

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

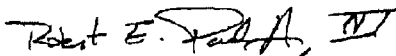
Commercial Operations Training and Development is responding to your enthusiastic response to Dr. James Pradko's presentation, Neuroreceptor Basis of Initial Antidepressant Choice. As you will remember, Dr. Pradko provided an essential part of your Wellbutrin SR training experience by sharing his views as 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) 483-7633 if you have any questions and continued success to you selling Wellbutrin SR.

Sincerely,



Robert Padgett

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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


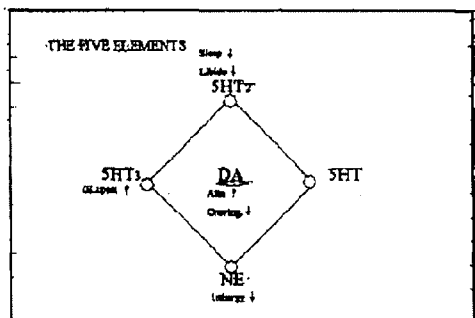
This talk is designed to present a simple five element approach to understanding the neurophysiologic actions of common antidepressants.

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 commit suicide
- 70% of suicide victims see doctor within 7 weeks
- Suicide is 7th leading cause of death overall

What is your favorite antidepressant ?

Side effects

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

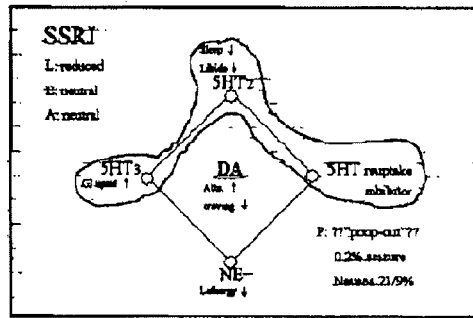
"LEAP"

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

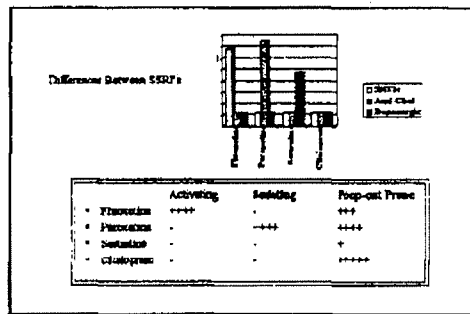
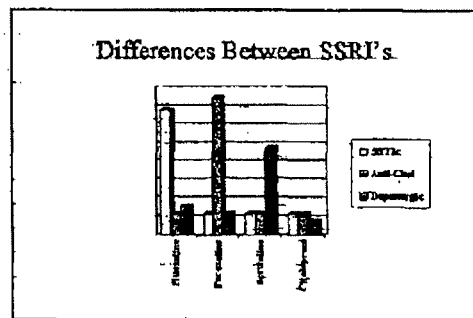
Neuroreceptor Basis of Antidepressant Choice

Common Antidepressants

- SSRI's
- Venlafaxine (Effexor XR)
- Nefazodone (Serzone)
- Mirtazapine (Remeron)
- Bupropion Hydrochloride (Wellbutrin SR)



How to SSRI's differ from one another



Difference Between Serotonin and Dopamine Reuptake

	Ratio of (K ⁺) ⁻¹	LOG Ratio of (K ⁺) ⁻¹
Fluoxetine	1,132.00	3.05
Paroxetine	17,586.00	4.25
Sertraline	253.00	2.40
Citalopram	22,222.00	4.35
Bupropion	0.03	-1.52
Venlafaxine	15.60	1.19

© Sanchez et al. Cellular and Molecular Neurobiology, Vol. 13, No. 4, 1999.

Neuroreceptor Basis of Antidepressant Choice

Differences Between SSRI's

REMEMBER:

ACTIVATING (Lower form of agitation) mediated by 5HT_{2a}.

ENERGIZING (Opposite of lethargy) mediated through Norepinephrine.

ACTIVATION by ENERGIZING

An SSRI's can be activating (Promac) but no SSRI is energizing

EFFEXOR^{XR} Over 22.5mg

E: decreased
E: increased
A: neutral/helpful

SHT_{2a} Glucoc 1
SHT₁ Glucoc 1
SHT_{1A} Glucoc 1
SHT_{2A} Glucoc 1
DA
NE
5HT reuptake inhibitor
NE reuptake inhibitor

P: Seizure 0.3%
Hypertension 3-7%
Sweating 14/3%
Nausea 4% D/C'd

SERZONE

L: neutral
E: neutral/reduced
A: neutral

SHT_{2a} Glucoc 1
SHT₁ Glucoc 1
SHT_{1A} Glucoc 1
SHT_{2A} Glucoc 1
DA
NE
5HT reuptake inhibitor
NE reuptake inhibitor

P: mCPP 3-10% (agitation)
Drug interactions
Dry mouth 25/13%

REMERON

L: neutral
E: reduced/neutral
A: neutral
P: Leucopenia 0.1%
weight gain 12/2%

SHT_{2a} Glucoc 1
SHT₁ Glucoc 1
SHT_{1A} Glucoc 1
SHT_{2A} Glucoc 1
DA
NE
5HT reuptake inhibitor
NE reuptake inhibitor

P: mCPP 3-10% (agitation)
Drug interactions
Dry mouth 25/13%

WELLBUTRIN^{SR} 150-300mg

L: neutral
E: increased
A: increased
P: 0.1% seizures
Preg. class B

SHT₁ Glucoc 1
SHT_{1A} Glucoc 1
SHT_{2A} Glucoc 1
DA
NE
5HT reuptake inhibitor
NE reuptake inhibitor

Patient Profiles

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

Neuroreceptor Basis of Antidepressant Choice

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
E: increase
A: increase

Tired Tony

	SSRI's	Effexor	Serzone	Remeron	Wellbutrin
Libido	reduce	reduce	neutral	neutral	neutral
Energy	neutral	increase	reduce	reduce*	increase
Agitation	neutral	helpful**	neutral	neutral	helpful

* neutral at higher dose
** neutral at lower dose

Active Alex

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

L: reduce
E: neutral
A: neutral

Active Alex

	SSRI's	Effexor	Serzone	Remeron	Wellbutrin
Libido	reduce	reduce	neutral	neutral	neutral
Energy	neutral	increase	reduce	reduce*	increase
Agitation	neutral	helpful**	neutral	neutral	helpful

* neutral at higher dose
** neutral at lower dose

Crying Casey

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

L: reduce
E: increase
A: neutral

Neuroreceptor Basis of Antidepressant Choice

Crying Casey

	SSRI's	Effexor	Serzone	Remeron	Wellbutrin
Libido	reduce	reduce	neutral	neutral	neutral
Energy	neutral	increase	reduce	reduce*	increase
Attention	neutral	helpful**	neutral	neutral	helpful

* neutral at higher dose
** neutral at lower dose

Pacing Pat

- Mild to severe impact on closest relationship
- Insomnia prior to depression
- Concentration ok

L: neutral
E: reduce
A: neutral

Pacing Pat

	SSRI's	Effexor	Serzone	Remeron	Wellbutrin
Libido	reduce	reduce	neutral	neutral	neutral
Energy	neutral	increase	reduce	reduce*	increase
Attention	neutral	helpful**	neutral	neutral	helpful

* neutral at higher dose
** neutral at lower dose

SYMPTOMS OF DEPRESSION:

SLEEP DISTURBANCES:		TREATMENT
Insomnia	35%	3wk Benzo + Antidepressant*
Hypersomnia	65%	Time + Non-sedating Antidepressant*
ANXIETY SYMPTOMS:		TREATMENT
Anxiety	65%	3wk Benzo + Antidepressant*
Lethargy	35%	Time + Non-sedating Antidepressant*

* Antidepressant chosen based on "LEAD"

"Ralphing" Robin

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

L: neutral
E: reduce/neutral
A: neutral

"Ralphing" Robin

	SSRI's	Effexor	Serzone	Remeron	Wellbutrin
Libido	reduce	reduce	neutral	neutral	neutral
Energy	neutral	increase	reduce	reduce*	increase
Attention	neutral	helpful**	neutral	neutral	helpful

* neutral at higher dose
** neutral at lower dose

Neuroreceptor Basis of Antidepressant Choice

Depression With Other Conditions

Premature Ejaculation
 Use SSRI⁺ Agonist

	SSRI's	Effexor	Serzone	Remeron	Wellbutrin
Libido	reduce	reduce	neutral	neutral	neutral
Energy	neutral	increase	reduce	reduce*	increase
Attention	neutral	helpful**	neutral	neutral	helpful

* neutral at higher dose
 ** neutral at lower dose

Chronic Fatigue Syndrome
 Increase Neuroplasticity

	SSRI's	Effexor	Serzone	Remeron	Wellbutrin
Libido	reduce	reduce	neutral	neutral	neutral
Energy	neutral	increase	reduce	reduce*	increase
Attention	neutral	helpful**	neutral	neutral	helpful

* neutral at higher dose
 ** neutral at lower dose

Marital Dysfunction
 Do not disturb sexual axis

	SSRI's	Effexor	Serzone	Remeron	Wellbutrin
Libido	reduce	reduce	neutral	neutral	neutral
Energy	neutral	increase	reduce	reduce*	increase
Attention	neutral	helpful**	neutral	neutral	helpful

* neutral at higher dose
 ** neutral at lower dose

Attention Deficit Disorder
 Increase DA

	SSRI's	Effexor	Serzone	Remeron	Wellbutrin
Libido	reduce	reduce	neutral	neutral	neutral
Energy	neutral	increase	reduce	reduce*	increase
Attention	neutral	helpful**	neutral	neutral	helpful

* neutral at higher dose
 ** neutral at lower dose

Chemical Dependency
 Increase DA

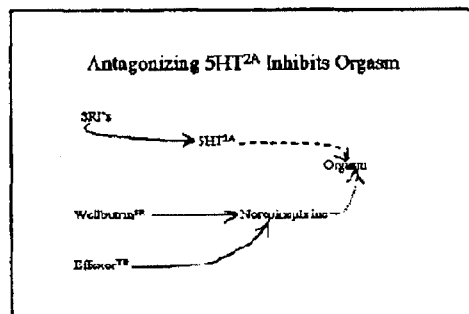
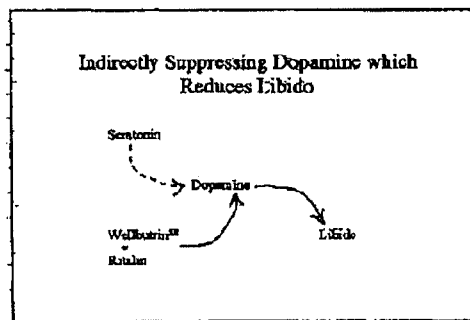
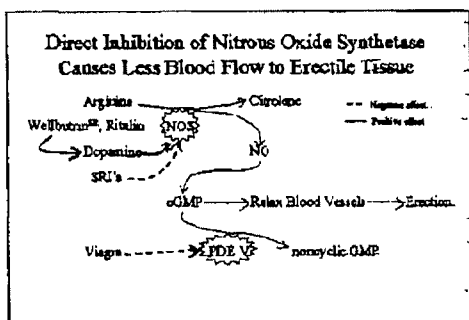
	SSRI's	Effexor	Serzone	Remeron	Wellbutrin
Libido	reduce	reduce	neutral	neutral	neutral
Energy	neutral	increase	reduce	reduce*	increase
Attention	neutral	helpful**	neutral	neutral	helpful

* neutral at higher dose
 ** neutral at lower dose

Neuroreceptor Basis of Antidepressant Choice

Mechanisms of Antidepressant Induced Sexual Dysfunction

- Antidepressants can effect sexual function in three ways:
1. Direct inhibition of Nitrous Oxide Synthetase causes less blood flow to erectile tissue
 2. Indirectly reducing Dopamine which reduces libido
 3. Stimulating 5HT_{2A} inhibits orgasm



Summary of Sexual Dysfunction

Medication	Erection (NO)	Libido (Dopamine)	Orgasm (Serotonin)	Corrective Action Add
SRIs	+	+	+	Wellbutrin [®] or Viagra + SRIs + PDE5i
Effexor [®]	+	+/+	+/+	Wellbutrin [®] or Trazodone + Viagra
Serzone	+/+	0	0	Viagra
Remeron	0	0	0	
Wellbutrin [®]	0	0	0	

Neuroreceptor Basis of Antidepressant Choice

Drug Interactions and Antidepressants

Interactions: P450

• Fluoxetine	2D6	3C	3A4	
• Paroxetine	2D6			
• Sertraline	2D6			
• Citalopram	2D6			
• Venlafaxine	2D6			Haloperidol
• Bupropion	2D6			
• Fluvoxamine	3C	3A4	1A2	
• Nefazodone		3A4		
• Mirtazapine				Sedation

The Important Substrates

• 2D6	M	Metoprolol
•	O	Oxycodone
•	B	Baclofen
•	A ³	tertiary Amine TCA's
•	N	Nefazodone
• 1A2	C	Caffeine
•	A	Acetaminophen
•	T	Ticarcillin

The Important Substrates

• 3A4	Q	Quinidine
•	U	Uric acid (Colchicine)
•	A	Alprazolam & Antivirals
•	C	Carbamazepine
•	K	Kay-mac (gabapentin)
•	E	Erythromycin
•	D	Diltiazem
• 2C19,9,10	F	Propranolol
•	A	Anti-inflammatories
•	W	Warfarin

Interactions: P450

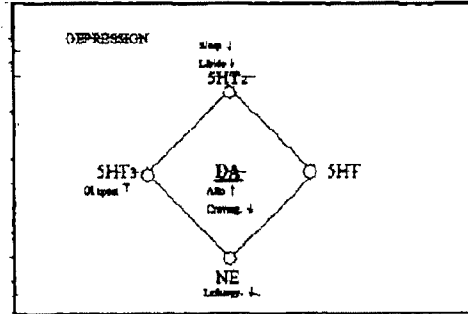
• Paroxetine	MCB/A ³ N
• Sertraline	MCB/A ³ N
• Citalopram	MCB/A ³ N
• Bupropion	MCB/A ³ N
• Venlafaxine	MCB/A ³ N and HALOPERIDOL
• Fluvoxamine	MCB/A ³ N and PAW and QUACKED
• Fluvoxamine	PAW and QUACKED and CAT
• Nefazodone	QUACKED
• Mirtazapine	SEDATION

Neuroreceptor Basis of Antidepressant Choice

Summary Chart

	SSRI's	Efficacy ¹²	Serzone- Remeron	Wellbutrin ¹¹
Libido	reduce	reduce	neutral	neutral
Energy	neutral	increase	reduce	increase
Addiction	neutral	helpful**	neutral	helpful

* neutral at higher dose
 ** neutral at lower dose



- ### "LEAP"
- Libido
 - Energy
 - Attention / Addiction
 - Points to ponder

What is your favorite antidepressant ?

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Neuroreceptor Basis of Antidepressant Choice