GlaxoWellcome Memo

To: RSDs
DSMs
Elion Sales Force

From: Robert Padgett, Associate Manager Sales Training
Date: 3/23/00
Subject: James Pradko, MD Slide Presentation

Commercial Operations Training and Development is responding to your enthusiastic response to Dr. James Pradko's presentation, Neuroreceptor Basis of Initial Antidepressant Choice. As you will remember, Dr. Pradko provided an essential part of your Wellbutrin SR training experience by sharing his views on a primary care physician treating depressed patients. As a follow-up to his presentation, please find attached a copy of his presentation slides.

Because all anti-depressants have been shown to be comparable in efficacy for the treatment of depression, Dr. Pradko's presentation focuses on the importance of selecting an antidepressant based on its neurotransmitter effects and related side effect profile. Based on the differences between the neurotransmitter effects of different antidepressants, Dr. Pradko encourages primary care physicians to ask themselves when selecting an antidepressant: "Where do I want my patients to be after four months of treatment?"

Remember, Wellbutrin SR offers patients efficacy comparable to an SSRI, Zoloft, with up to a 72% lower incidence of orgasm dysfunction. Additionally, a low incidence of sedation and weight gain has been demonstrated by Wellbutrin SR, making it an excellent first-line choice for many depressed patients.

These materials are for your information only and should not be used for promotion or in discussions with healthcare professionals. Please contact me at (919) 483-7833 if you have any questions and continued success to you selling Wellbutrin SR.

Sincerely,

Robert Padgett

Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park, NC
27709-2398

Telephone (919) 483-7833 Fax (919) 483-9881

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GSKCO-0066-015309
GCO783-7519 FL

GOV0096-001

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Neuroreceptor Basis of Initial Antidepressant Choice

James Pradko, M.Sc., M.D.

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Neuroreceptor Basis of Antidepressant Choice

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Introduction

This talk is designed to present a simple five element approach to understanding the neurophysiologic actions of common antidepressants.

This talk will present a method of using three of these elements to help in the selection of the best first choice antidepressant for a variety of patient types.

DEPRESSION

- 7% lifetime prevalence
- 1 of 7 with recurrent depression commits suicide
- 70% of suicide victims see doctor within 7 weeks
- Suicide is 7th leading cause of death overall

What is your favorite antidepressant?

THE FIVE ELEMENTS

- Dopamine
- Serotonin
- Norepinephrine
- Acetylcholine
- Gamma-aminobutyric acid (GABA)

Side effects

- Side effects may not happen
- Side effects that affect a patient in a negative way reduce compliance
- Side effects that affect a patient in a positive way increase compliance
- A likely side effect is NOT an indication for use

"LEAP"

- Libido
- Energy
- Attention / Addiction
- Points to ponder

Neuroreceptor Basis of Antidepressant Choice
Common Antidepressants

- SSRIs
- Venlafaxine (Effexor XR)
- Nefazodone (Serzone)
- Mirtazapine (Remeron)
- Buproprion Hydrochloride (Wellbutrin SR)

How to SSRI's differ from one another

Differences Between SSRI's.

Difference Between Serotonin and Dopamine Reuptake

<table>
<thead>
<tr>
<th></th>
<th>Fluoxetine</th>
<th>Paroxetine</th>
<th>Sertraline</th>
<th>Citalopram</th>
<th>Desipramine</th>
<th>Venlafaxine</th>
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</thead>
<tbody>
<tr>
<td>Amount</td>
<td>1.131000</td>
<td>17.984000</td>
<td>231.00</td>
<td>22.233000</td>
<td>9.02</td>
<td>11.60</td>
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<tr>
<td>Concentration of OR1</td>
<td>3.25</td>
<td>4.25</td>
<td>2.40</td>
<td>4.84</td>
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Neuroreceptor Basis of Antidepressant Choice

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Neuroreceptor Basis of Antidepressant Choice

Differences Between SSRIs

**REMEMBER:**
- ACTIVATING (same form of agitation) mediated by SSRIs.
- ENERGIZING (opposite of inertia) mediated through serotonin.

**ACTIVATION by ENERGIZING**
An SSRI can be activating (phased) but an SSRI is energizing.

**SERZONE**
- \( \delta \) control
- E: neutral
- A: neutral

**REMERON**
- \( \delta \) control
- E: neutral/neutral
- A: neutral

**WELLBUTRIN SR**
- \( \delta \) control
- E: increased
- A: increased

EFEXOR
- \( \delta \) control
- E: increased
- A: neutral

Patient Profiles

"What is the best first choice of antidepressant therapy?"
Patient Profiles

"What is the best first choice of antidepressant therapy?"

Tired Tony

- Mild to severe impact on closest relationship
- Tired, poor energy
- Trouble concentrating now
- Does not want to gain weight.

L: neutral
B: decrease
A: increase

Active Alex

- Acting out sexually to increase self esteem
- Fair energy
- Concentration ok

L: reduce
B: neutral
A: increased

Active Alex

- Acting out sexually to increase self esteem
- Reduced, poor energy
- Concentration ok

L: reduce
B: neutral
A: neutral

Crying Casey

- Acting out sexually to increase self esteem
- Reduced, poor energy
- Concentration ok

L: reduce
B: neutral
A: neutral

Neuroreceptor Basis of Antidepressant Choice
Crying Casey

<table>
<thead>
<tr>
<th>SSRI's</th>
<th>Effect</th>
<th>Serum</th>
<th>Well-being</th>
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<tbody>
<tr>
<td>Libido</td>
<td>reduce</td>
<td>neutral</td>
<td>neutral</td>
</tr>
<tr>
<td>Energy</td>
<td>neutral</td>
<td>increase</td>
<td>neutral</td>
</tr>
<tr>
<td>Anexia</td>
<td>neutral</td>
<td>helpful</td>
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* scored at higher dose
** scored at lower dose

Pacing Pat

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Symptoms of Depression

<table>
<thead>
<tr>
<th>SLEEP DISTURBANCES</th>
<th>TREATMENT</th>
</tr>
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<tbody>
<tr>
<td>Insomnia 35%</td>
<td>SSRI + Antidepressant*</td>
</tr>
<tr>
<td>Hypersomnia 60%</td>
<td>TCA + Fluoxetine Antidepressant*</td>
</tr>
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</table>

ANXIETY SYMPTOMS: TREATMENT

Anxiety 90%
Lethargy 39%
TCA + Venlafaxine Antidepressant*

* Antidepressant choice based on "SAID"

"Ralphing" Robin

- Mild to severe impact on closest relationship
- Food considered "poison", low weight
- Good energy
- Concentration ok

L: neutral
E: moderate/mild
A: neutral

"Ralphing" Robin

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Neuroreceptor Basis of Antidepressant Choice

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Depression With Other Conditions

Premature Ejaculation
(SSRI's, Efferon, Serzone, Remeron, Wellbutrin)

- Libido: reduce, reduce, neutral, neutral, neutral
- Energy: neutral, increase, reduce, reduce, neutral
- Attitude: neutral, helpful, neutral, neutral, helpful

Chronic Fatigue Syndrome
(SSRI's, Efferon, Serzone, Remeron, Wellbutrin)

- Libido: reduce, reduce, neutral, neutral, neutral
- Energy: neutral, increase, reduce, reduce, increase
- Attitude: neutral, helpful, neutral, neutral, helpful

Marital Dysfunction

- Libido: reduce, reduce, neutral, neutral, neutral
- Energy: neutral, increase, reduce, reduce, increase
- Attitude: neutral, helpful, neutral, neutral, helpful

Attention Deficit Disorder

- Libido: reduce, reduce, neutral, neutral, neutral
- Energy: neutral, increase, reduce, reduce, increase
- Attitude: neutral, helpful, neutral, neutral, helpful

Chemical Dependency

- Libido: reduce, reduce, neutral, neutral, neutral
- Energy: neutral, increase, reduce, reduce, increase
- Attitude: neutral, helpful, neutral, neutral, helpful

Neuroreceptor Basis of Antidepressant Choice

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Mechanisms of Antidepressant Induced Sexual Dysfunction

Antidepressants can affect sexual function in these ways:
1. Direct inhibition of Nitric Oxide Synthetase causes less blood flow to erectile tissue
2. Indirectly reducing Dopamine which reduces libido
3. Stimulating 5HT2A inhibits orgasm

Direct Inhibition of Nitric Oxide Synthetase Causes Less Blood Flow to Erectile Tissue

Indirectly Suppressing Dopamine which Reduces Libido

Antagonizing 5HT2A Inhibits Orgasm

Summary of Sexual Dysfunction

<table>
<thead>
<tr>
<th>Medication</th>
<th>Effect</th>
<th>Libido</th>
<th>Orgasm</th>
<th>Corrective Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSRIs</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>Varenicline</td>
</tr>
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<td>SNRIs</td>
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<td>+</td>
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<td>Varenicline</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>+</td>
<td>o</td>
<td>o</td>
<td>Varenicline</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>Varenicline</td>
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Neuroreceptor Basis of Antidepressant Choice
Drug Interactions and Antidepressants

The Important Substrates
- ID6  M  Metoprolol
- O  Citricacid
- B  Benzepine
- A\(^a\)  tertiary Amine TCA's
- N  Nefazodone

- IA2  C  Caffeine
- A  Aminazapine
- T  Tramata

The Important Substrates
- SM  Q  Otranside
- U  Uracil ( Oxidines)
- A  Allopurinol & Anti-Inflam.
- C  Carbamazepine
- K  Keyne- (Pheny)
- E  Etoxadine
- D  Dibazepine

- 201995  F  Propanolol
- A  Azo-reaction
- W  Wafolmic

Interactions: P450
- Paroxin    MCBAN
- Sertraline  MCBAN
- Citalopram MCBAN
- Imipram MCBAN
- Venlafaxine MCBAN and HALOPRIDOL.
- Fluoxetine MCBAN and PARM and QUACKED
- Fluvoxamine PARM and QUACKED and CAT
- Nefazodone QUACKED
- Venlafaxine IBERATION

Neuroreceptor Basis of Antidepressant Choice

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Summary Chart

| SSRI  | Effect | Serotonin Released | Wellbeing
|-------|--------|--------------------|------------
| Libido| reduce | neutral reshape    | neutral     |
| Energy| neutral| increase           | reduce      |
| Affect| neutral hospital | neutral | neutral | hospital |

"LEAP"

- Libido
- Energy
- Attention / Addiction
- Points to ponder

What is your favorite antidepressant?

Neuroreceptor Basis of Antidepressant Choice

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