Botox for treating Depression: 
What you need to know

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Objectives

1. Discuss the scientific basis for the use of botulinum toxin A for the treatment of depression

2. Review the 3 major trials that have studied the treatment of depression using botulinum toxin A

3. Where do we go from here?
DISCLOSURE OF RELEVANT RELATIONSHIPS

• NARSAD Grant (National Alliance for Research on Schizophrenia and Depression)

• Married to the field: Michelle Magid, MD (Psychiatry)
  – As a result of research, she is a consultant for Allergan and Galderma pharmaceuticals

• I have a financial interest in Psych-Derm issues
The Beginning
2006: Mayo Clinic Journal Review

Treatment of Depression with Botulinum Toxin A: A Case Series

ERIC FINZI, MD, PhD,1 AND ERIKO WASSERMAN, PhD1

BACKGROUND: Major depression is a common and serious disease that may be resistant to routine pharmacologic and psychotherapeutic treatment approaches.

OBJECTIVE: To evaluate the efficacy of botulinum toxin A treatment of glabellar frown lines in treating patients with major depression, using a small open pilot trial.

METHODS: Patients who met DSM-IV criteria for ongoing major depression in spite of pharmacologic or psychotherapeutic treatment were evaluated with the Beck Depression Inventory II (BDI-II) before receiving botulinum toxin A to their glabellar frown lines. Two months later, all patients were re-evaluated clinically and with the BDI-II.

RESULTS: Ten depressed patients were treated with botulinum toxin A, and 9 of 10 patients were no longer depressed 2 months after treatment. The tenth patient had an improvement in mood.

CONCLUSION: To our knowledge, these are the first reported cases of depression treated with botulinum toxin A.

Dr. Finzi has applied for a patent using botulinum toxin A to treat depression.

Questions:

• Could this possibly be true???
• If so, why is this working?
Facial Feedback Hypothesis

Facial movement can influence emotional experience

Charles Darwin 1872

“The free expression, by outward signs, of an emotion intensifies it. On the other hand repression, as far as this is possible, of all outward signs softens our emotions…He who gives way to violent gestures will increase his rage: he who does not control the signs of fear will experience fear in a greater degree.”

Charles Darwin, 1872

What chapter of the book is this from?
A. Chapter 7: Grief and Despair
B. Chapter 8: Love and Joy
C. Chapter 10: Hatred and Anger
D. Chapter 11: Contempt and Disgust
E. Chapter 12: Surprise and Fear
The Power of Smiling

• One smile can generate the same level of brain stimulation as eating 2,000 bars of chocolate.

  in comparison: one orgasm = 2 cheeseburgers

Modern Day

How to Lift Your Mood? Try Smiling
By John Cloud Friday, Jan. 16, 2009

“Just smile, you’ll feel better!” Will you? Really?
By Dave Munger April 6, 2009

• “Fake it ‘til you make it”  • Gayle Foreman

• “Relaxing your face when you are angry will help you control your emotions”  • Marsha Linehan (DBT expert)
Why do facial expressions influence emotion perceptions?

• **Theory # 1: It’s all about environment**
  - If you smile, others will perceive you as more approachable and will be more likely to interact with you.
  - If you look angry, others will avoid you and you will internalize that you are unlikeable.
  - Positive facial expression will positively affect social interactions and therefore self esteem and mood. Negative facial expression will do the opposite.

• **Theory # 2: It’s all about biology**
  - functional MRI showed that patients treated with botulinum toxin had decreased activity in the left amygdala when mimicking angry facial expressions.
  - These findings are important, since hyperactivity in the left amygdala has been linked to anxiety, depression, PTSD, and heightened fear responses.

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References:

Does Facial Expression affect the Autonomic Nervous System?

- 12 Professional actors and 4 face scientists were shown videotapes of six emotions (surprise, disgust, sadness, anger, fear, and happiness).
- They were asked to emulate the facial expressions (i.e. just the facial movement...no emotion attached)
- Autonomic Nervous system activity was monitored

Autonomic changes from facial expressions of established emotional response WITHOUT emotion attached to it

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Ekman Levenson Autonomic nervous system activity distinguishes among emotions
Science. 221(4616):1208-10, 1983 Sep 16
How do you know this is not all an *aesthetic* mechanism of action?

25 Participants
12- Botulinum
13- Restylane, Glycolic Peels, Botulinum in other areas, laser treatments

Let’s take a quick break

LEFT SIDE

Keep your teeth together
Hold your pen in your lips
Don’t let it touch your teeth

RIGHT SIDE

Hold your pen in your teeth
Don’t let it touch your lips

“Running my own business has given me an ulcer, two heart attacks and four nervous breakdowns. I manufacture relaxation tapes.”
Rate the image:
0- lowest funniness and difficulty
9 highest funniness and difficulty

“Running my own business has given me an ulcer, two heart attacks and four nervous breakdowns. I manufacture relaxation tapes.”

LEFT HALF
Keep your teeth together
Hold your pen in your lips
Don’t let it touch your teeth

RIGHT HALF
Hold your pen in your teeth
Don’t let it touch your lips
Biological Mechanism of Action

- “The effect may be due to the relaxed facial muscles cooling the blood flowing to the brain in a manner similar to relaxation disciplines like yoga and tai chi.”
  - Stanford psychologist Robert Zajonc

- Peripheral feedback from facial movements (via trigeminal nerve) leading to reduced activity in the amygdala and brainstem


http://www.psychologytoday.com/blog/the-beauty-prescription/201001/botox-cure-depression
Ok. Lets do this.

The plan…

3 independent sites
3 independent studies
1 set of assessment criteria

Glabellar Region- made up of the frown muscles:
- Procerus
- Corrugator Superficii

http://www.uic.edu/com/eye/Botox/BotoxProcess.shtml
Self assessments and Psychiatrist Assessments with Blinding

Week 0 2 4 6

Group 1

33 Placebo

Group 2

41 Botulinum

Finzi
Group 1
15 Placebo injections

Group 2
15 Botulinum Toxin injections

Week 0 2 4 6 8 12 16

Wollmer

Week 0 3 6 12 15 18 24

Group 1
19 Placebo
19 Botulinum

Group 2
11 Botulinum
11 Placebo

Magid/ Reichenberg
<table>
<thead>
<tr>
<th>Category</th>
<th>Variable</th>
<th>Placebo (N=75)</th>
<th>Botulinum (N=59)</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td>Demographics</td>
<td>Age</td>
<td>49.35</td>
<td>49.14</td>
<td>0.90</td>
</tr>
<tr>
<td></td>
<td>Sex, % Female</td>
<td>86.67%</td>
<td>93.22%</td>
<td>0.38</td>
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<tr>
<td></td>
<td># of years with depression, mean</td>
<td>19.72</td>
<td>18.78</td>
<td>0.69</td>
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<tr>
<td></td>
<td>Duration of current episode in months, mean</td>
<td>28.91</td>
<td>19.81</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>% of patients on current antidepressants</td>
<td>64.00%</td>
<td>64.41%</td>
<td>0.96</td>
</tr>
<tr>
<td></td>
<td># of current antidepressants, mean</td>
<td>0.89</td>
<td>0.85</td>
<td>0.74</td>
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<tr>
<td></td>
<td># of previous episodes, mean</td>
<td>5.65</td>
<td>6.93</td>
<td>0.09</td>
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<tr>
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<td>% of patients with recurrent depression</td>
<td>84.00%</td>
<td>86.44%</td>
<td>0.64</td>
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<tr>
<td></td>
<td>% of patients with mild depression</td>
<td>13.33%</td>
<td>8.47%</td>
<td>0.38</td>
</tr>
<tr>
<td></td>
<td>% of patients with moderate depression</td>
<td>46.67%</td>
<td>45.76%</td>
<td>0.92</td>
</tr>
<tr>
<td></td>
<td>% of patients with severe depression</td>
<td>38.67%</td>
<td>44.07%</td>
<td>0.53</td>
</tr>
<tr>
<td>BDI</td>
<td>Baseline score, mean</td>
<td>26.28</td>
<td>28.98</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td>Week 6 score, mean</td>
<td>21.23</td>
<td>14.73</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td></td>
<td>Change in score, mean</td>
<td>5.05</td>
<td>14.25</td>
<td>&lt;.0001</td>
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<tr>
<td></td>
<td>% change in score</td>
<td>-16.19%</td>
<td>-47.38%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td></td>
<td>% patient responders</td>
<td>8.00%</td>
<td>52.54%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>HAM-D / MADRS</td>
<td>% change in score</td>
<td>-14.60%</td>
<td>-45.69%</td>
<td>&lt;.0001</td>
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<tr>
<td></td>
<td>% patient responders</td>
<td>10.67%</td>
<td>54.24%</td>
<td>0.001</td>
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<tr>
<td></td>
<td>% patient remitters</td>
<td>6.67%</td>
<td>30.51%</td>
<td>0.03</td>
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<tr>
<td>CSS-GFL</td>
<td>Baseline frown score, mean</td>
<td>2.08</td>
<td>2</td>
<td>0.589</td>
</tr>
<tr>
<td></td>
<td>Week 6 frown score, mean</td>
<td>2.20</td>
<td>0.73</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

**Meta-analysis Results:**

at 6 weeks
Results: 12 weeks

- BDI: -42% vs. -35% vs. -15%
  - Botulinum 1st: 27.5 - 16 = 11.5 point drop (42%)
  - Botulinum 2nd: 23.7 - 15.4 = 8.3 point drop (35%)
  - Placebo: 23.7 - 20.1 = 3.6 point drop (15%)

- Response: 45% vs. 33% vs. 5% (>50% reduction in BDI)
- Remission: 27% vs. 32% vs. 5% (BDI ≤ 7)

At week 24, the mean frown score (CSS-GFL) in the BTA first group was back to baseline (baseline score = 2.7; wk 24 score = 2.7), indicating that the botulinum toxin had worn off. Nonetheless, all three measurement scales showed continued reduction in depression MDD scores throughout the 24 weeks, indicating that mood continued to improve despite the BTA effects wearing off.
Is botulinum toxin safe?

- No severe adverse reactions were reported in the trials.
- Mild adverse reactions including temporary headaches and local irritation immediately after injection (p = 0.46).

Any predictors of patients who will respond?

Agitation predicts response of depression to botulinum toxin treatment in a randomized controlled trial


Table 1 Association of agitation with response

<table>
<thead>
<tr>
<th>Response</th>
<th>Agitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>HA: 5 (100%)</td>
</tr>
<tr>
<td>-</td>
<td>HA: 0 (0%)</td>
</tr>
</tbody>
</table>

Fisher's exact test p=0.04, risk ratio=2.5, 95% CI=1.17-5.34

Ham D Question 9: HA= score ≥2, LA= score ≤1

RATING BASED ON OBSERVATION DURING INTERVIEW ONLY

9. Agitation:
- 0 - None (movements within normal range)
- 1 - Fidgetiness
- 2 - Playing with hands, hair, etc.
- 3 - Moving about, can't sit still
- 4 - Hand-wringing, nail-biting, hair-pulling, biting of lips (interview impossible)
Does it work by treating wrinkles?

- Baseline wrinkle score does not correlate with baseline depression score
- Baseline wrinkle score does not predict response to BTA
- Change in wrinkle score is not correlated to change in depression score

Is botulinum better as a monotherapy or an augmentation strategy?

<table>
<thead>
<tr>
<th>Number and % of patients taking antidepressants who were responders, according to Patient Rating Scales</th>
<th>Number (%) of patient responders</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BTA (n=59)</td>
</tr>
<tr>
<td>Taking Antidepressants</td>
<td>19/38 (50%)</td>
</tr>
<tr>
<td>Not taking antidepressants</td>
<td>12/21 (57%)</td>
</tr>
</tbody>
</table>

The was no statistically significant difference in the response rates for patients using the botulinum as a monotherapy (patients on no psychotropic medication) vs. an adjunct agent (patients on 1-3 psychotropic medications), indicating that BTA was similarly effective as both a monotherapy and adjunctive therapy.
Conclusion

- There is increasing evidence that patients suffering from MDD may benefit from injections of botulinum toxin A into the frown lines.

- Psychotherapy and medication management remain the mainstay for the treatment of MDD. We await the results from the new, larger trial before this treatment can be recommended for either monotherapy or as an augmentation strategy.
Surprised?
Thank you!

Jason Reichenberg, MD
jreichenberg@seton.org

Does it work better in women than in men?

• There was no statistical difference in efficacy between men (n = 14) and women (n=120)
• Larger studies with a higher number of male participants are warranted.
Food for thought

Could we be treating something we don’t know we are treating?

COSMETIC USES OF BOTULINUM TOXIN

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age prevention</td>
<td>10-12</td>
</tr>
<tr>
<td>Chemical brow lift</td>
<td>13-18</td>
</tr>
<tr>
<td>Dermatochalasis</td>
<td>19</td>
</tr>
<tr>
<td>Enhancing effect on surface procedure²</td>
<td>20-22</td>
</tr>
<tr>
<td>Facial flushing</td>
<td>23</td>
</tr>
<tr>
<td>Hyperkinetic facial lines:</td>
<td></td>
</tr>
<tr>
<td>Bunny lines</td>
<td>24</td>
</tr>
<tr>
<td>Lateral canthal lines (crow’s feet)³</td>
<td>25</td>
</tr>
<tr>
<td>Dimpled chin</td>
<td>24, 26</td>
</tr>
<tr>
<td>Forehead</td>
<td>18</td>
</tr>
<tr>
<td>Glabella (frown line)³</td>
<td>18</td>
</tr>
<tr>
<td>Lip and perioral</td>
<td>27-29</td>
</tr>
<tr>
<td>Nasolabial fold</td>
<td>30</td>
</tr>
<tr>
<td>Neck (platysmal band)</td>
<td>31</td>
</tr>
<tr>
<td>Neferiti lift</td>
<td>32, 33</td>
</tr>
<tr>
<td>Supraciliary wrinkles</td>
<td>34, 35</td>
</tr>
<tr>
<td>Hypertrophic scars</td>
<td>36</td>
</tr>
<tr>
<td>Medical rhinoplasty</td>
<td>37</td>
</tr>
<tr>
<td>Oral commissure elevation</td>
<td>38</td>
</tr>
<tr>
<td>Rosacea</td>
<td>39</td>
</tr>
<tr>
<td>Treating of gummy smile</td>
<td>40, 41</td>
</tr>
</tbody>
</table>
COSMETIC USES OF BOTULINUM TOXIN

Reference

Age prevention 1 10-12
Chemical brow lift 13-18
Dermatochalasis 19
Enhancing effect on surface procedure 2 20-22
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Hyperkinetic facial lines:
Bunny lines 24
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Supraciliary wrinkles 34-35
Hypertrophic scars 36
Medical rhinoplasty 4 37
Oral commissure elevation 38
Rosacea 39
Treating of gummy smile 40, 41

1. Allergic Rhinitis
2. Granulosis rubra nasi
3. Frey’s Syndrome
4. Hyperhidrosis
5. Hairy–Hairy
6. Sialorrhea
7. Ophthalmic disorders
8. Duanne’s eye-retraction syndrome
9. Nystagmus
10. Oscillopsia
11. Strabismus
12. Therapeutic ptosis for corneal protection
13. Detrusor-sphincter dyssynergia
14. Overactive bladder
15. Urinary incontinence associated with neurologic conditions
16. Vaginismus
17. Other
18. Excitement algomasia
19. Excitement polyphonomy
20. Inverse pseudoptosis
21. Idiodynia
22. Pagetoidia congenital
23. Raynaud’s phenomenon

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2. Granulosis rubra nasi 86
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17. Other 105
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19. Excitement polyphonomy 107-109
20. Inverse pseudoptosis 110
21. Idiodynia 111
22. Pagetoidia congenital 112
23. Raynaud’s phenomenon 113
Food for thought

• Is this cost-effective?

| Cost (USD) of Various Common Antidepressants (Obtained From Drugstore.com) |
|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| Drug                     | Dose | One-Month Supply | Three-Month Supply | Four-Month Supply | Annual Cost |
| Wellbutrin sr 100 mg     | 100 mg | 205.88 | 620.04 | 826.72 | 2480.16 |
| Budeprion sr 100 mg      | 100 mg | 69.99 | 209.97 | 279.96 | 839.88 |
| Paxil CR (paroxetine)    | 25 mg | 113.34 | 337.03 | 449.36 | 1348.98 |
| Remeron (mirtazapine) 30 mg | 30 mg | 109.99 | 329.97 | 439.96 | 1319.88 |
| Zoloft (sertraline)      | 125.77 | 375.81 | 501.08 | 1503.24 |
| Citala (citalopram) 20 mg | 20 mg | 114.47 | 341.43 | 457.88 | 1373.64 |
| Sertralini 50 mg          | 50 mg | 14.99 | 44.97 | 59.96 | 179.88 |
| Ciprofloxa               | 20 mg | 39.99 | 114.97 | 159.96 | 478.88 |
| Prozac 20 mg             | 20 mg | 185.38 | 556.02 | 741.36 | 2234.08 |
| Fluoxetine 20 mg         | 20 mg | 23.09 | 71.97 | 95.96 | 287.88 |


Food for thought

• Can Botulinum dull your ability to understand the emotion of others?

• People read emotions partly by mimicking facial expression, so "if muscular signals from the face to the brain are dampened, you're less able to read emotions."

• 126 patients
  – Botox vs. Restylane vs. a gel that amplifies muscular signals
  – Participants viewed computer images of faces and identified the emotions they saw.

• "When the facial muscles are dampened, you get worse in emotion perception, and when the facial muscles are amplified, you get better at emotion perception."

• Users should "consider whether these procedures are having any indirect costs — reducing their ability to empathize and understand people's emotions."

Neal D. Amplifying and dampening facial feedback modulates perception accuracy Social Psych and Personality. April 2011
Food for thought

• Does Botulinum in the Glabellar region make you look neutral or does it actually make you look happier?
  • Heckman et al sought to see how faces were perceived by others after botox in glabellar region.
  • “Temporary denervation with Botox enhances facial expression with positive emotion resulting in a shift rather than a loss of facial affect.”

Food for thought

• Can Botox used in other areas have the opposite effect?

• Recent study of 24 patients treated with botulinum toxin in the crow’s feet (smile lines on the sides of the eyes) felt more depressed after treatment

• Dr Michael Lewis of the School of Psychology, Cardiff, Wales
Food for thought

• What about treating the depressor anguli oris?

• May have similarly negative effects

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td># of Patients</td>
<td>30</td>
<td>74</td>
<td>30</td>
</tr>
<tr>
<td>Sex</td>
<td>Females and Males</td>
<td>Females and Males</td>
<td>Females and Males</td>
</tr>
<tr>
<td>Age</td>
<td>25-65</td>
<td>18-65</td>
<td>18-65</td>
</tr>
<tr>
<td>Units of BTA Given</td>
<td>29 Female, 39 Male</td>
<td>29 Female, 40 Male</td>
<td>29 Female, 39 Male</td>
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<tr>
<td>Baseline CSS-GFL score*</td>
<td>2.3</td>
<td>1.7</td>
<td>2.6</td>
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<tr>
<td>Measurement Scale</td>
<td>HAM-D-17</td>
<td>BDI</td>
<td>MADRS</td>
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<tr>
<td>Mean Baseline Score</td>
<td>20.1</td>
<td>25.3</td>
<td>31.4</td>
</tr>
<tr>
<td>Botulinum Response Rate</td>
<td>60%</td>
<td>40%</td>
<td>52%</td>
</tr>
<tr>
<td>Placebo Response Rate</td>
<td>13%</td>
<td>0%</td>
<td>15%</td>
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<tr>
<td>Botulinum Percent Change in Score</td>
<td>-47%</td>
<td>-40%</td>
<td>-47%</td>
</tr>
<tr>
<td>Placebo Percent Change in Score</td>
<td>-9%</td>
<td>3%</td>
<td>-21%</td>
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<tr>
<td>Botulinum Remission Rate</td>
<td>33%</td>
<td>33%</td>
<td>27%</td>
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<tr>
<td>Placebo Remission Rate</td>
<td>13%</td>
<td>0%</td>
<td>7%</td>
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<tr>
<td>Length of trial in weeks</td>
<td>16</td>
<td>6</td>
<td>24</td>
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<tr>
<td>Medications</td>
<td>0-2</td>
<td>Not failed ≥3 trials</td>
<td>0-3</td>
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<tr>
<td>Guessed intervention correctly?</td>
<td>90% Patients</td>
<td>=50% Participants</td>
<td>N/A</td>
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<tr>
<td>Augmentation or Primary treatment?</td>
<td>Augmentation</td>
<td>Both</td>
<td>Both</td>
</tr>
</tbody>
</table>
For More Information…

- Ron Gutman TED Talks “The hidden power of smiling” 5-11-2011
- Ekman Levenson Autonomic nervous system activity distinguishes among emotions Science. 221(4616):1208-10, 1983 Sep 16
- HerrmannRot A, Dresel C, Castrop F. The link between facial feedback and neural activity within central circuitries of emotion- new insights from botulinum-toxin induced denervation of frown muscles. Cerebral Cortex (2009); 19: 537-542
- Practical Psychodermatology by Anthony Bewley, Ruth E. Taylor, Jason S. Reichenberg and Michelle Magid (Book)