIDS)
   f. Patient Health Questionnaire (PHQ-9)

VI. Initial use of Botulinum Toxin for the treatment of MDD¹² (Appendix C)
   a. Dr. Eric Finzi, a dermosurgeon, found that some of his patients who were not seeking cosmetic improvement showed a dramatic decrease in depression symptoms
   b. In 2006, Finzi and Wasserman conducted an open study of botulinum toxin A injected into the glabellar frown muscles of ten depressed patients
      i. Nine of the ten patients experienced a resolution of their depression symptoms
      ii. First study to suggest that the enhancement of facial expressions with botulinum toxin A may reduce depression symptoms

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Botulinum Toxin

I. History¹³-¹⁵
   a. Botulinum toxin is a neurotoxin produced by *Clostridium botulinum* and other related *Clostridium* species
   b. The bacterium produces seven serologically distinct toxins that are potent neuroparalytic agents, possess similar molecular weights and have a common subunit structure
      i. Type A, B, C, D, E, F, and G
      1. Different intracellular targets
      2. Different duration of effect
   ii. Botulinum toxin type A has been successfully used in worldwide clinical trials for over a decade for the treatment of abnormal muscle contractions

II. Mechanism of Action¹⁵,¹⁶
   a. Exerts paralytic effects at the neuromuscular junction by inhibiting the release of acetylcholine
   b. Three steps involved in toxin mediated paralysis
      i. Internalization
      ii. Disulfide reduction and translocation
      iii. Inhibition of neurotransmitter release
   c. Multiple steps take place after injection of botulinum toxin into the muscle
      i. The neurotoxin is taken up by the adjacent nerve terminal
      ii. Within the terminal, the neurotoxin prevents proper binding of the synaptic vesicle containing acetylcholine
      iii. The neurotoxin accomplishes this by cleaving SNAP-25, a protein that is integral for docking of the vesicle to the nerve ending
      iv. Neurotransmitter release into the synaptic cleft is inhibited and muscle contraction cannot occur
Figure 2. Mechanism of Action of Botulinum Toxin A

III. Botulinum Toxin Product Information

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Botulinum Toxin Type</th>
<th>Trade Name</th>
<th>Labeled Indications</th>
<th>Dosage Forms and Strengths Available</th>
<th>Route of Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>AbobotulinumtoxinA</td>
<td>Type A</td>
<td>Dysport®</td>
<td>Cervical dystonia; glabellar lines (moderate to severe)</td>
<td>Injection, powder for solution: 300 and 500 units</td>
<td>IM</td>
</tr>
<tr>
<td>IncobotulinumtoxinA</td>
<td>Type A</td>
<td>Xeomin®</td>
<td>Blepharospasm, cervical dystonia, glabellar lines (moderate to severe) Additional uses: Hypertonicity disorders of the seventh nerve; poststroke spasticity of upper limb(s)</td>
<td>Injection, powder for solution: 50 and 100 units</td>
<td>IM</td>
</tr>
<tr>
<td>OnabotulinumtoxinA</td>
<td>Type A</td>
<td>BOTOX®, BOTOX® Cosmetic</td>
<td>Botox®: Axillary hyperhidrosis (severe); blepharospasm associated with dystonia; cervical dystonia; migraine (chronic) prophylaxis; overactive bladder; strabismus; upper limb spasticity (severe); urinary incontinence Botox Cosmetic®: Glabellar and lateral canthal lines (moderate to severe) Additional uses: Equinus foot deformity in pediatric cerebral palsy patients; forehead lines in adults</td>
<td>Injection, powder for solution: Botox: 100 and 200 units Botox Cosmetic: 50 and 100 units</td>
<td>IM, intradermal, intradetrusor</td>
</tr>
</tbody>
</table>
Table 3. Botulinum Toxin A Products\textsuperscript{12-24}

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Dosing</th>
<th>Pharmacodynamics/Pharmacokinetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>AbobotulinumtoxinA</td>
<td>Glabellar lines: Adults &lt;65 years: IM: Inject 10 units (0.05 mL or 0.08 mL) into each of 5 sites (2 injections in each corrugator muscle and 1 injection in the procerus muscle) for a total dose of 50 units; do not administer at intervals &lt;3 months</td>
<td>Onset of action: Peak effects: Cervical dystonia: 2-4 weeks Duration: Cervical dystonia: Up to 4 months Absorption: Not expected to be present in peripheral blood at recommended doses following intramuscular (IM) injection</td>
</tr>
<tr>
<td>IncobotulinumtoxinA</td>
<td>Glabellar lines: IM: Inject 4 units into each of the 5 sites (2 injections in each corrugator muscle and 1 injection in the procerus muscle) for a total dose of 20 units per treatment session. Administer no more frequently than every 3 months</td>
<td>Onset of action: ~4-7 days Duration: ~3-4 months Absorption: Not expected to be present in peripheral blood at recommended doses following IM injection</td>
</tr>
<tr>
<td>OnabotulinumtoxinA</td>
<td>Glabellar lines: IM: Inject 0.1 mL (4 units) dose into each of five sites, two in each corrugator muscle and one in the procerus muscle for a total dose 0.5 mL (20 units) administered no more frequently than every 3-4 months</td>
<td>Onset of action (improvement): Reduction of glabellar lines (Botox Cosmetic): 1-2 days, increasing in intensity during first week Duration: Reduction of glabellar lines (Botox Cosmetic): ~3-4 months Absorption: Not expected to be present in peripheral blood at recommended doses following intramuscular (IM) injection</td>
</tr>
</tbody>
</table>

IV. Safety\textsuperscript{16,18-20,25}

Table 4. Safety and Complications

<table>
<thead>
<tr>
<th>Most Common Side Effects\textsuperscript{16}</th>
<th>Complications and Precautions\textsuperscript{18-20}</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Pain</td>
<td>• Potency units are not interchangeable with other preparations of botulin toxin products</td>
</tr>
<tr>
<td>• Swelling</td>
<td>• Spread of toxin effects</td>
</tr>
<tr>
<td>• Erythema</td>
<td>• Respiratory, speech or swallowing difficulties</td>
</tr>
<tr>
<td>• Ecchymosis</td>
<td>• Concomitant neuromuscular disorder may exacerbate clinical effects of treatment</td>
</tr>
<tr>
<td>• Respiratory infection</td>
<td>• Use with caution in patients with compromised respiratory function</td>
</tr>
<tr>
<td>• Headache</td>
<td>• Corneal exposure and ulceration</td>
</tr>
<tr>
<td>• Nasopharyngitis</td>
<td>• Retrobulbar hemorrhages and compromised retinal circulation</td>
</tr>
<tr>
<td>• Sinusitis</td>
<td>• Bronchitis and upper respiratory tract infections in patients treated for upper limb spasticity</td>
</tr>
<tr>
<td>• Flu-like symptoms</td>
<td>• Potency units are not interchangeable with other preparations of botulin toxin products</td>
</tr>
<tr>
<td>• Nausea</td>
<td>• Spread of toxin effects</td>
</tr>
<tr>
<td>• Limited hypesthesia</td>
<td>• Respiratory, speech or swallowing difficulties</td>
</tr>
<tr>
<td>• Potency units are not interchangeable with other preparations of botulin toxin products</td>
<td></td>
</tr>
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<td>• Potency units are not interchangeable with other preparations of botulin toxin products</td>
</tr>
</tbody>
</table>

In 2009 the FDA revised prescribing information for all FDA licensed Botulinum Toxin Products\textsuperscript{25}

- A Boxed Warning was added to all botulinum toxin products
  - Highlighting the possibility of potentially life-threatening distant spread of toxin effects after local injection
  - A Risk Evaluation and Mitigation Strategy (REMS) was added to include a Medication Guide for patients containing information about the risks associated with botulinum toxin products
V. Facial Feedback Hypothesis
   a. In 1884, William James and Carl Lange postulated that vasomotor reactions have a substantial impact on emotions
   b. Charles Darwin noted “even the simulation of an emotion tends to arouse it in our minds”
   c. Suggests that muscular manipulations, which result in more positive facial expressions may lead to more positive emotional states in affected individuals

![Figure 3. Facial Feedback Hypothesis](image)

VI. Potential Benefit of Botulinum Toxin in Depression
   a. Injection of botulinum toxin to the corrugator supercilii and the procerus, which are responsible for brow furrowing (glabellar frown lines), leads to relaxation of these muscles, reducing the ability to frown
   b. The face appears more happy and less sad; this more positive facial expression leads to internal emotional experience of happiness in the affected individual
   c. Happy expression elicits happier expressions from bystanders, thus further reinforcing the happy expression and happy emotional state

![Figure 4. Procerus and Corrugator Muscles](image)
VII. Clinical Rating Scale

a. The four-point Clinical Severity Score for Glabellar Frown Lines (CSS-GFL)

b. Most frequent scoring system used to assess folds at rest and/or during maximum frowning: 0, no facial wrinkles; 1, mild facial wrinkles; 2, moderate facial wrinkles; and 3, severe facial wrinkling

Figure 5. CSS-GFL: (A) score 0; (B) score 1; (C) score 2; (D) score 3

Cost Considerations

I. The Cost of Treating Depression

a. Economic burden of depression in year 2000 was $87 billion with $26 billion associated with the cost of treatment

b. The CDC reports 118 million out of 2.4 billion drugs prescribed in the U.S. in 2005 were antidepressants

II. Comparing Antidepressants and Botulinum Toxin: Preliminary Cost Effectiveness Analysis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>One-Month Supply</th>
<th>Three-Month Supply</th>
<th>Annual Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wellbutrin SR® 100mg (bupropion)</td>
<td>100mg</td>
<td>206.88</td>
<td>620.04</td>
<td>2480.16</td>
</tr>
<tr>
<td>Paxil CR® (paroxetine)</td>
<td>25mg</td>
<td>112.34</td>
<td>337.02</td>
<td>1348.08</td>
</tr>
<tr>
<td>Zoloft® 50mg (sertraline)</td>
<td>50mg</td>
<td>375.81</td>
<td>375.81</td>
<td>1503.24</td>
</tr>
<tr>
<td>Fluoxetine 20mg</td>
<td>20mg</td>
<td>23.99</td>
<td>71.97</td>
<td>287.88</td>
</tr>
</tbody>
</table>

Table 6. Cost (USD) of Botox and Dysport in One practice (Beer K. J Drugs Dermatol.)

<table>
<thead>
<tr>
<th>Botox® or Dysport® 25 u, one area</th>
<th>Botox or Dysport 3x year</th>
<th>Botox or Dysport 4x year</th>
<th>Botox or Dysport One year</th>
</tr>
</thead>
<tbody>
<tr>
<td>400</td>
<td>1200</td>
<td>1600</td>
<td>1200-1600</td>
</tr>
</tbody>
</table>
III. Limitations\textsuperscript{31}
   a. Article compares brand name antidepressants, most of which are available as a cheaper generic product
   b. Not all botulinum toxin cost considerations are accounted for
      i. Physician’s fee
      ii. Physician’s facility cost
      iii. Health insurance generally does not cover use of botulinum toxin products

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### Clinical Question and Literature Evaluation

**I. Clinical Question:** Is botulinum toxin an effective treatment option for MDD?

**II. Literature Evaluation**

a. 2012 - Wollmer et al: a randomized, double-blind, placebo controlled trial\textsuperscript{32}  
b. 2014 - Finzi et al: a randomized, double-blind, placebo controlled trial\textsuperscript{33}  
c. 2014 - Magid et al: a randomized, double-blind, placebo-controlled study\textsuperscript{34}

#### Table 7. Wollmer MA, De boer C, Kalak N, et al. Facing depression with botulinum toxin: a randomized controlled trial\textsuperscript{32}

<table>
<thead>
<tr>
<th>Purpose</th>
<th>To explore if attenuation of facial psychomotor features, associated with depression, may produce alleviation in affective symptoms</th>
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<tbody>
<tr>
<td>Design</td>
<td>Randomized, double-blind, placebo-controlled trial</td>
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**Patient Population**

- **Inclusion Criteria**
  - Age 25-65 years, on-going MDD
  - Diagnosed according to the Structured Clinical Interview for Axis I DSM-IV disorders (SCID I; >15 points on the 17 item Hamilton Depression Rating Scale (HAM-D-17) at screening) with or without a history of dysthyemic disorder (DSM-IV)
  - Moderate to severe vertical glabellar line during maximum voluntary frowning according to a four-point clinical severity score
  - Qualitatively and quantitatively stable treatment with one or at most two antidepressants for at least four weeks

- **Exclusion Criteria**
  - Psychotic symptoms, suicidal tendency, clinical severity requiring immediate intervention
  - DSM-IV axis I diagnoses, clinically manifest personality disorder, severe premenstrual syndrome or premenstrual dysphoric syndrome, regular occurrence of migraine or other forms of cephalalgia, psychological strain associated with glabellar frown lines
  - Contraindications of botulinum toxin treatment, previous treatment with botulinum toxin, further psychopharmacological treatment other than a demand medication with limited amounts of sedatives or hypnotics
  - On-going disorder-specific psychotherapy or any other specific therapy of depression
Table 7 (continued). Wollmer MA, De boer C, Kalak N, et al. Facing depression with botulinum toxin: a randomized controlled trial.32

### Intervention
- **Botox**: onabotulinumtoxinA (OBA) was dissolved in 0.9% NaCl solution at a concentration of 100 units/2.5 ml
  - Women received 29 units
    - Seven U to the procerus muscle, 6 U bilaterally to the medial part of the corrugator muscles, and 5 units bilaterally to the lateral part of the corrugator muscles
  - Men received 39 units total (to account for greater muscle mass)
- **Placebo**: Identical volumes of 0.9% NaCl solution were administered according to the described injection scheme

### Outcomes
- **Primary**
  - A change in the HAM-D-17 score at the six week visit versus baseline
  - Clinical response measured by the HAM-D-17 score
    - Nonresponse (<25% reduction)
    - Partial response (25%-49% reduction)
    - Response (>50% reduction)
    - Remission (ham-d-17 score <7)
- **Secondary**
  - At each visit participants were also assessed using the following:
    - The validated German translation of the Structured Interview Guide for the HAM-D with Atypical Depression Supplement (SIGH-ADS)
    - BDI self-rating questionnaire
    - CGI
    - CSS-GFL
    - A standardized photograph of the face during maximum frowning
    - An inquiry regarding side effects and changes in concomitant treatment

### Methods
- Participants were randomized using a computer-generated system
- Syringes prepared for OBA or placebo injection were indistinguishable
- Participants were asked for an appraisal of their cosmetic change on a five point Likert scale

### Statistical Analyses
- Sample size of <30 participants would be sufficient to detect comparable effects with a power of >80% at a significance level of p< 0.05
- Data were analyzed using two-way analyses of variance (ANOVA)
- Where appropriate, post-hoc tests with a Bonferroni Holm adjustment were used
- To assess linear relationship between scales, Pearson’s correlation coefficients (r) were calculated
- Test results with an alpha level 0.05 are reported as significant
### Results

- **n=30**, 15 in OBA treatment arm, 15 in placebo arm
  - 12 females in OBA treatment arm and 11 females in placebo arm
  - No significant difference in any of the demographic or clinical baseline variables

- **Primary Outcome**
  - HAM-D-17 at six weeks found significant improvement in the OBA group compared to the placebo group versus baseline (p=0.002)
  - Partial response rate 86.7% vs. 26.7 (95% CI = 2.7 - 116.9, p=0.003)
  - Response rate 60.0% vs. 13.3% (95% CI = 1.6 - 59.7, p=0.02)
  - Remission rates were not significantly different

- **Secondary Outcomes**
  - OBA group: Glabellar frown lines at maximum frowning were attenuated by almost one point on the four-point CSS-GFL
    - This effect occurred at 2 weeks and remained constant
  - Placebo group: CSS-GFL remained unchanged
  - There was a significant clinical improvement in depression over time in the OBA group versus placebo group per both HAM-D-17, BDI, CGI scales (p<0.001, p=0.01, p<0.001 respectively)

### Figure 7a. Efficacy Outcomes

### Authors’ Conclusion

- This study provides new evidence that botulinum toxin injection to the glabellar region may be an effective, safe, and sustainable intervention in the treatment of depression

### Strengths

- Use of validated rating scales for depression
- Randomized, double-blind, placebo-controlled trial
- Assessed blinding quality

### Limitations

- Proportion of male participants too low to make conclusions regarding efficacy in men
- Generalizability is limited by the selection of patients with moderate to severe frown lines
- OBA was applied as an adjunctive intervention in patients with stable pharmacological therapy
### Purpose
- To determine the antidepressant effect of OBA treatment of corrugator and procerus muscles in people with MDD.

### Design
- Double blind, randomized, placebo-controlled trial.

### Patient Population
- **Inclusion Criteria**
  - Male or female outpatients aged 18-65 years, with a DSM-IV diagnosis of current MDD.
  - MADRS score 26 at screening, and a CGI-S score \( \geq 4 \) at screening.
  - Judged by the investigator to be able to comply with all requirements of the study.

- **Exclusion Criteria**
  - Axis I disorder as a principal diagnosis in the 6 months prior to screening excluding MDD.
  - History of substance abuse or dependency in the 2 months prior to screening who tested positive for illicit drugs on urine drug screen.
  - MADRS item 10 (suicidal ideas) rated \( \geq 5 \) or history of suicide attempt in the 6 months prior.
  - Considered to be at a significant risk of committing homicide, or had an unstable medical condition treated with OBA in the 12 months prior to screening.
  - Subjects were also excluded if there had been a change in their medication or psychotherapy treatment regimen in the month preceding screening, or had been refractory to three or more adequate antidepressant treatments.

### Intervention
- **OBA**
  - 29 units given to females, divided into five injections:
    - 0.07 ml (7 units) in the procerus muscle, 0.06 ml (6 units) in the medial part of the corrugator muscle, and 0.05 ml (5 units) in the middle part of the corrugator muscle.
  - 40 units given to males - as per usual clinical protocol.

- **Placebo**: 0.9%NaCl injections.

### Outcomes
- **Primary**
  - Response to treatment, as defined as a 50% or greater decrease in MADRS from baseline.

- **Secondary**
  - Remission rate, as defined by a MADRS score of 10 or lower.
  - Changes in BDI and CGI scores.

### Methods
- The study was of 6 weeks duration and patients were assessed psychiatrically at screening 3 and 6 weeks after injection with OBA or placebo.
- Syringes were prepared by a study nurse under the direction of a physician who did not have contact with the patients.
- All patients were assessed photographically at the time of injection and at the final patient visit (at rest and after maximal voluntary frowning).
- Photographs of subjects were rated blindly by two Board-certified dermatologists who did not know or treat any of the study subjects.
- All patients were assessed at three visits (screening, and 3- and 6-weeks post injection) with the MADRS and with the CGI by trained research psychiatrists.
  - Also assessed with BDI at those three visits.

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Table 8. Finzi E, Rosenthal NE. Treatment of depression with onabotulinumtoxinA: a randomized, double-blind, placebo controlled trial.\(^{33}\)
Table 8 (continued). Finzi E, Rosenthal NE. Treatment of depression with onabotulinumtoxinA: a randomized, double-blind, placebo controlled trial.33

Statistical Analyses
- Chi square statistics and Fisher exact tests were used to assess response rates, and differences in response rates were assessed with the non-parametric Mann-Whitney U test
- Time point data were analyzed using mixed model analysis of variance to assess the difference in MADRS scores between the two treatment groups over time
- Statistical significance was set at the 0.05 level (two-tailed)
- Analyzed difference in scores by means of logistic regression to assess the relationship between frown variables and MADRS response to OBA

Results
- 121 subjects were screened
  - 36 subjects were excluded
- 85 subjects randomized: 44 to placebo group and 41 to OBA
  - Eleven patients were excluded
  - 74 subjects used in the analysis, 69 had complete data
    - 33 subjects in the OBA group and 41 in the placebo group
    - 32 females in OBA arm and 37 females in placebo arm
  - OBA and placebo groups did not differ significantly in any of the demographic or clinical baseline variables
  - Fisher’s exact test did not reveal any significant differences in dropout rate between the two arms

Table 8a. MADRS scores [mean (SD)]33

<table>
<thead>
<tr>
<th>Week 0</th>
<th>Week 3</th>
<th>Week 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>OBA</td>
<td>31.6 (3.9)</td>
<td>18.9 (9.3)</td>
</tr>
<tr>
<td>Placebo</td>
<td>31.2 (3.7)</td>
<td>24.9 (7.9)</td>
</tr>
</tbody>
</table>

- Response rates at 6 weeks from the date of injection were 52% and 15% in the OBA and placebo groups, respectively (p<0.001)
- MADRS remission rates at 6 weeks were significantly higher (p<0.02) in the OBA group than in the placebo group (27% (9 of 33) versus 7% (3 of 41))
  - There was a 47.0% reduction in MADRS scores for OBA, versus a 20.6% reduction for placebo subjects (p<0.0005)
- Secondary Measures:
  - CGI data at 3 weeks showed that for the OBA subjects, 16 of 32 were much improved vs 9 of 38 placebo subjects
  - BDI at week 6 showed significant difference between the two groups (p<0.001)

Authors Conclusion
- The present study supports earlier research suggesting that OBA injected into the corrugator and procerus muscles can have antidepressant effects in people with MDD

Strengths
- Double blind, randomized, placebo-controlled trial
- Patient population was not selected for treatment resistance
- Did not require subjects to have any specific facial characteristics
- Used of validated rating scales for depression
- Assessed blinding quality

Limitations
- Proportion of male participants was too low to make conclusions regarding efficacy in men
- Short follow-up

**Purpose**
- To determine whether botulinum toxin A (BTA) can treat MDD and whether these effects last beyond the cosmetic effects (usually 12 weeks)

**Design**
- Randomized, double-blind, crossover, placebo-controlled trial

**Patient Population**
- **Inclusion Criteria**
  - Age: 18-65 years of both genders
  - Psychiatrist-diagnosed MDD according to DSM-IV criteria for at least 6 months
  - HAM-D-21 ≥ 14
  - Severity of patients’ glabellar folds during maximum voluntary frowning were rated on a scale of 0–10, those having a score ≥ 7 were included in study
  - No changes to current psychiatric medications for 60 days prior to study enrollment
- **Exclusion Criteria**
  - Active substance abuse
  - History of bipolar disorder
  - Pregnant, nursing, or trying to become pregnant during study participation
  - Three or more psychotropic medications at time of enrollment
  - Unstable medical condition
  - Previous botulinum toxin A treatment
  - Patients with significant Axis II comorbidity or other issues involved with cosmetic procedures

**Intervention**
- **BTA:** onabotulinumtoxinA injected into the glabella region in accordance with standard protocols of cosmetic botulinum toxin application
  - Female: 29 units, Male: 39 units
  - BTA-first group: BTA given at 0 weeks, BTA-second group: BTA given at 12 weeks
- **Placebo:** 0.9% NaCl solution injected into the glabella region in similar fashion to BTA

**Outcomes**
- **Primary**
  - Change in HAM-D-21 score at week 6 after injection
    - Score < 25% is nonresponse, 25-49% is partial response, ≥ 50% is response
    - Remission, as defined by HAM-D-21 score < 7
- **Secondary and Tertiary**
  - Change in BDI and PHQ-9 scores at week 6
    - Self-reported BDI score evaluated at 6 weeks (score ≤ 9 represents remission)
  - Photographs were rated by 2 physicians using both the 0–3 CSS-GFL and the 0–10 frowning severity scale

**Methods**
- Simple unrestricted randomization method
- Evaluated at weeks 0, 6, 12, 18, and 24
  - Week 12: groups crossed over
- Photographs of facial expression evaluated by same psychiatrist throughout study
### Statistical Analyses
- Calculated power=80% (n=28)
- P<0.05 or 3-point change with SD=4 in HAM-D-21 score is statistically significant
- Two-way ANOVA (cell means model and time-since-BTA model)
- Secondary outcomes measured by logistic regression

### Results
- n=30; 11 in BTA treatment arm, 19 in placebo arm
  - Majority of participants female (93%)
  - Two dropouts in the BTA second group
- No statistically significant differences in baseline characteristic
- Week 6 HAM-D-21 response rate (p< 0.0001):
  - 55% in the BTA-first group
  - 24% in the BTA-second group
  - 0% in the placebo group
  - Remission according to HAM-D-21 score nonsignificant (p = 0.09)
- Week 6 BDI response rate (p= 0.0067):
  - 45% in the BTA-first group
  - 33% in the BTA second group
  - 5% in the placebo group
- PHQ-9 scores reduction were significant regarding MDD symptoms in the BTA-first and BTA-second group vs placebo with a -34%, -30%, and -13% reduction in PHQ-9 rating scores respectively (p=0.0006)
- Improvement in HAM-D-21 scores continued over 24 weeks in BTA-first group even though cosmetic effects can disappear as early as 12-16 weeks

### Authors Conclusions
- Significant improvement in depressive symptoms occurred with a single injection of botulinum toxin A and could be a safe and sustainable intervention in treating MDD

### Strengths
- Randomized, double-blind, crossover, placebo-controlled trial
- Used of validated rating scales for depression
- Calculated power
- Patients were their own comparators

### Limitations
- Did not assess blinding quality
- Potential carryover effect from crossover
- Sample only included those with moderate to severe frown lines
- Proportion of male participants was too low
Summary and Conclusion

I. Major Depressive Disorder
   a. Depression is a common disorder in the United States, with high prevalence rates and economic burden
   b. Goals of treatment include alleviating functional impairments, improving quality of life, achieving symptom resolution and episode remission
      i. Treatment options for depression include psychotherapy, pharmacotherapy, and electroconvulsive therapy
      ii. According to STAR*D trial, a significant amount of patients will not respond to initial treatment and after two treatment options, chances of subsequent remission are much lower

II. Postulated mechanism of botulinum toxin in the treatment of major depressive disorder
   a. The facial feedback hypothesis suggests that muscular manipulations which result in more positive facial expressions may lead to more positive emotional states in affected individuals
   b. Injection of botulinum toxin to the glabellar region leads to relaxation of muscles which allows the face to appear more happy and less sad → internal emotional experience of happiness → happy expression elicits happier expressions from others, reinforcing the happy expression and happy emotional state

III. Literature Based Conclusion
   a. Although the current evidence is limited, there appears to be a growing body of evidence supporting the antidepressant effects of botulinum toxin A in the treatment of MDD
   b. Botulinum toxin A appears to be relatively safe for use in patients with MDD, more data needed
   c. The effects on mood last beyond the maximal cosmetic effects of botulinum toxin A
   d. Botulinum toxin A can potentially be an additional or alternative novel treatment option for people suffering with depression, further studies needed

IV. Recommendations
   a. Due to lack of robust studies, botulinum toxin should not be considered first line in the treatment of MDD
   b. With further evidence, there may be a potential place in therapy for botulinum toxin in those individuals who are part of a specific patient population including
      i. Females
      ii. Individuals with moderate to severe depression
      iii. Individuals with treatment resistant depression
   c. Additional studies are warranted on larger sample sizes, with improved placebo controls, and should focus on demographic/disease findings that may further determine the role of botulinum toxin in MDD
References

19. Xeomin (IncobotulinumtoxinA) [prescribing information]. Greensboro, NC: Merz Pharmaceuticals; July 2011.
Appendix A. Star*D Algorithm

<table>
<thead>
<tr>
<th>STAR*D algorithm: Treatment levels</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Level 1</strong></td>
</tr>
<tr>
<td><strong>Citalopram</strong> (Celexa)</td>
</tr>
<tr>
<td><strong>Patients could choose one of the following:</strong></td>
</tr>
<tr>
<td>SWITCH (stop citalopram, be randomized to also receive one of the following)</td>
</tr>
<tr>
<td>- Bupropion sustained-release (Wellbutrin SR)</td>
</tr>
<tr>
<td>- Venlafaxine extended-release (Effexor XR)</td>
</tr>
<tr>
<td>- Sertraline (Zoloft) Cognitive therapy*</td>
</tr>
<tr>
<td>AUGMENT (keep citalopram, be randomized to also receive one of the following)</td>
</tr>
<tr>
<td>- Bupropion sustained-release Buspirone (BuSpar) Cognitive therapy*</td>
</tr>
<tr>
<td>- Cognitive therapy*</td>
</tr>
</tbody>
</table>

| **Level 2** (only for those receiving cognitive therapy in level 2) |
| SWITCH (stop cognitive therapy, be randomized to receive one of the following) |
| - Bupropion sustained-release or |
| - Venlafaxine extended-release |
| **Patients could choose one of the following** |
| SWITCH (stop cognitive therapy, be randomized to receive one of the following) |
| - Mirtazapine (Remeron) |
| - Nortriptyline (Pamelor) |
| AUGMENT (keep current therapy, be randomized to also receive one of the following) |
| - Lithium |
| - T3 thyroid hormone (Cytomel) |

| **Level 3**                        |
| SWITCH (stop current therapy, be randomized to receive one of the following) |
| - Tranylcypromine (Parnate) |
| - Mirtazapine plus venlafaxine extended-release |
| **Patients could choose one of the following** |
| AUGMENT (keep current therapy, be randomized to also receive one of the following) |
| - Bupropion sustained-release Buspirone (BuSpar) Cognitive therapy* |
| - Cognitive therapy* |

*Patients could refuse cognitive therapy as a randomization option. All treatments were unblinded. Patients advanced to successively higher treatment levels if they failed to achieve remission with their current regimen.
<table>
<thead>
<tr>
<th>Rating Scale</th>
<th>Description/Use</th>
<th>Interpretation</th>
</tr>
</thead>
</table>
| Hamilton Depression Rating Scale (HAM-D or HDRS) | -Clinician-administered  
- 17 items: 0(absent) to 4 (very severe) or 2(definite) depending on item  
-Assesses symptom severity over the past week  
-Includes evaluation of somatic symptoms                                                                 | Scoring  
>23: very severe depression  
19-22: severe depression  
14-18: moderate depression  
8-13: mild depression  
0-7: normal  
Response: > 50% reduction in score  
Remission: score < 7 |
| Montgomery-Åsberg Depression Rating Scale (MADRS) | -Clinician-administered  
-10 items: 0(absent) to 6 (severe)  
-Assesses symptom severity with no time frame specified                                                                                           | Scoring  
35-60: severe depression  
20-34: moderate depression  
7-19: mild depression  
0-6: symptoms absent  
Response: > 50% reduction in score  
Remission: score < 8 |
| Beck Depression Inventory (BDI)                  | -Self-administered  
-21 items: 0(absent) to 3 (severe)  
-Assesses symptoms and attitudes over the previous 2 weeks                                                                                     | Scoring  
30-63: severe depression  
17-29: moderate depression  
10-16: mild depression  
0-9: no depression  
Response: > 50% reduction in score  
Remission: score < 10 |
| Clinical Global Impression (CGI) Scale           | -Clinician administered  
-CGI Severity of Illness Scale (CGI-S) and CGI Improvement Scale (CGI-I)  
-Assesses severity of illness, symptoms and symptom response  
-1-7 scale with 3 subscales                                                                                                                     | CGI-S: 0=not rated, 1=normal, 2=borderline mentally ill, 3=mildly ill, 4=moderately ill, 5=markedly ill, 6=severely ill, 7=most extremely ill |
| Quick Inventory of Depressive Symptoms (QIDS)    | Clinician-rated and self-rated (QIDS-SR)  
-16 items: 0(not present) to 3(significant impairment)  
-Assesses 9 core depressive symptoms in the past 7 days                                                                                         | Scoring  
>21: very severe depression  
16-20: severe depression  
11-15: moderate depression  
6-10: mild depression  
≤5: normal  
Response: > 50% reduction in score  
Remission: score < 5 |
| Patient Health Questionnaire (PHQ-9)             | -Self-administered  
-9 items: 0(not at all) to 3(nearly every day)  
-Assesses symptom frequency over the previous 2 weeks                                                                                         | Scoring  
20-27: severe depression  
15-29: moderately severe depression  
10-14: moderate depression  
5-9: mild depression  
1-4: minimal depression  
Response: > 50% reduction in score  
Remission: score < 5 |
Appendix C. Case Series (Finzi et al)\textsuperscript{12}

### Summary of Patient Characteristics and Response of Depression to Treatment with Botulinum Toxin A

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (Years)/Sex</th>
<th>Previous Treatments</th>
<th>Current Treatment</th>
<th>Duration of Depression (Years)</th>
<th>Pretreatment BDI-II score</th>
<th>Post-treatment BDI-II score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>62/f</td>
<td>B, P, Psy</td>
<td>B</td>
<td>11</td>
<td>27</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>37/f</td>
<td>B, P</td>
<td>-</td>
<td>5</td>
<td>30</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>36/f</td>
<td>B, F, V, Psy</td>
<td>F</td>
<td>2</td>
<td>41</td>
<td>6</td>
</tr>
<tr>
<td>5</td>
<td>47/f</td>
<td>B, D, G</td>
<td>B, D, G</td>
<td>17</td>
<td>46</td>
<td>33</td>
</tr>
<tr>
<td>6</td>
<td>63/f</td>
<td>E</td>
<td>-</td>
<td>2</td>
<td>22</td>
<td>8</td>
</tr>
<tr>
<td>7</td>
<td>38/f</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>27</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>63/f</td>
<td>B, Psy</td>
<td>B</td>
<td>10</td>
<td>21</td>
<td>4</td>
</tr>
<tr>
<td>9</td>
<td>38/f</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>31</td>
<td>2</td>
</tr>
<tr>
<td>10</td>
<td>38/f</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>32</td>
<td>14</td>
</tr>
</tbody>
</table>

*8, Bupropion, D, divalproex sodium, E, escitalopram, F, fluoxetine, G, gabapentin, P, paroxetine, Psy, psychotherapy, R, remeron, V, venlafaxine*