CLINICAL TOXICOLOGY OF NEW DRUGS©--Part 2

SPI WEBCAST
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CLINICAL TOXICOLOGY OF NEW DRUGS©--Part 2

- DULOXETINE
- EXENATIDE
- GEPIRONE
- REBOXETINE
- TOLRESTAT
- VILOXAZINE

CLINICAL TOXICOLOGY OF NEW DRUGS©--Part 2

Current Status

- MINIMAL TOXICITY INFO
- NONE APPROVED IN PREGNANCY
- ONLY DULOXETINE APPROVED

Drugs@FDA

A Catalog of FDA Approved Drug Products
http://www.fda.gov/cder/index.html

OTHER RESOURCES

- Poisindex
- Drugdex
- Google
- Medline
- Merck
- Martindale

AAPCC TESS EXPOSURES
All Years

DULOXETINE	5
EXENATIDE	0
GEPIRONE	0
REBOXETINE	6
TOLRESTAT	2
VILOXAZINE	7

CLINICAL TOXICOLOGY OF NEW DRUGS©--Part 2
Objectives

- THERAPEUTIC USES
- MECHANISM(S) OF ACTION
- PHARMACOKINETICS
- ADVERSE/TOXIC EFFECTS
- MANAGEMENT OF OVERDOSE

CLINICAL TOXICOLOGY OF NEW DRUGS©--Part 2
Treatment Considerations

- DO NO HARM!
- SUPPORTIVE THERAPY
- GI DECON RX
  AC Only
- SERUM CONCENTRATIONS
  No Value
- NO EXTRACORPOREAL

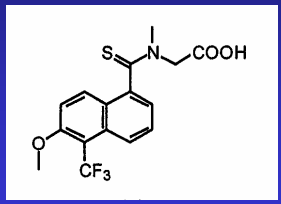
NEW DRUGS©
Categorization

- DIABETIC THERAPY
  Tolrestat
  Exenatide
- ANTIDEPRESSANTS
  Duloxetine
  Gepirone
  Reboxetine
  Viloxazine

ANTIDIABETIC AGENTS

TOLRESTAT
EXENATIDE

TOLRESTAT
(Alredase®)



TOLRESTAT
Therapeutic Uses

- PREVENT DIABETES COMPLICATIONS
  - Neuropathy
  - Retinopathy
  - Cataracts
- DOSE
  - 200 mg QD
  - Single or Divided Doses
- MECHANISM OF ACTION
  - Aldose Reductase Inhibitor

TOLRESTAT
Pathophysiology of DM Complications
…A Link To Sorbitol

GLUCOSE*

↓ *Aldose Reductase*

SORBITOL → FRUCTOSE

Sorbitol Reductase

Galactose
↓ *AR*
Galactitol

*Does not occur in healthy people

ROLE OF SORBITOL
Diabetic Complications

- POOR PENETRATION OF MEMBRANES
  Both Directions
- ACCUMULATION OF SORBITOL IN CELLS

SORBITOL ACCUMULATION

↓ *Osmotic Effect*

H_2O INFLUX INTO CELLS

↓ LOSS OF CELL PERMEABILITY

TOLRESTAT
Mechanism of Action

GLUCOSE

↓ *Aldose Reductase* ✗

SORBITOL

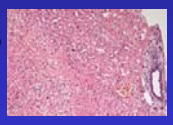
TOLRESTAT
Pharmacokinetics

- ABSORPTION
  Rapid
- DISTRIBUTION
  99.25% Protein Bound
- METABOLISM
  Hepatic
- ELIMINATION
  Renal 63-69%
  Fecal 25-27%
  $t_{1/2}$ ~ 11 Hours*

*Independent of dose at 10-800 mg
Clin Pharmacol Ther 1996;59:603-612

TOLRESTAT
Adverse Effects

- EXTENSION OF SIDE EFFECTS
- ELEVATED LFTs
- HEPATIC NECROSIS
- DIZZINESS
- RASH



TOLRESTAT
Management of Overdose

- DO NO HARM!
- LOW TO NO RISK
- SUPPORTIVE CARE
- ACTIVATED CHARCOAL?

EXENATIDE

Synthetic Exendin-4
39-Amino Acid Peptide

EXENATIDE
Therapeutic Uses

- TYPE 2 DIABETES MELLITUS
  - Not Type 1
  - Viable Pancreas
- ADJUNCT TO HYPOGLYCEMICS
  - Sulfonylureas
  - Biguanides
- DOSE
  - 5 mcg BID SC x 30 Days
  - Then 5-10 mcg QD

PATHOGENESIS
Type 2 Diabetes Mellitus

PERIPHERAL INSULIN RESISTANCE

PROGRESSIVE BETA CELL FAILURE

↓ ↓

INADEQUATE INSULIN

TYPE 2 DIABETES
Progression

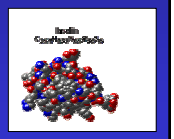
- EARLY THERAPY
  - Diet
  - Exercise
  - Weight Control
- GLUCOSE CONTROL DETERIORATES
  - Oral Therapy: 1-2 Agents
  - Insulin
- BETA CELL FUNCTION FAILURE = CONTINUES
- RESISTANCE DOES NOT PROGRESS AS FAST

TYPE 2 DIABETES
Goals of Therapy

- ß CELL DETERIORATION
  Delay
  Arrest
  Reverse
- ß CELL ENHANCEMENT
- NEW THERAPIES
  Additive or Synergistic to Oral Hypoglycemics
  Preserve/Enhance ß Cell Function

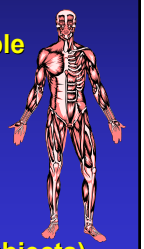
EXENATIDE-The Future?
Mechanisms of Action

- ↑ INSULIN SECRETION
- ↓HIGH GLUCAGON SECRETION
- ↓GASTRIC EMPTYING
- ↓FOOD INTAKE
- ↑ß CELL PROLIFERATION



EXENATIDE
Pharmacokinetics

- ABSORPTION
  Parenteral-65-76% Bioavailable
- DISTRIBUTION
  V_d 64 mL/kg
- METABOLISM
  ?
- ELIMINATION
  $t_{1/2}$ 26-33 Minutes (Healthy Subjects)



EXENATIDE
Adverse Effects

- HEADACHE
- VOMITING
- NAUSEA
- MILD-MODERATE ↓ BS

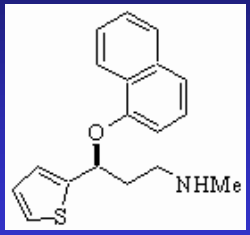
EXENATIDE
Management of Overdose

- DO NO HARM!
- SUPPORTIVE CARE
- GLUCOSE MONITORING
  Effects = Short Duration
  ~3-6 Hours?
- INGESTION
  Parenteral Product
  Destruction in GIT

NEW
ANTIDEPRESSANT AGENTS

DULOXETINE
GEPIRONE
REBOXETINE
VILOXAZINE

DULOXETINE
Cymbalta®



FDA Approves Lilly's Cymbalta for the Treatment of Depression

August 04, 2004

Dual-reuptake inhibitor judged safe and effective, giving doctors and patients a new option for treating the emotional and painful physical symptoms of depression

The U.S. Food and Drug Administration has approved Cymbalta® (duloxetine HCl, pronounced SIM-BALL-TA), judging it a safe and effective treatment for major depressive disorder, Eli Lilly and Company announced today.

Cymbalta, a balanced and potent reuptake inhibitor of serotonin and norepinephrine, has been studied in more than 6,000 adults with major depression worldwide. Its approval gives healthcare professionals and patients a long-awaited new option for treating the broad range of emotional and physical symptoms of depression. Today, only 25-35 percent of patients treated for depression in clinical studies experience relief from all of their disease symptoms.[1]

"Depression is a whole-body illness, but most modern antidepressants treat the emotional symptoms, such as crying and sadness, better than they treat the physical symptoms of depression," said Dr. Stephen Stahl, chairman of the Neuroscience Education Institute and adjunct professor of psychiatry at the University of California at San Diego School of Medicine. "Because of its dual action on serotonin and norepinephrine, Cymbalta offers physicians a new opportunity to help patients with depression, particularly those who experience the common physical symptoms of the disease, such as vague aches and pains."

Neurotransmitters are believed to help regulate a person's emotions and sensitivity to pain. Scientists believe that if these neurotransmitters are out of balance, a person may become depressed and be more likely to feel painful physical symptoms. The combination of emotional and painful physical effects of depression can have a tremendous negative impact on a person's quality of life.[2]

"Lilly's leadership in neuroscience and dedication to the treatment of depression is well established," said Sidney Taurel, Lilly's chairman, president and chief executive officer. "Lilly is committed to solving the world's most pressing neuroscience problems, through research programs in Alzheimer's and Parkinson's as well as through our established expertise in depression, schizophrenia, bipolar disorder and Attention-Deficit Hyperactivity Disorder."

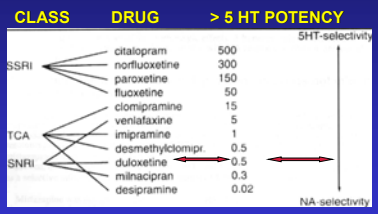
DULOXETINE
Therapeutic Uses

- MAJOR DEPRESSION
  Pts with Vague Aches/Pains
- BIPOLAR DISORDER
- URINARY INCONTINENCE
- DAILY DOSE
  40-60 mg Total
  QD or B.I.D

DULOXETINE
Mechanisms of Action

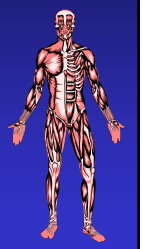
- DUAL-SELECTIVE MOA
  Serotonin Norepinephrine Reuptake Inhibitor (SNRI)
  Combination SSRI and NRI
- DUAL MOA
  > Efficacy in Major Depression

EVOLUTION OF ANTIDEPRESSANTS
Where is Duloxetine?



DULOXETINE
Pharmacokinetics

- ABSORPTION
  70% Bioavailable
  2 Hr Lag
  Cmax 6-10 Hr
- DISTRIBUTION
  Large V_d 1940 L
  Protein-Binding >90%
- METABOLISM
  Hepatic
  Active Metabolites-Desmethyl > SSRI
- ELIMINATION
  $t_{1/2}$ 11-16 Hours (Mean = 12.5 Hr)
  Renal 77%



J Clin Pharmacol 2000;40:161-167

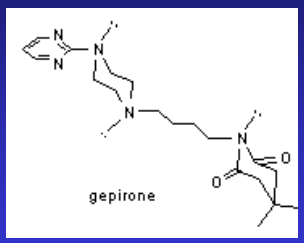
DULOXETINE
Adverse Effects

- NAUSEA-20%
- INSOMNIA-20%
- HEADACHE-16%
- OTHERS
  Dry Mouth
  Dizziness
- CARDIOVASCULAR?
  HR Minimal
  BP Minimal

DULOXETINE
Management of Overdose

- DO NO HARM!
- SUPPORTIVE CARE
- ACTIVATED CHARCOAL
  Delayed Absorption
- MONITOR CV
  Probably Not TCA Toxicity
- WITHDRAWAL SYNDROME
  Abrupt Withdrawal

GEPIRONE



An Azapirone Compound
June 24, 2004-FDA "Not Approved"

GEPIRONE
Therapeutic Uses

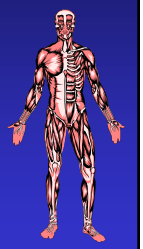
- BUSPIRONE ANALOGUE
- ANXIOLYTIC
- ANTIDEPRESSANT
- NO ADVANTAGES OVER OTHER RXs
- DOSE
  Immediate Release 10-90 mg QD
  Extended Release 20-100 mg QD

GEPIRONE
Mechanisms of Action

- SEROTONIN 1A (5 HT-1A) Agonist
- >RECEPTOR POTENCY THAN BUSPIRONE
- <DOPAMINE RECEPTOR BINDING
- NO EFFECT ON BENZO OR GABA RECEPTORS
- NO ANTICONVULSANT PROPERTIES

GEPIRONE
Pharmacokinetics

- IR vs ER PRODUCTS
- ONSET
  Anxiety 3-6 Weeks
  Depression 2-3 Weeks
- TIME TO PEAK
  IR 1 Hour
  ER 5 Hours



GEPIRONE
Pharmacokinetics

- ABSORPTION
  14% Bioavailable (IR)
  Buspirone 4%
- DISTRIBUTION
  Large V_d
  Highly Protein-Bound
- METABOLISM
  Hepatic
  Active Metabolites-1-(2-pyrimidinyl) piperazine [1-PP]
  Same Metabolite as Buspirone
- ELIMINATION $t_{1/2}$
  Parent Cpd: IR 2-3 Hr; ER 6 Hr
  1-PP 7 Hr

GEPIRONE
Adverse Effects

- EXTENSION OF SIDE EFFECTS
- DROWSINESS-Unexpected
- DIZZINESS
- HEADACHE
- NAUSEA
- VOMITING
- SEIZURES-Rare
- SIMILAR TO BUSPIRONE-Without Dopamine

BUSPIRONE
Range of Toxicity

- THERAPEUTIC DOSE
  Max = 60 mg QD
- TOLERATED
  375 mg QD x 30 Days
- OVERDOSE
  420 mg: Lethargic, combative, seizure at 36 hours
  250 mg with diazepam 25 mg: no ADRs

GEPIRONE
Management of Overdose

- DO NO HARM!
- SUPPORTIVE CARE
- ACTIVATED CHARCOAL
- CV TOX UNLIKELY
- CNS DEPRESSION RX

REBOXETINE
(Edronax®)

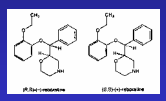
Available in Europe

REBOXETINE
Therapeutic Use

- ANTIDEPRESSANT-3rd Generation
  Major Depression
- ALTERNATIVE TO SSRIs
- ADVANTAGE = < SE
- DOSE
  Usual 8 mg
  Max 12 mg
  BID Dosing

REBOXETINE
Mechanisms of Action

- STRUCTURE SIMILAR TO FLUOXETINE
- RACEMIC MIXTURE
- SELECTIVE NOREPINEPHRINE REUPTAKE INHIBITOR (SNRI)
  1ST Available SNRI
  Binds NE Transporter
  Blocks Reuptake of Extracellular NE
- NO AFFECT
  5 HT
  Dopamine
- MINIMAL AFFECT ON OTHER RECEPTORS
  Muscarinic
  Histaminic
  Adrenergic

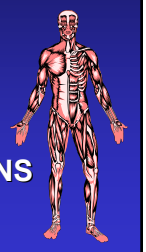


Rev Psychiatr Neurosci 2002;27:418-422

IJMT 2000;3:26—www.ijmt.net/3_4/3_4_26.html

REBOXETINE
Pharmacokinetics

- ONSET
  10-14 Days
- TIME TO PEAK
  1.5-2.4 Hours
- SERUM CONCENTRATIONS
  Irrelevant in OD



REBOXETINE
Pharmacokinetics

- ABSORPTION-2 Hours
  92-94%
- DISTRIBUTION
  V_d
  R- racemer 0.385 L/kg
  S+ racemer 0.920 L/kg
  Protein Binding 96-98%
- METABOLISM
  Hepatic by CYP3A4
  Does Not Induce or Inhibit
  No Active Metabolites
  ELIMINATION
  Renal 76%
  $t_{1/2}$ 12-14 Hours

Clin Pharmacokinet 2000;39:413-427

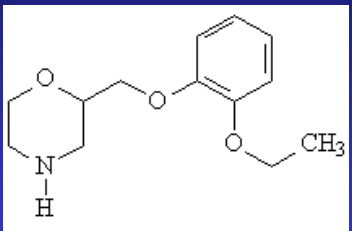
REBOXETINE
Adverse Effects

- EXTENSION OF SIDE EFFECTS
- LIMITED VIA MOA
- DRY MOUTH
- CONSTIPATION
- HEADACHE
- NO EFFECT ON CARDIAC REPOLARIZATION
  Mild Hypotension
  Mild Hypertension
  Tachyarrhythmia
- SEIZURES-Theoretical, No Evidence

REBOXETINE
Management of Overdose

- SURVIVAL 240 mg
- ANTICIPATE SYMPATHOMIMETIC
- DO NO HARM!
- SUPPORTIVE CARE
- ACTIVATED CHARCOAL
- CV TOX UNLIKELY

VILOXAZINE
Vivalan®



Studied Since the 1970's

VILOXAZINE
Therapeutic Uses

- ANTIDEPRESSANT
  2nd Generation Bicyclic
- THERAPEUTIC USES
  Cataplexy & Narcolepsy-Withdrawn
  Endogenous Depression
  Anxiety
  Nocturnal Enuresis
- ADVANTAGE = < SE???
  Elderly
- DAILY DOSE
  150-450 mg
  T.I.D. Dosing

VILOXAZINE
Mechanisms of Action

- ADRENERGIC AGONIST
  Amphetamine-Like Stimulant
  No Dependence Liability
- INHIBITS NOREPINEPHRINE REUPTAKE
- NO AFFECT
  5 HT

VILOXAZINE
Pharmacokinetics

- ABSORPTION
  ~85%--Rapid
  Peak Concentration-2 Hours
- DISTRIBUTION
  V_d 0.7-0.8 L/kg
- METABOLISM
  Hepatic
  Metabolites Inactive
- ELIMINATION
  Renal 12-15% Unchanged
  $t_{1/2}$ 2-5 Hours

VILOXAZINE
Adverse Effects

- CARDIOVASCULAR-Low Incidence
  Orthostatic Hypotension
  Hypertension
  Palpitations/Tachycardia
- CENTRAL NERVOUS SYSTEM
  CNS Depression-Drowsy, Dizzy
  Headache-↑↑
  Seizures-Uncommon
- GASTROINTESTINAL
  Nausea
  Vomiting
  Epigastric Pain
  Diarrhea
  Dry Mouth

VILOXAZINE
Overdosage

- 12 REPORTS OF OVERDOSAGE
  1-6.5 g (Mean 3.25 g)
  15-44 yr
  7 Co-ingestants
  Drowsiness = Most Common Sx
  No CV Toxicity
  J Int Med Res 1976;4:83-85
- FATAL TOXICITY INDEX
  3rd Highest Behind Desipramine and Amoxapine
  Flawed Interpretation
  Only 2 Fatalities in 10 Years
  Drug Safety 1998;18:369-381
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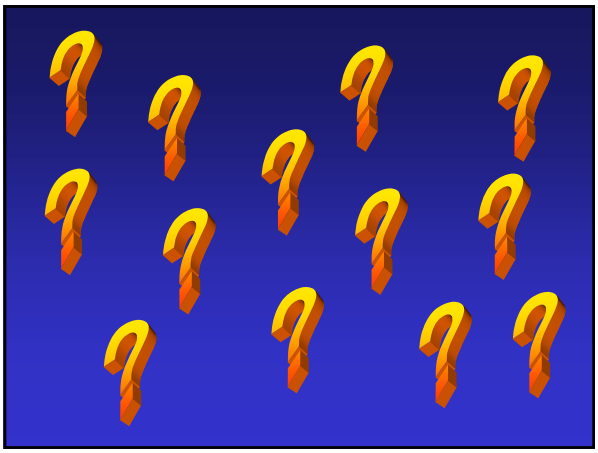
VILOXAZINE
Management of Overdose

- SURVIVAL – 6.5 gm
- DO NO HARM!
- SUPPORTIVE CARE
- ACTIVATED CHARCOAL
- CV TOX UNLIKELY