



Knowledge-Based Lead Discovery and Design

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Anne Tobak, Ph.D.



Presentation Outline

1. Knowledge-Based Lead Discovery and Design Strategies
 - Knowledge-Base for Transporter Program
 - Structure-target relationships
 - The privileged structures
2. DOV Chemistry Strategy
3. Pharmacophore Elucidation and Analysis
4. Summary and Future Directions

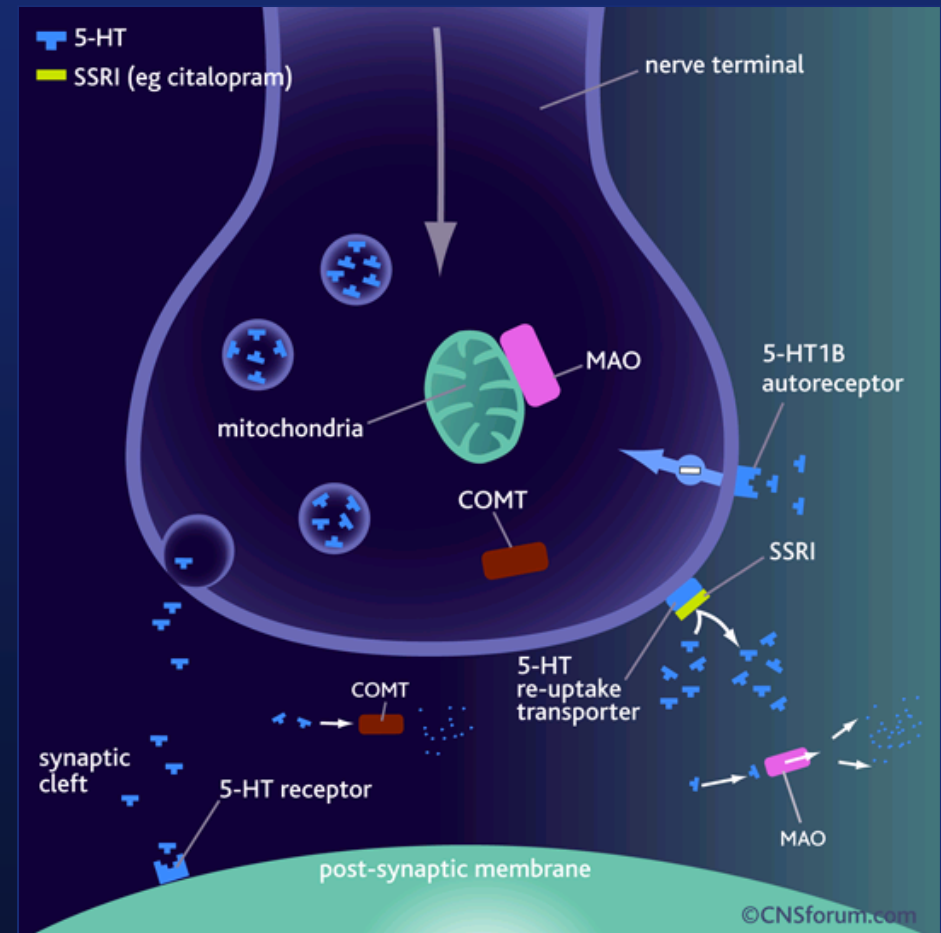
Knowledge-based Drug Disc. & Devl.

- Drugs from Existing Drugs
 - Enantiomer of existing drugs
 - Metabolite of existing drugs
 - Combination of existing drugs
 - Reposition of existing drugs
- Lead Discovery Strategy
 - Mimics of the endogenous ligands/mediators
 - Privileged structures as leads
 - Known ligands and drugs as lead
 - Analog research

Monoamine Hypothesis of Depression

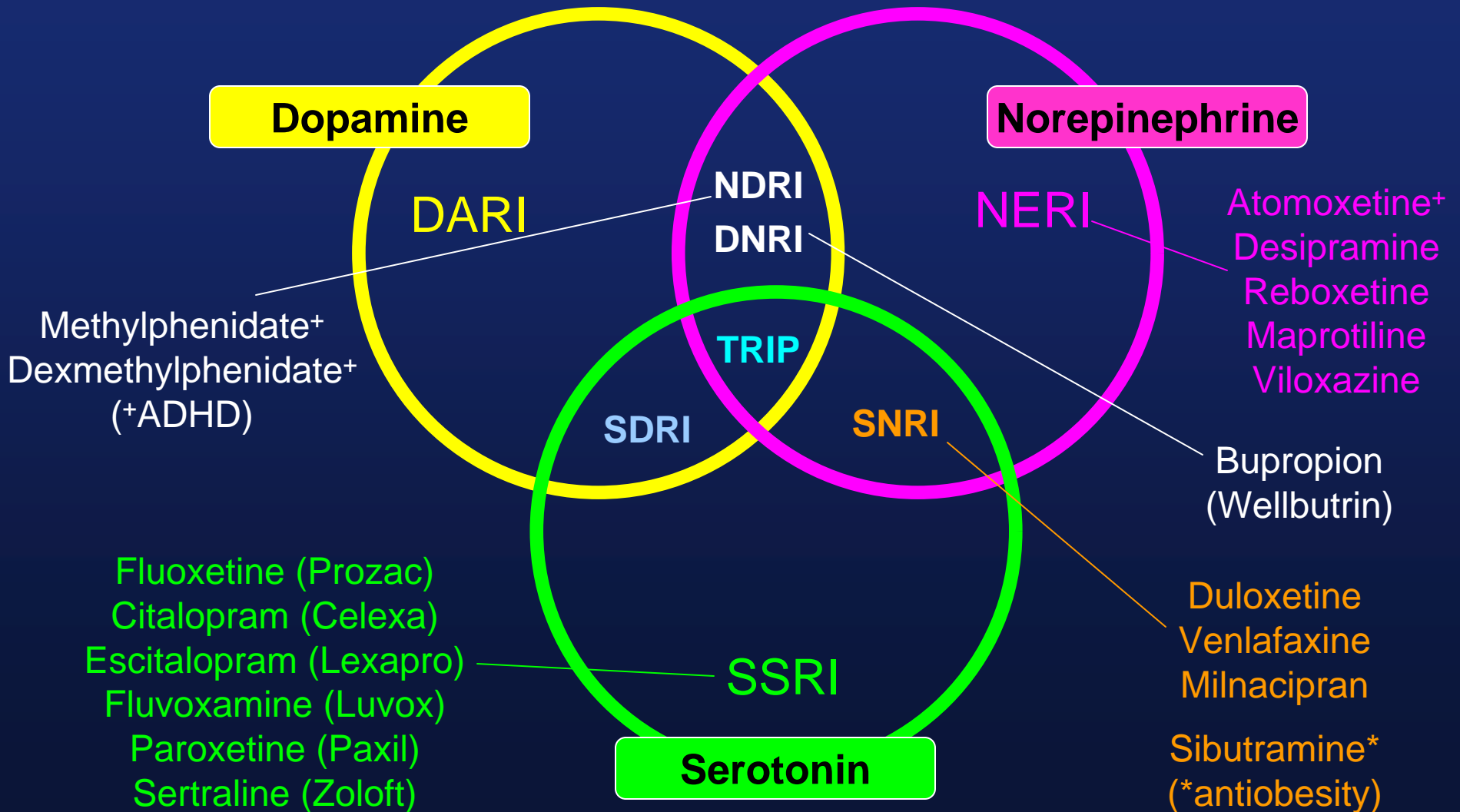
- Neurotransmitters, such as serotonin (5-HT), norepinephrine (NE/NA), and dopamine (DA) are chemical messengers that carry information throughout the body.
- Major depression is believed to be caused by a shortage of neurotransmitters in the synaptic cleft.
- All antidepressants cause an increase of neurotransmitters in the synaptic cleft.

Serotonin in Action

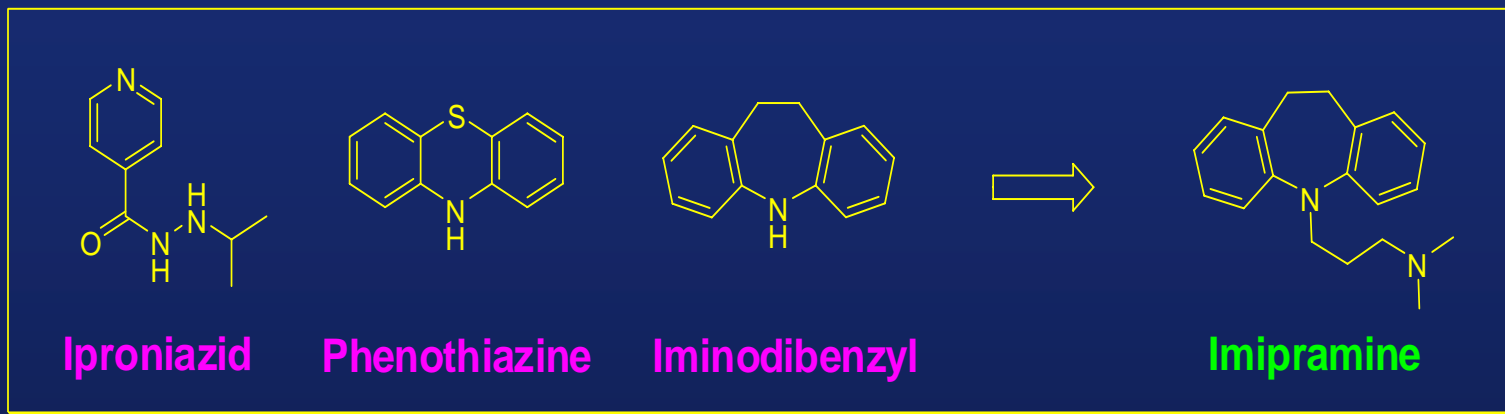


Approved Drug Classes

(Uptake Inhibitors)

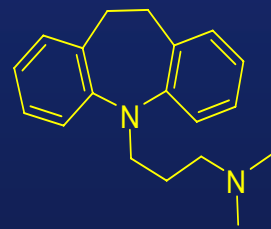


Discovery of The First Marketed Antidepressant

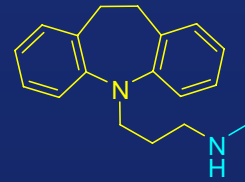


- Iproniazid was originally developed as an antitubercular drug in the early 1950's, but it was later prescribed widely to patients with major depression (MAOI).
- Iminodibenzyl, synthesized in 1898, is the prototypical structure for tricyclic antidepressant.
- 42 analogs of iminodibenzyl were made in 1950s at Geigy.
 - One drug discovered – a new measurement of medicinal chemistry efficiency?

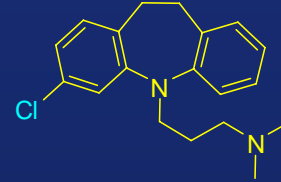
The Tricyclic Antidepressants (TCAs)



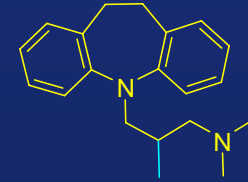
Imipramine



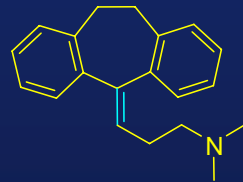
Desipramine



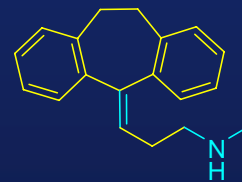
Clomipramine



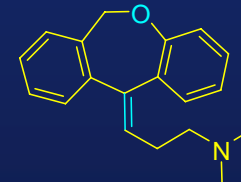
Trimipramine



Amitriptyline



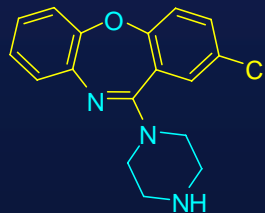
Nortriptyline



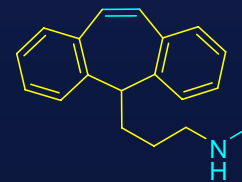
Doxepin



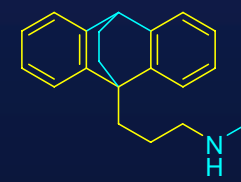
Dothiepin



Amoxapine



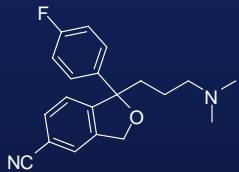
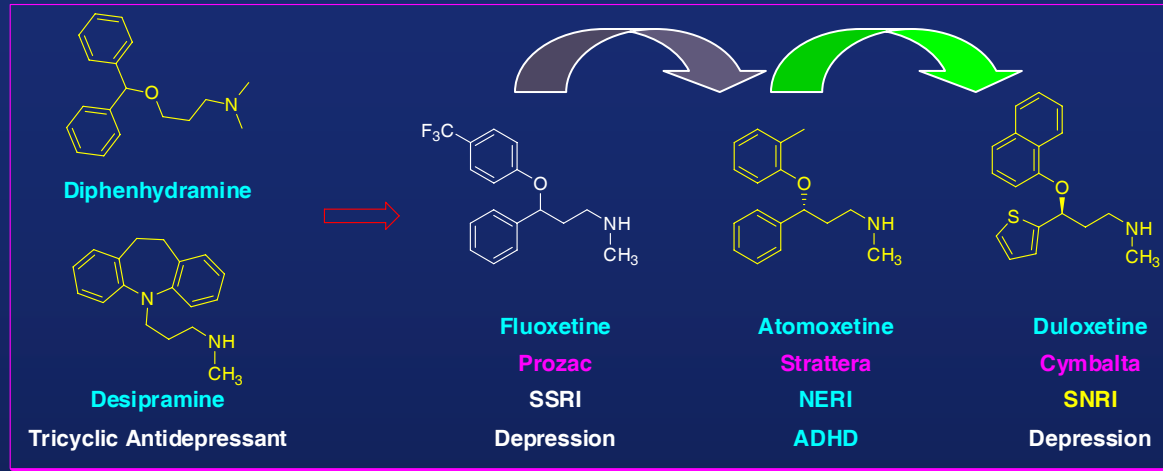
Protriptyline



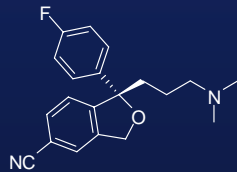
Maprotiline

- Mode of Action: *Monoamine reuptake inhibition plus α_1 , α_2 , H₁, M₃, etc.*

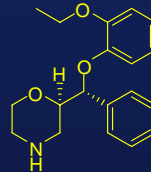
Design of the 2nd/3rd Generations



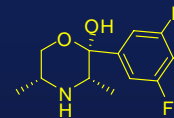
Citalopram (Celexa)



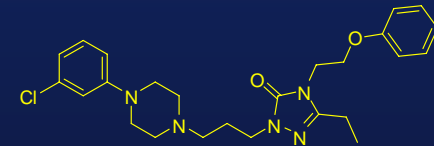
Escitalopram (Lexapro)



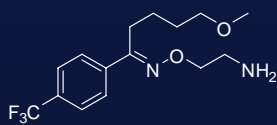
Reboxetine



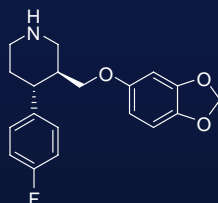
Manifaxine



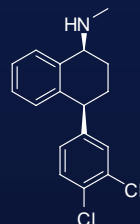
Nefazodone (Serzone)



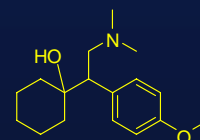
Fluvoxamine (Luvox)



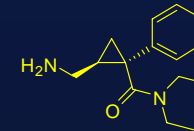
Paroxetine (Paxil)



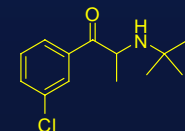
Sertraline (Zoloft)



Venlafaxine (Effexor)

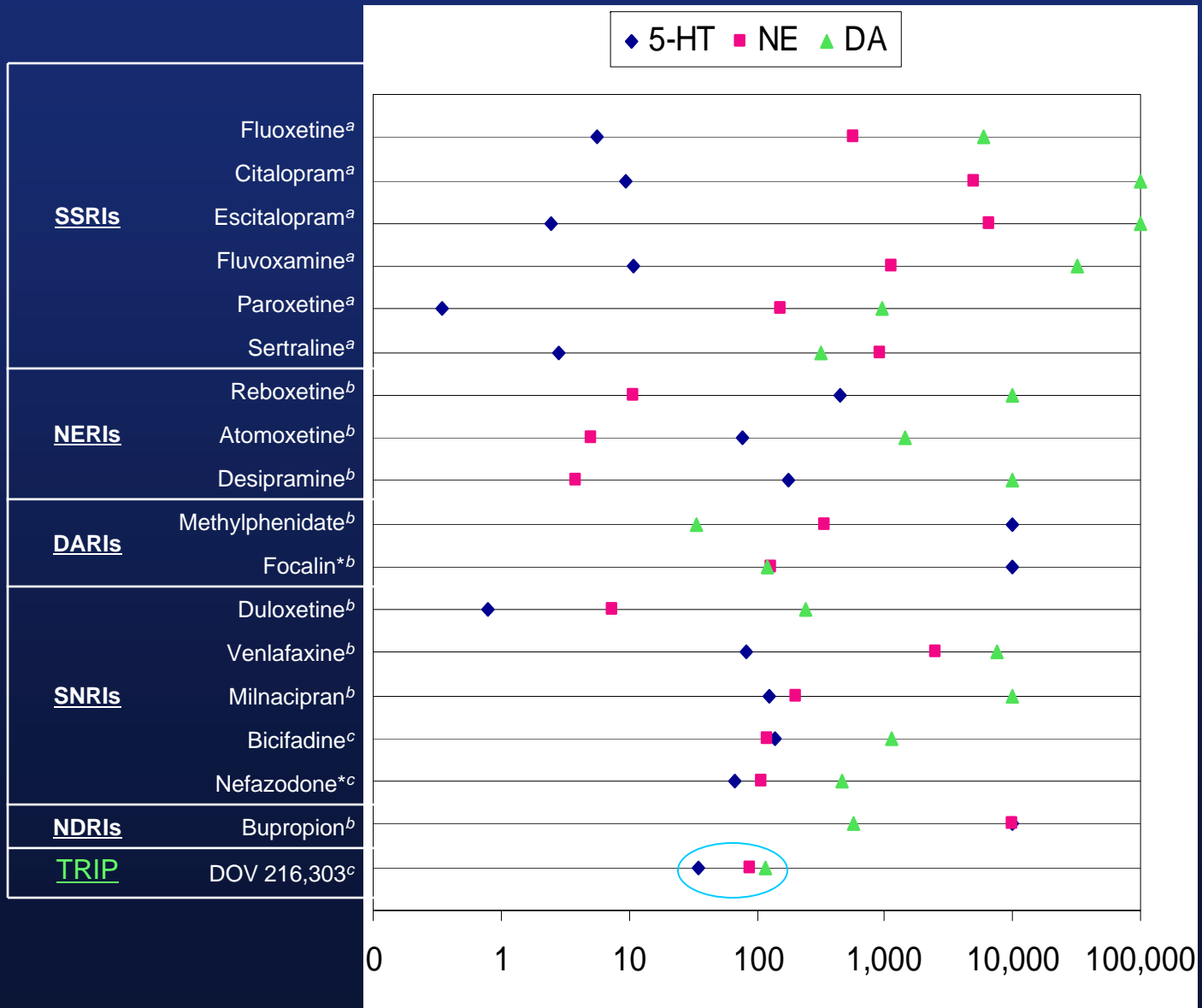


Milnacipran (Dalcipran/lxel)



Bupropion (Wellbutrin)

Different Classes of Uptake Inhibitors



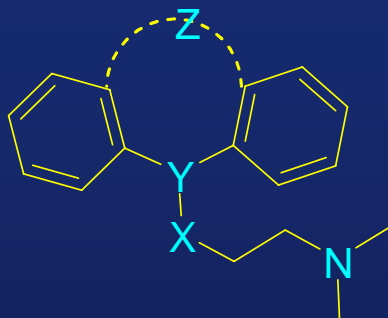
Structure-target Relationships

- **Structure-target Relationship:**
 - What chemical structural features are required for a specific target protein (**monoamine transporter**)?
- **Key Structural Feature 1:**
 - All 25 marketed transporter inhibitors have a **basic amino group** in the molecule:
 - 2 of them have a primary amino group,
 - 14 of them have a secondary amino group
 - methylamino group: 8; piperidine ring: 3; piperazine: 1; morpholine: 1; t-butylamine: 1
 - 9 of them have a tertiary amino group (all dimethylamino groups)
- **Key Structural Feature 2:**
 - 18 of them have 2 phenyl groups; 6 of them have one **phenyl group** with a hydrophobic ring or chain; 1 has 2 aryl groups (duloxetine).

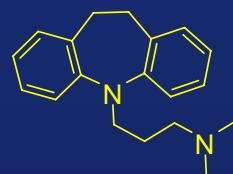
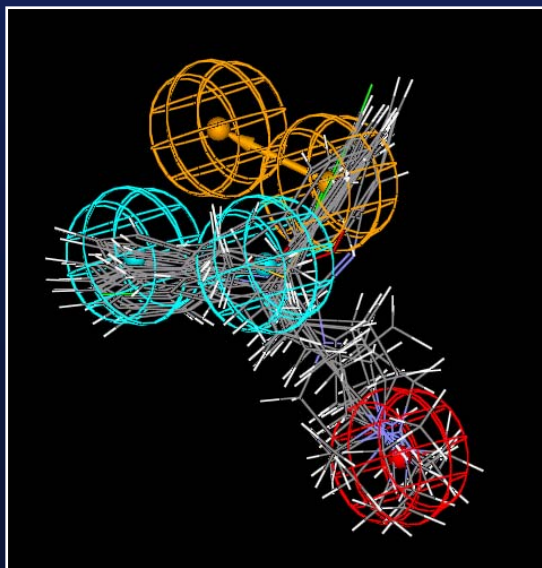
Structure-target Relationships

- **Lipophilicity:**
 - ClogP ranges from 2.12 to 4.76 with an average of 3.52, **median 3.53**
- **Molecular Weight (MW):**
 - Molecular weight of all 25 marketed transporter inhibitors (antidepressants) ranges from 233 to 329 with an average of 285, **median 280**
- **Rotatable Bonds:**
 - Number of rotatable bonds ranges from 1 to 9 with an average of 4.4, **median 4.0**
- **Hydrogen Bonding:**
 - Number of hydrogen bond acceptors range from 1 to 4 with an average of 2.3, **median 2.0**.
 - Number of hydrogen bond donors range from 0 to 2 with an average of 0.8, **median 1.0**.

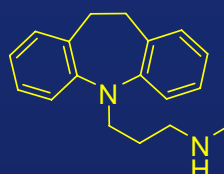
The Privileged Structures



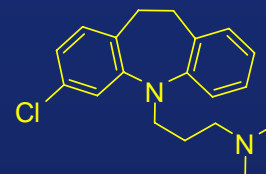
Privileged Structure 1



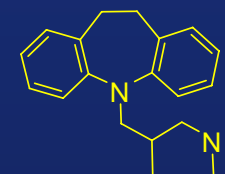
Imipramine



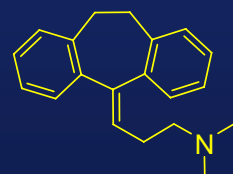
Desipramine



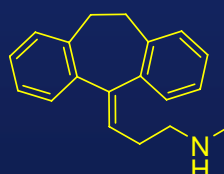
Clomipramine



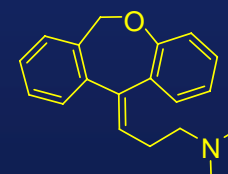
Trimipramine



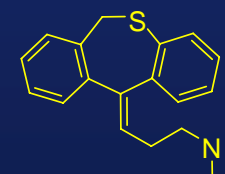
Amitriptyline



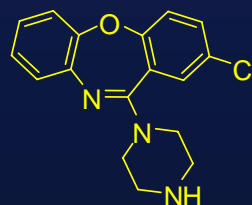
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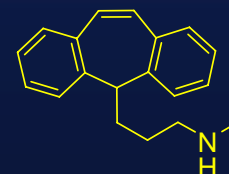
Doxepin



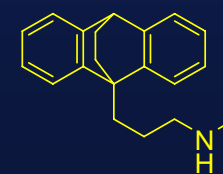
Dothiepin



Amoxapine

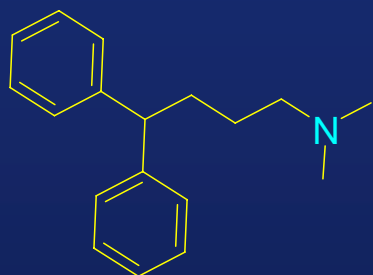


Protriptyline

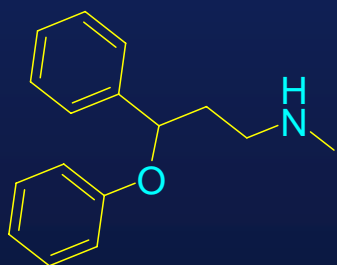


Maprotiline

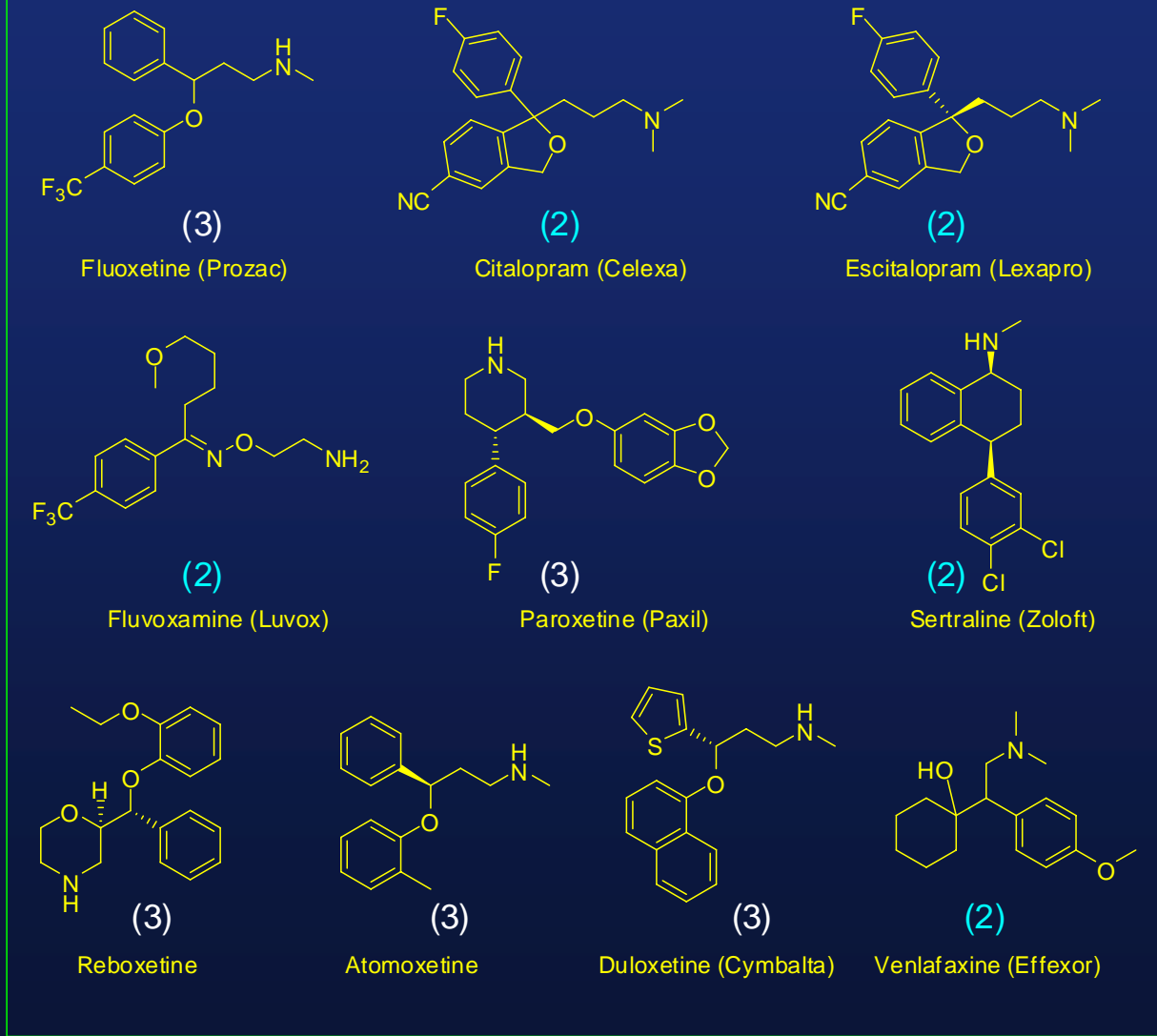
The Privileged Structures



Privileged Structure 2

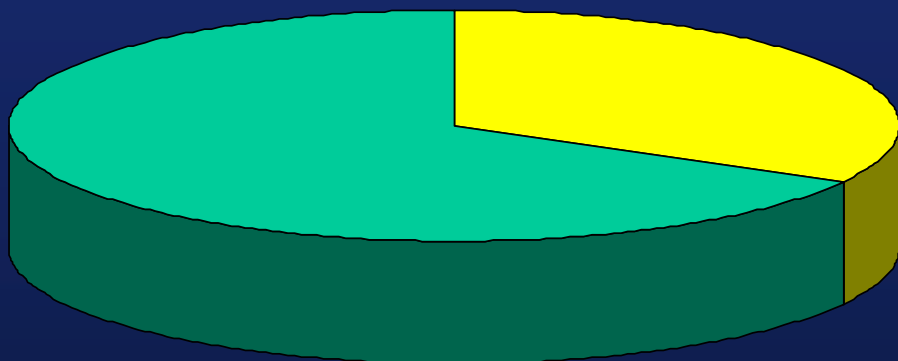


Privileged Structure 3



Depression - Therapeutic Need

33% of the general public are affected by depression at some point in their lives



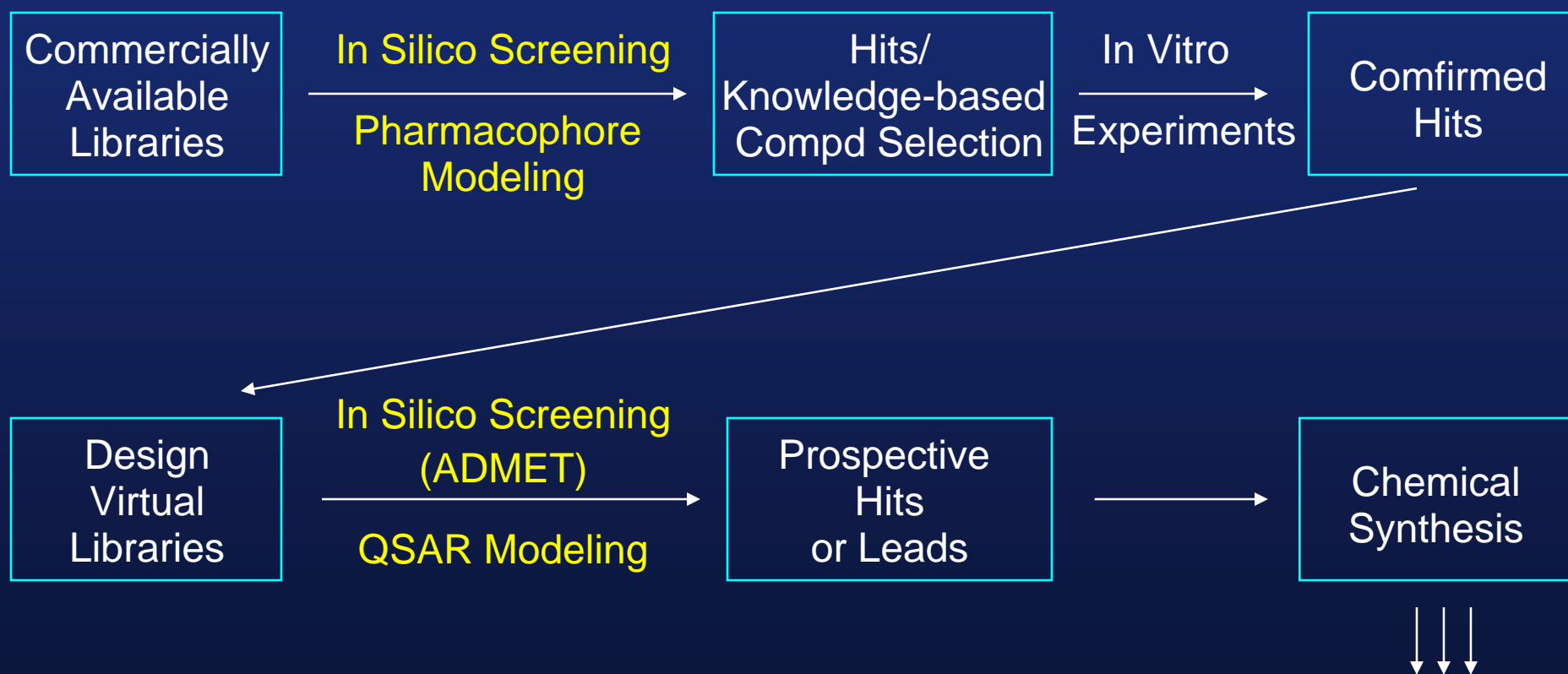
30-40% of those diagnosed do not satisfactorily respond to antidepressant treatment

2-8 week delayed onset of action

➔ Need new inhibitors with structural diversity and different pharmacology profiles

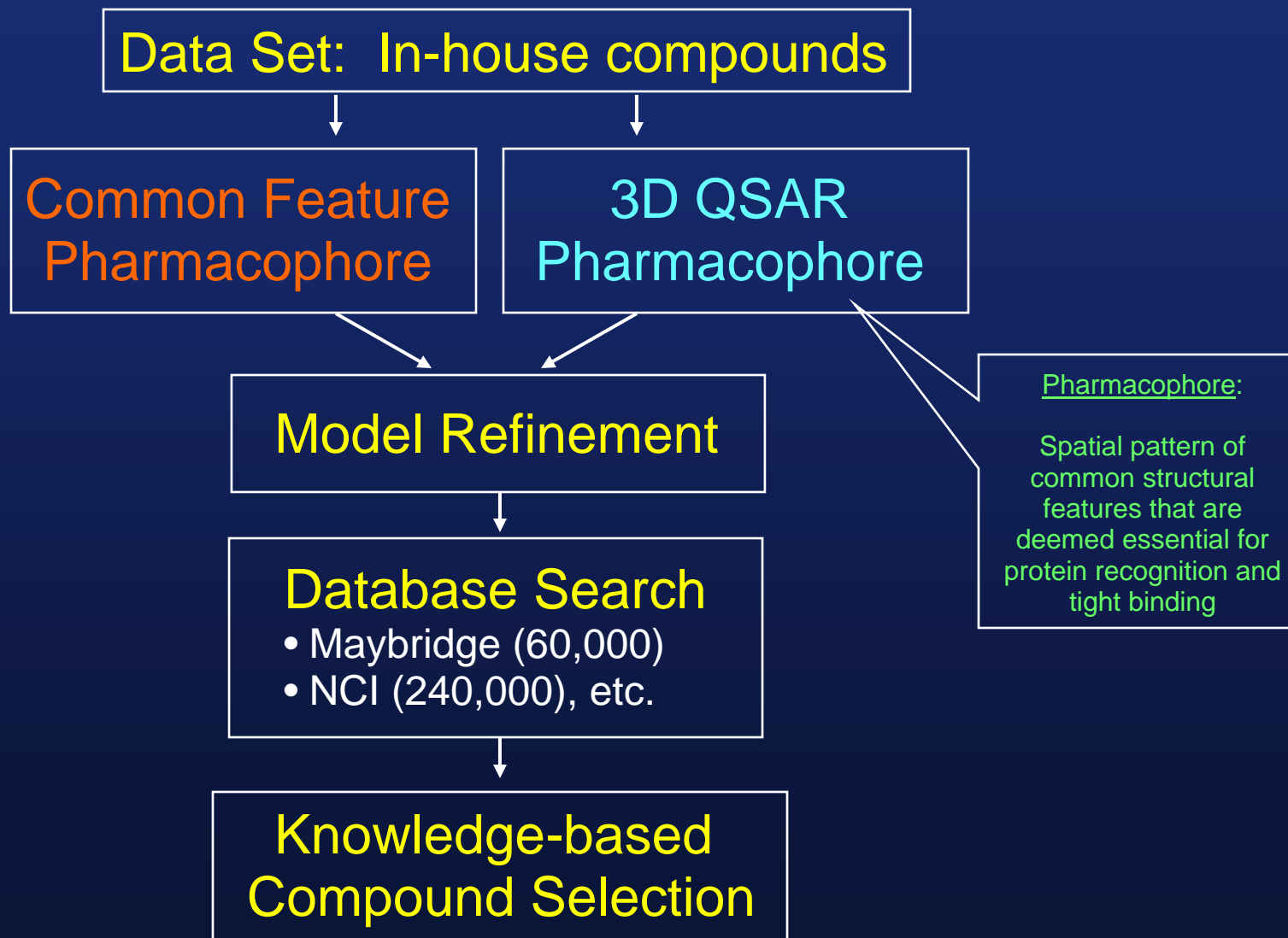
Knowledge-Based Lead Generation

- Strategies for new lead generation:

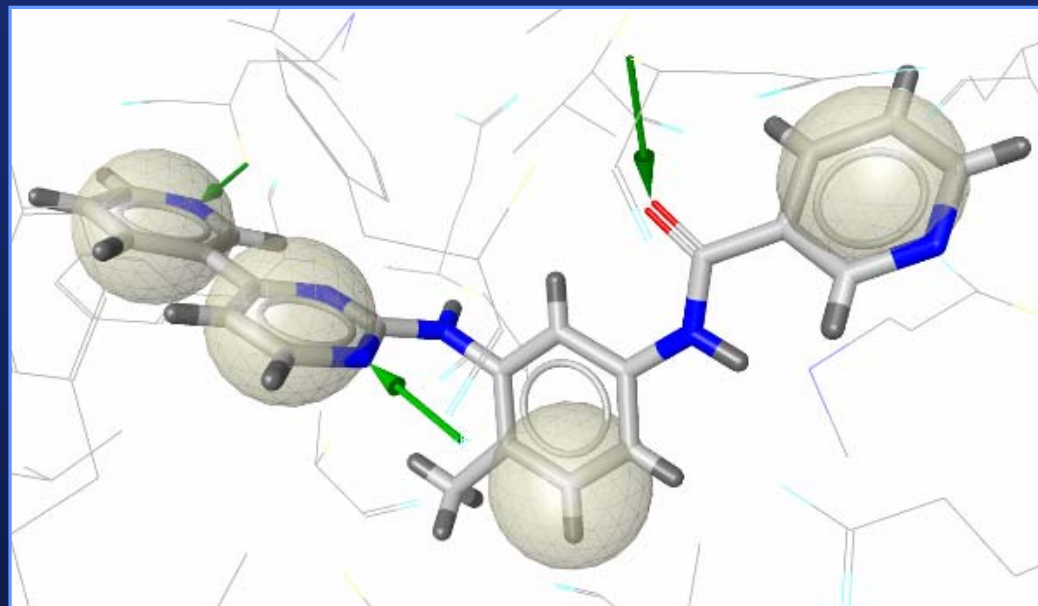


- Enhance our intelligent drug design platform
- Initial focus will be on the new chemotypes

Knowledge-Based Lead Generation



Pharmacophore Elucidation for Transporter Program



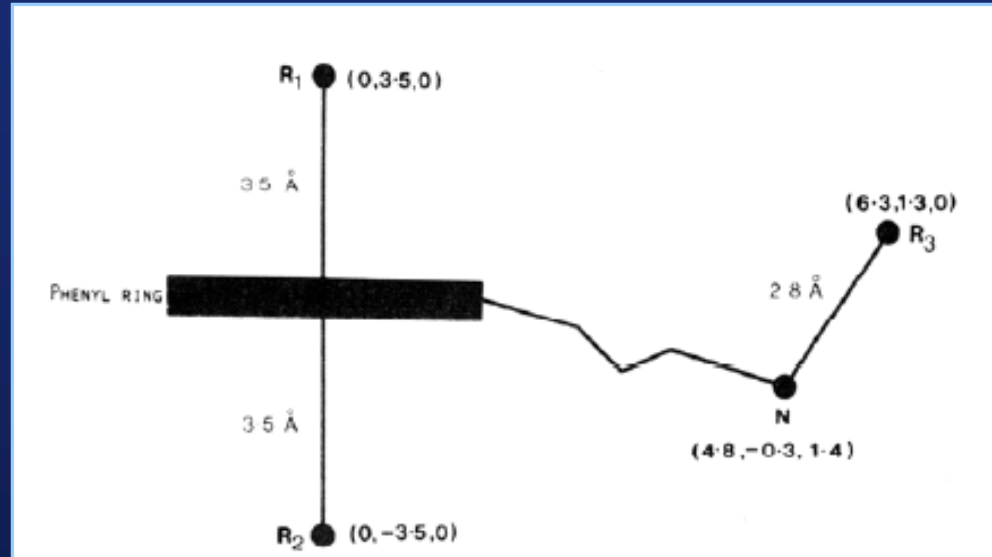
“A molecular framework that carries the essential features responsible for a drug’s biological activity”

- Paul Ehrlich 1909

CNS Drugs

Dataset:

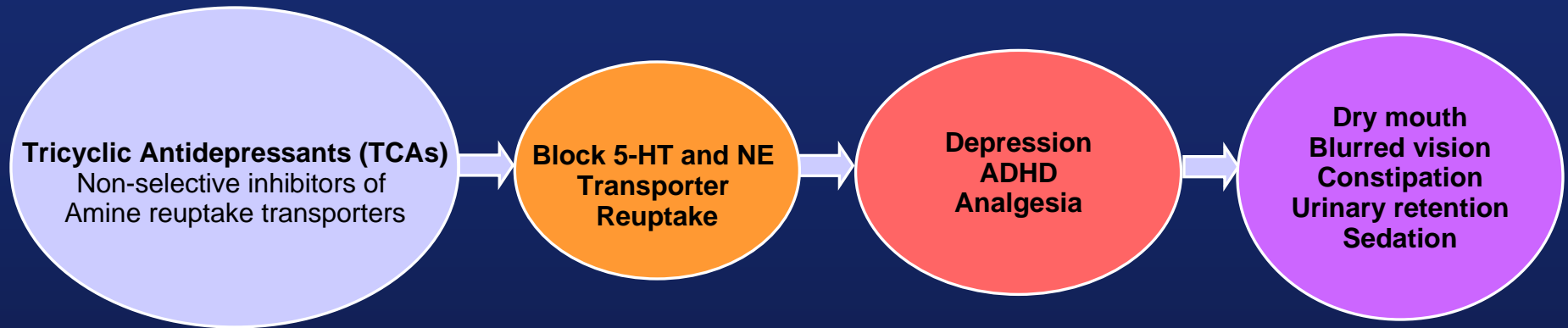
- Morphine
- Strychnine
- LSD
- Apomorphine
- Mianserin
- Phenobarbitone
- Clonidine
- Diazepam
- Bicuculline
- Diphenylhydantoin
- Amphetamine
- Imipramine
- Chlorpromazine
- Procyclidine



Key Features:

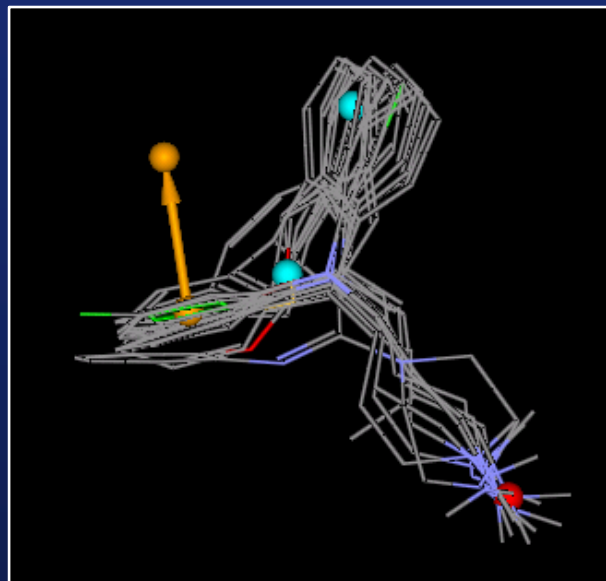
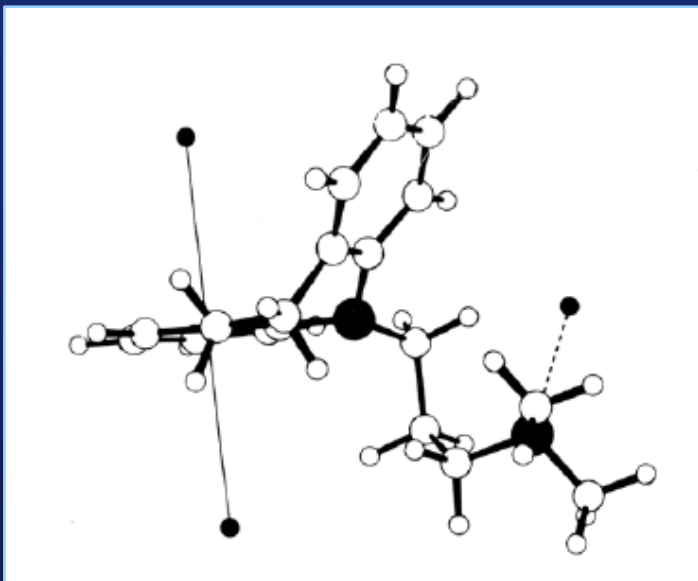
- 1) Phenyl Ring
- 2) Nitrogen Atom
- 3) 5.0 Angstrom Distance

TCA - Tricyclic Antidepressant



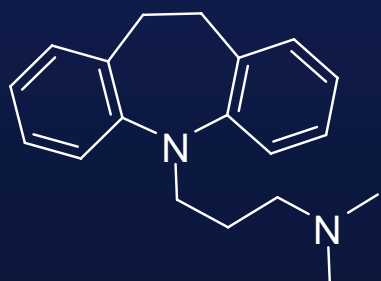
-  Antidepressant type
-  Affinities
-  Clinical Use
-  Side effects

TCA - Tricyclic Antidepressant



Dataset:

- Amitriptyline
- Amoxapine
- Clomipramine
- Desipramine
- Dothiepin
- Imipramine
- Maprotiline
- Nortriptyline
- Protriptyline
- Trimipramine

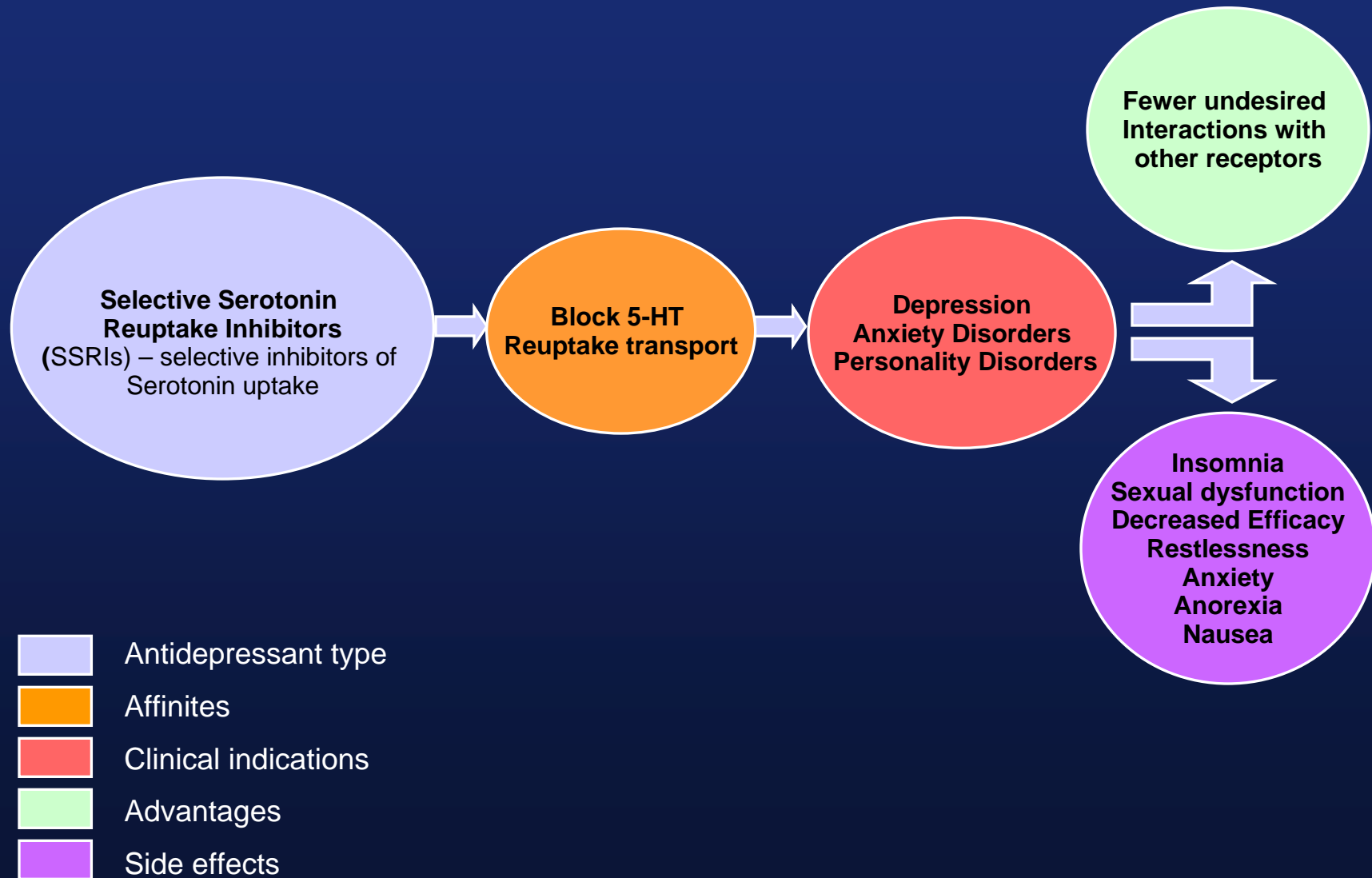


Imipramine

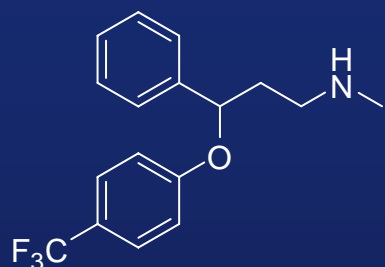
Key Features:

- Phenyl Ring
- Basic Nitrogen
- 2 Hydrophobic Regions

SSRI - Selective Serotonin Reuptake Inhibitor



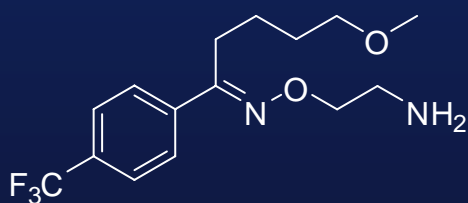
SSRI - Selective Serotonin Reuptake Inhibitor



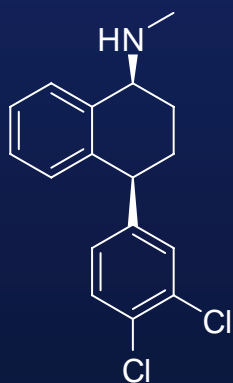
Fluoxetine (Prozac)



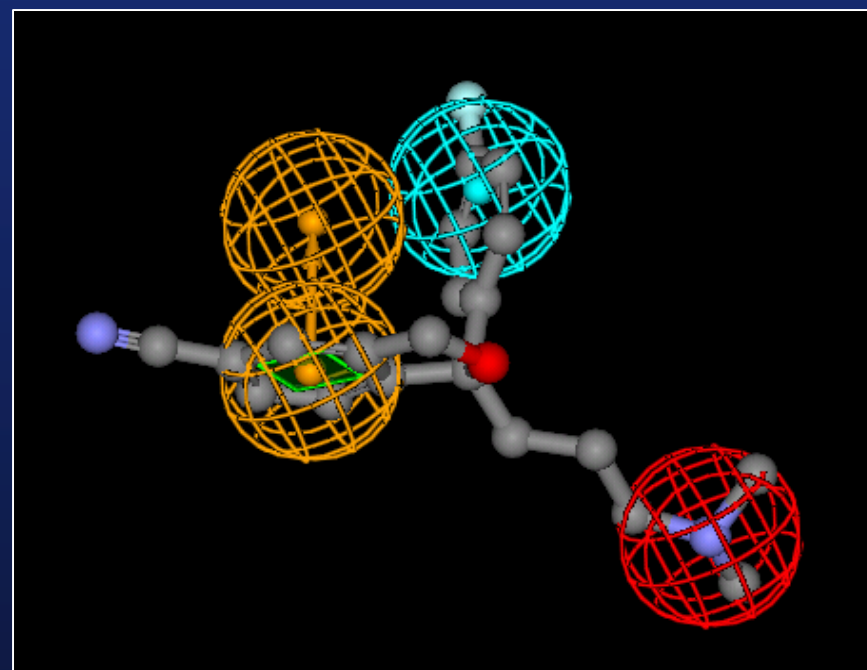
Citalopram (Celexa)



Fluvoxamine (Luvox)

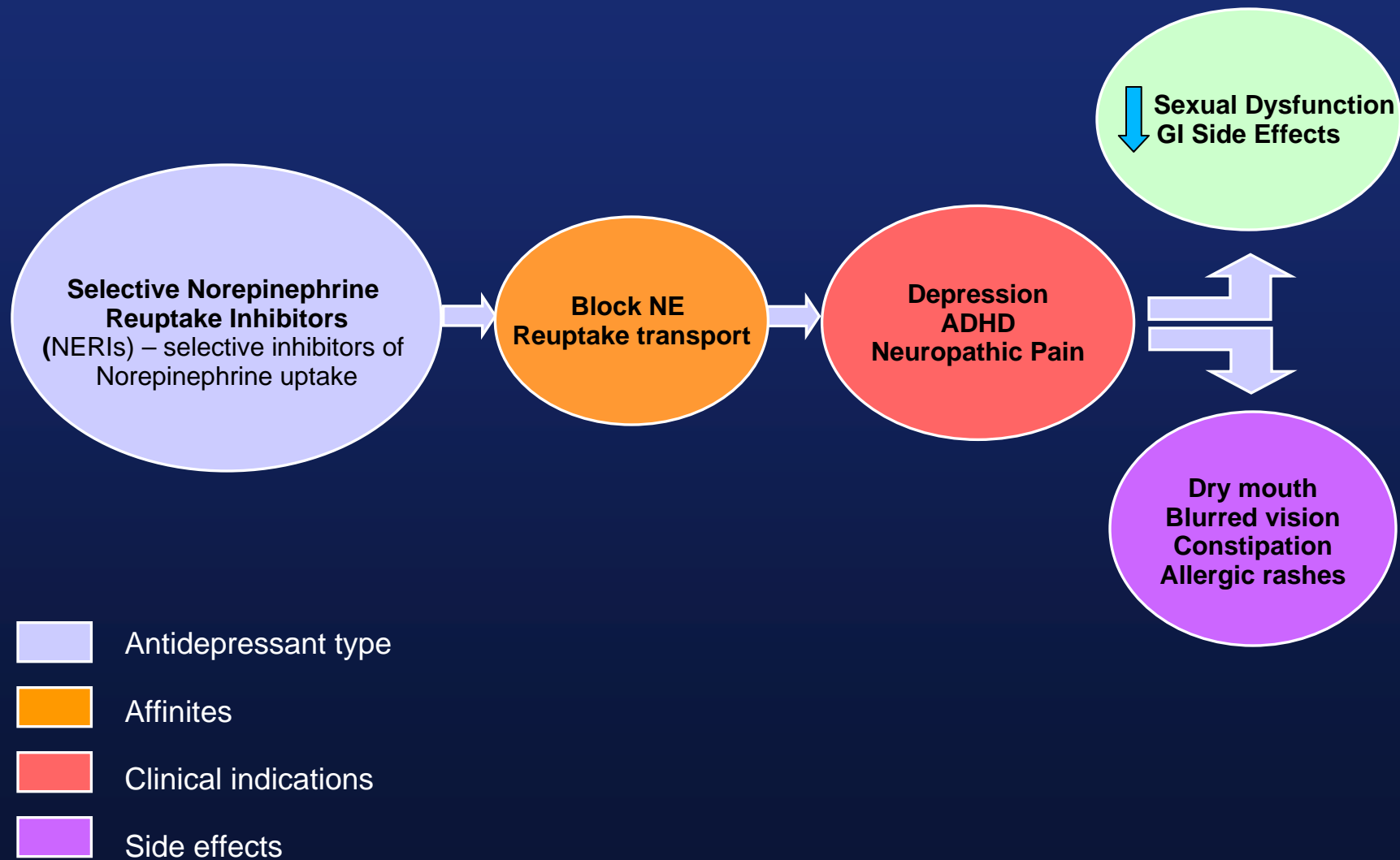


Sertraline (Zoloft)

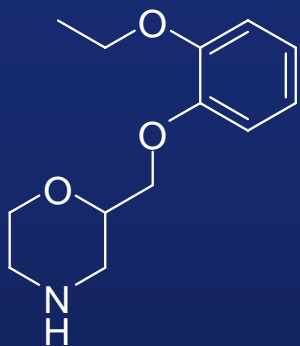


-  Hydrophobic Region
-  Positive Ionizable Region
-  Aromatic Ring

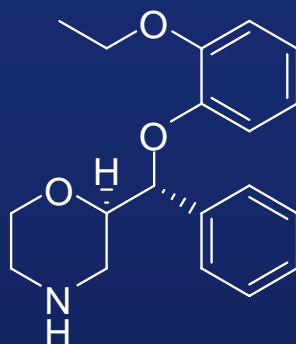
NERI - Selective Norepinephrine Reuptake Inhibitor



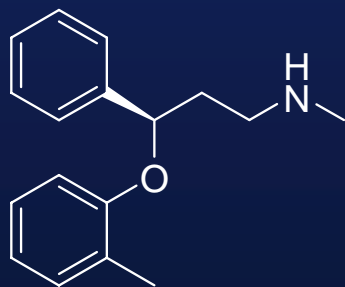
NERI - Selective Norepinephrine Reuptake Inhibitor



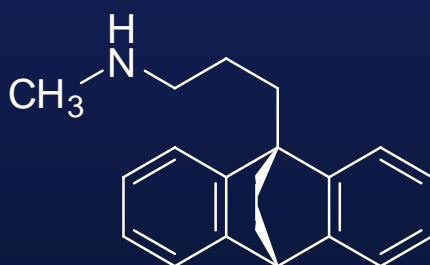
Viloxazine



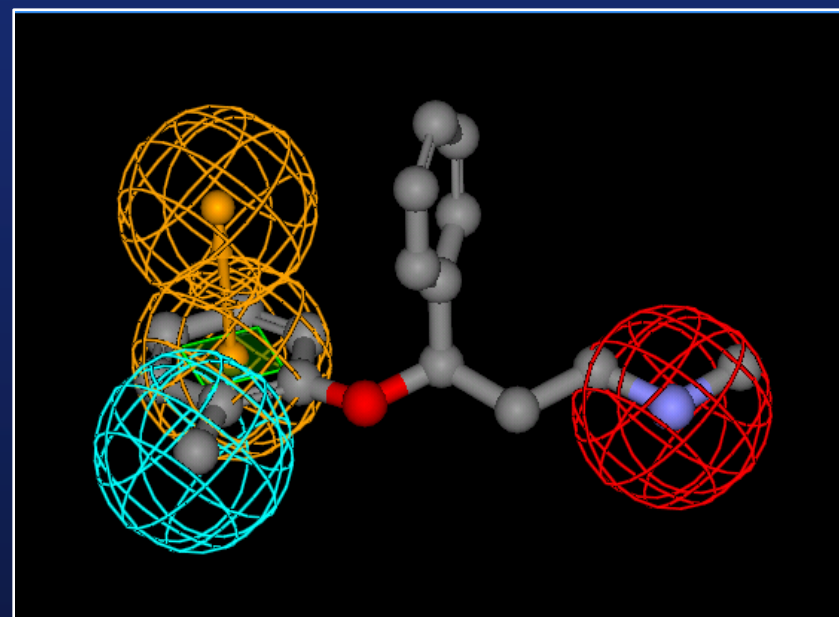
Reboxetine



Atomoxetine

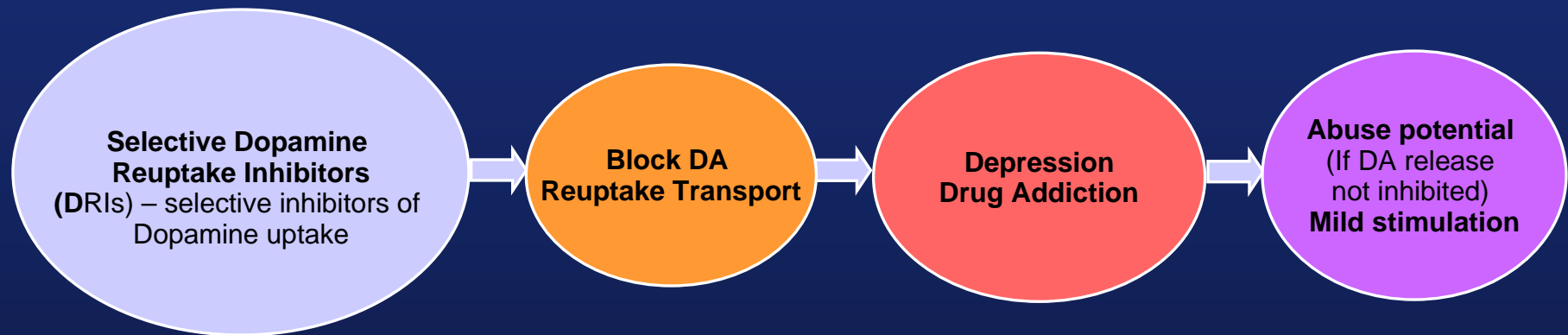


Maprotiline



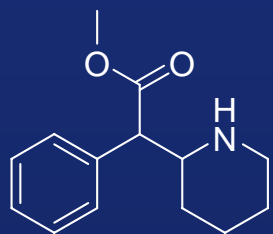
- Hydrophobic Region
- Positive Ionizable Region
- Aromatic Ring

DRI - Selective Dopamine Reuptake Inhibitor

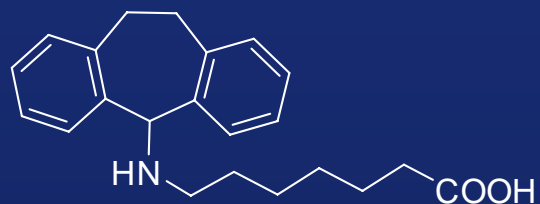


-  Antidepressant type
-  Affinites
-  Clinical indications
-  Side effects

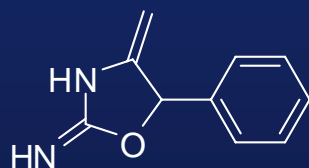
DRI - Selective Dopamine Reuptake Inhibitor



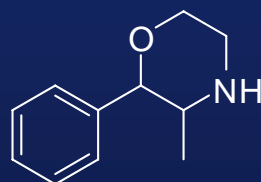
Methylphenidate



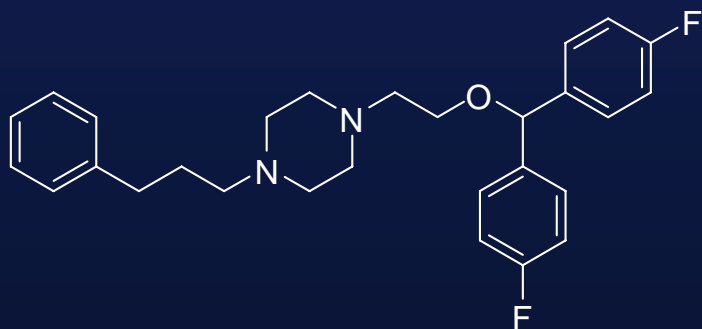
Amineptine



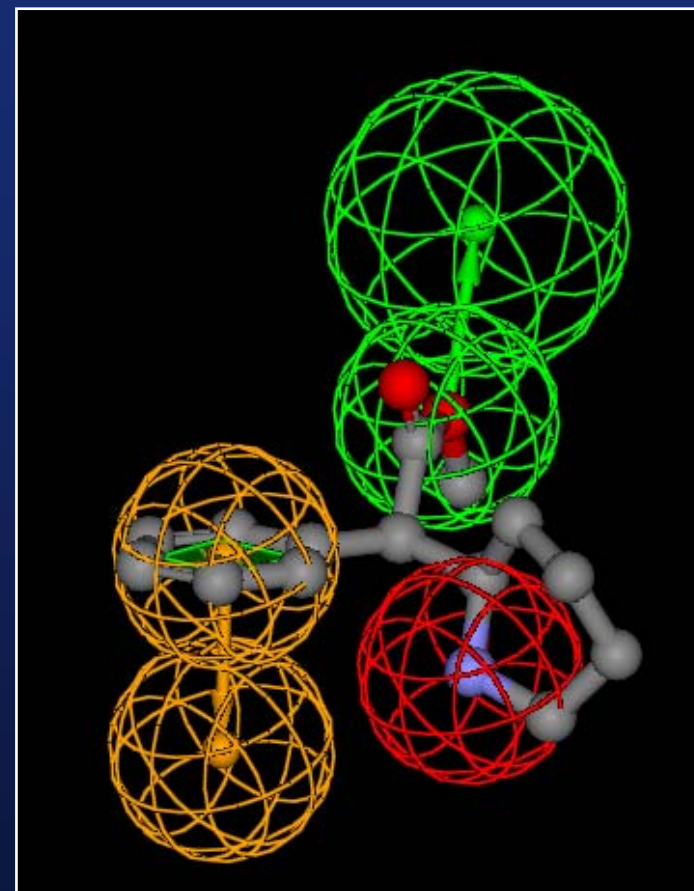
Pemoline



Phenmetrazine

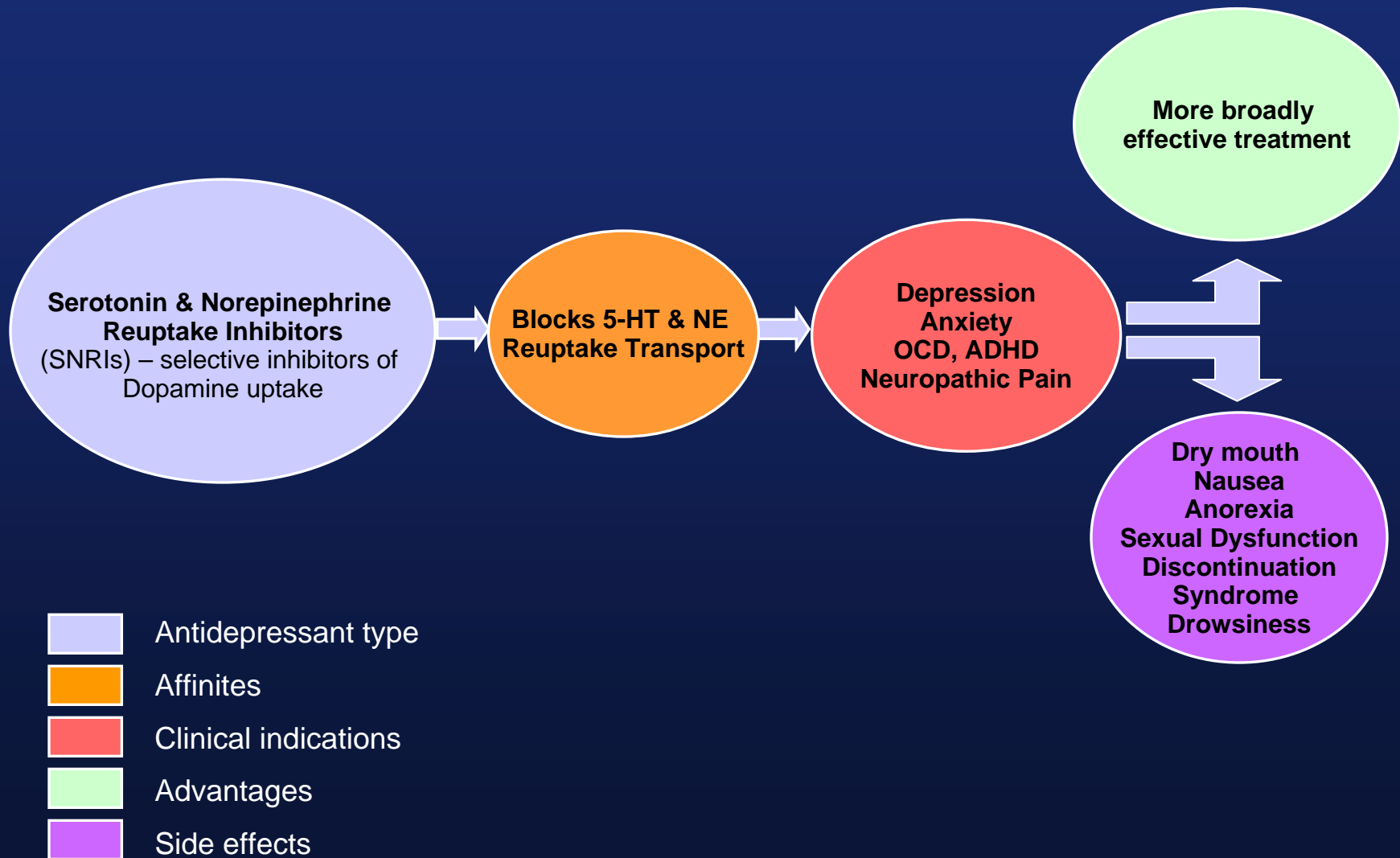


Vanoxerine

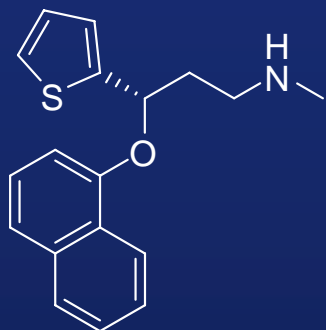


- Hydrogen Bond Acceptor
- Positive Ionizable Region
- Aromatic Ring

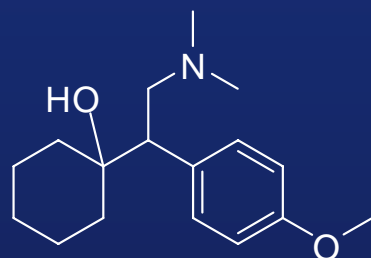
SNRI - Serotonin Norepinephrine Reuptake Inhibitor



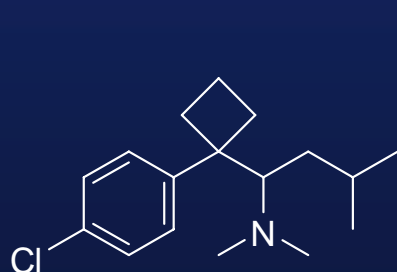
SNRI - Serotonin Norepinephrine Reuptake Inhibitor



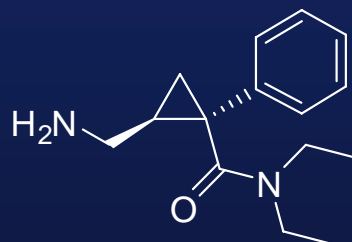
Duloxetine (Cymbalta)



Venlafaxine (Effexor)

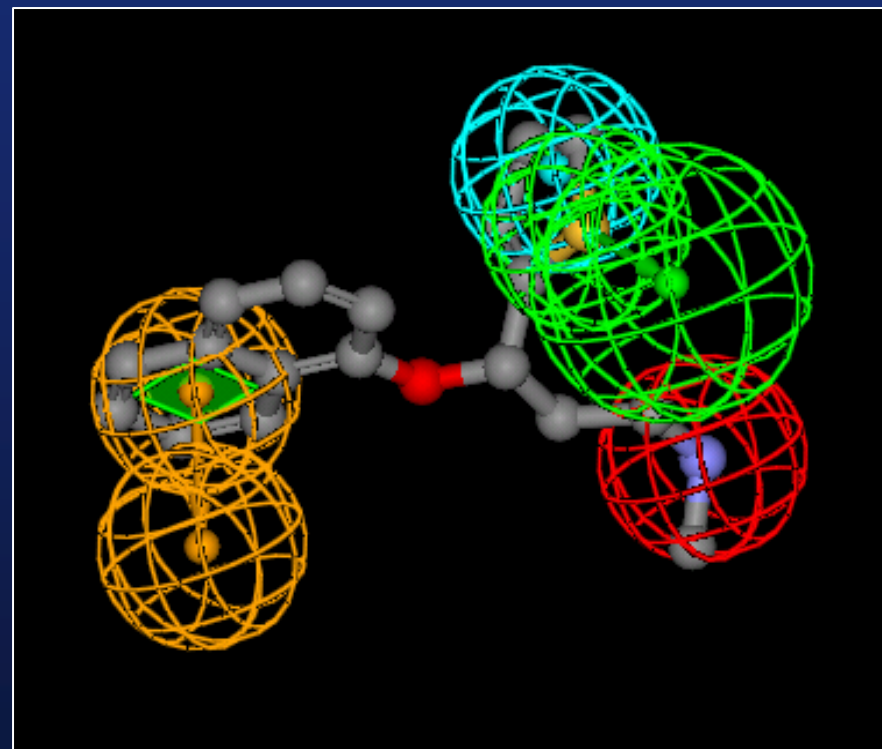






Sibutramine (Meridia)



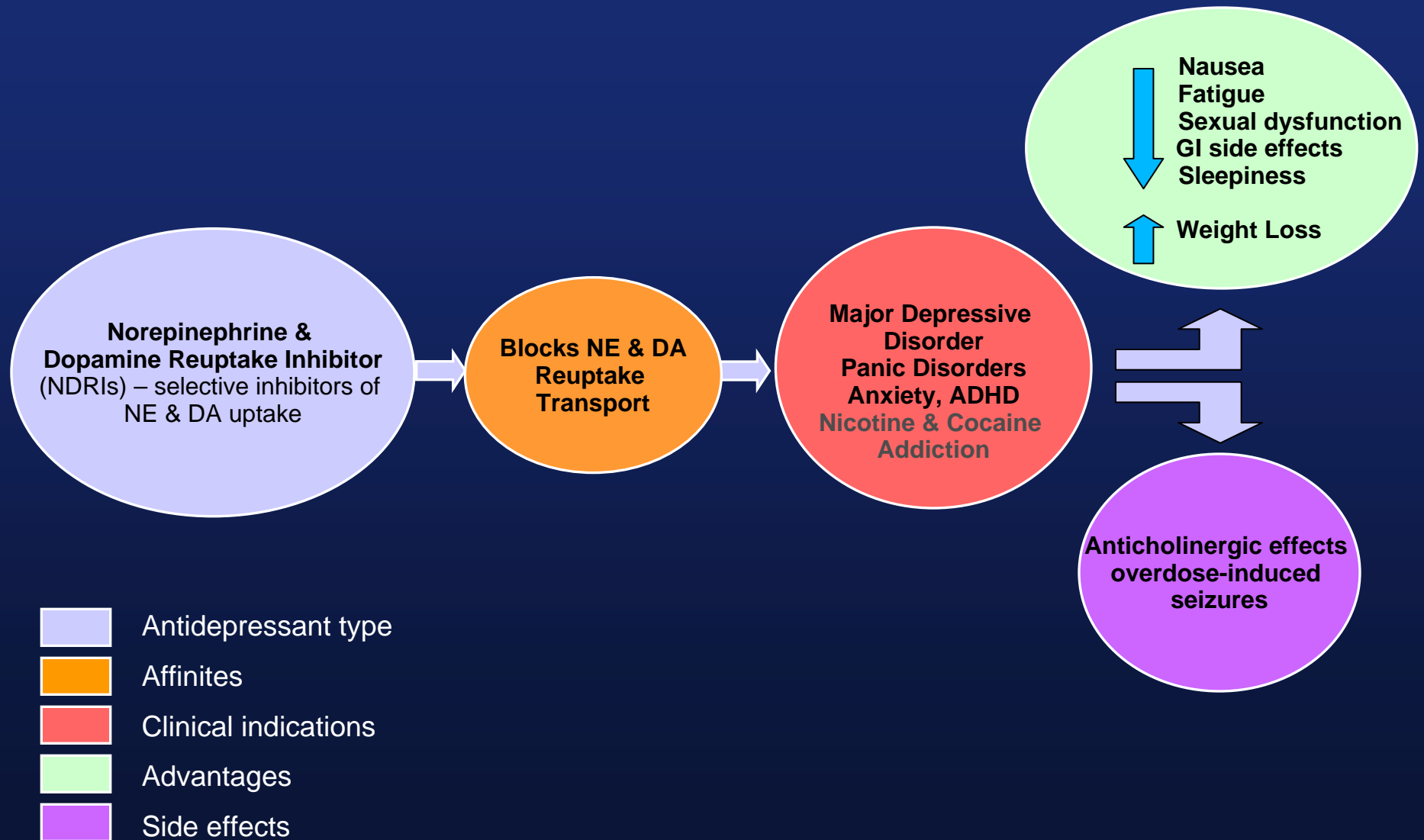
Milnacipran (Dalcipran/Ixel)

Duloxetine

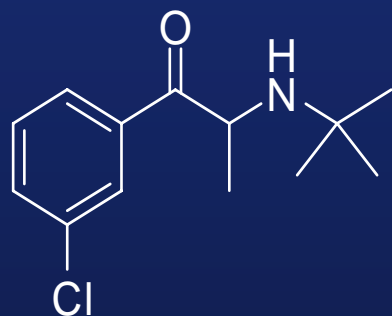


-  Hydrophobic Region
-  Hydrogen Bond Acceptor
-  Positive Ionizable Region
-  Aromatic Ring

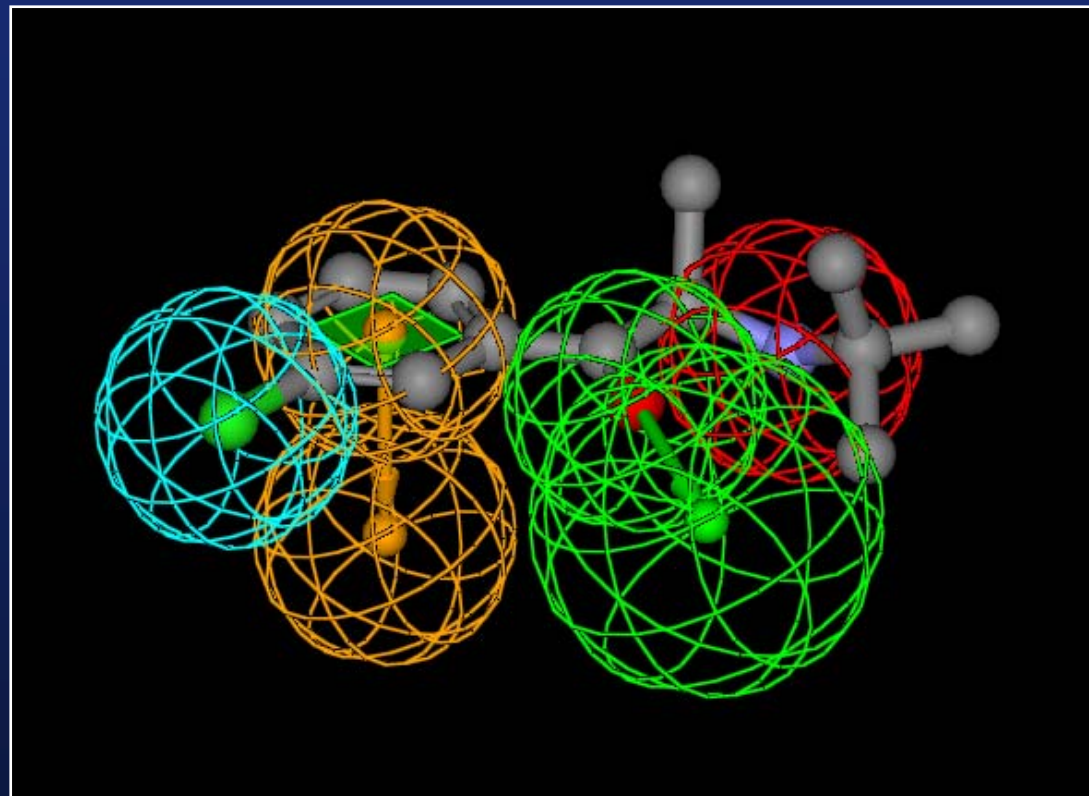
NDRI - Norepinephrine and Dopamine Reuptake Inhibitor







NDRI - Norepinephrine and Dopamine Reuptake Inhibitor



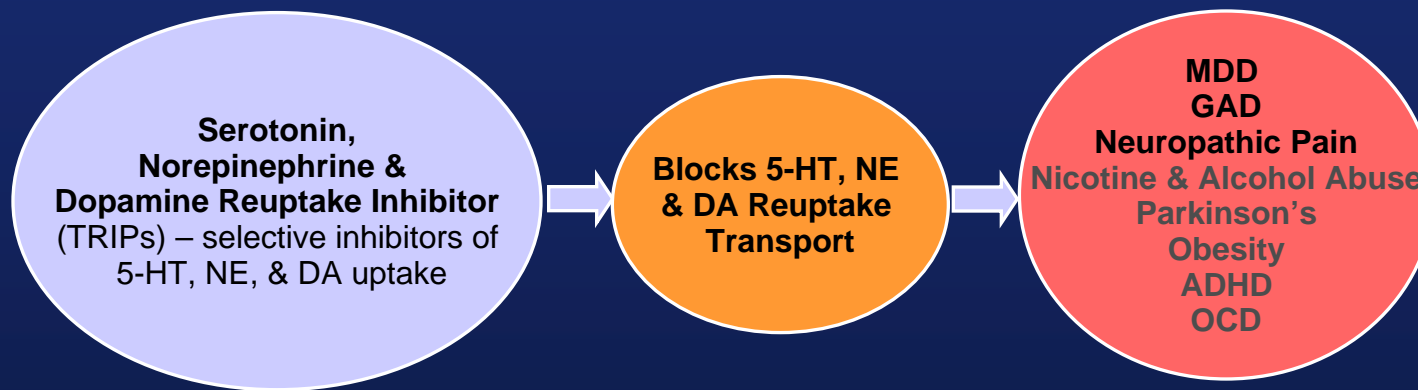
Bupropion (Wellbutrin)






-  Hydrophobic Region
-  Hydrogen Bond Acceptor
-  Positive Ionizable Region
-  Aromatic Ring

TRIP

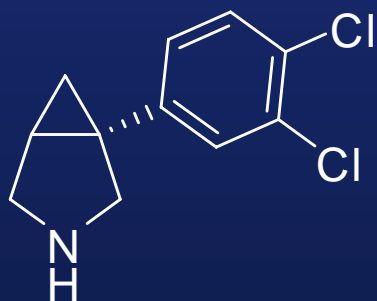
Serotonin, Norepinephrine and Dopamine Reuptake Inhibitor



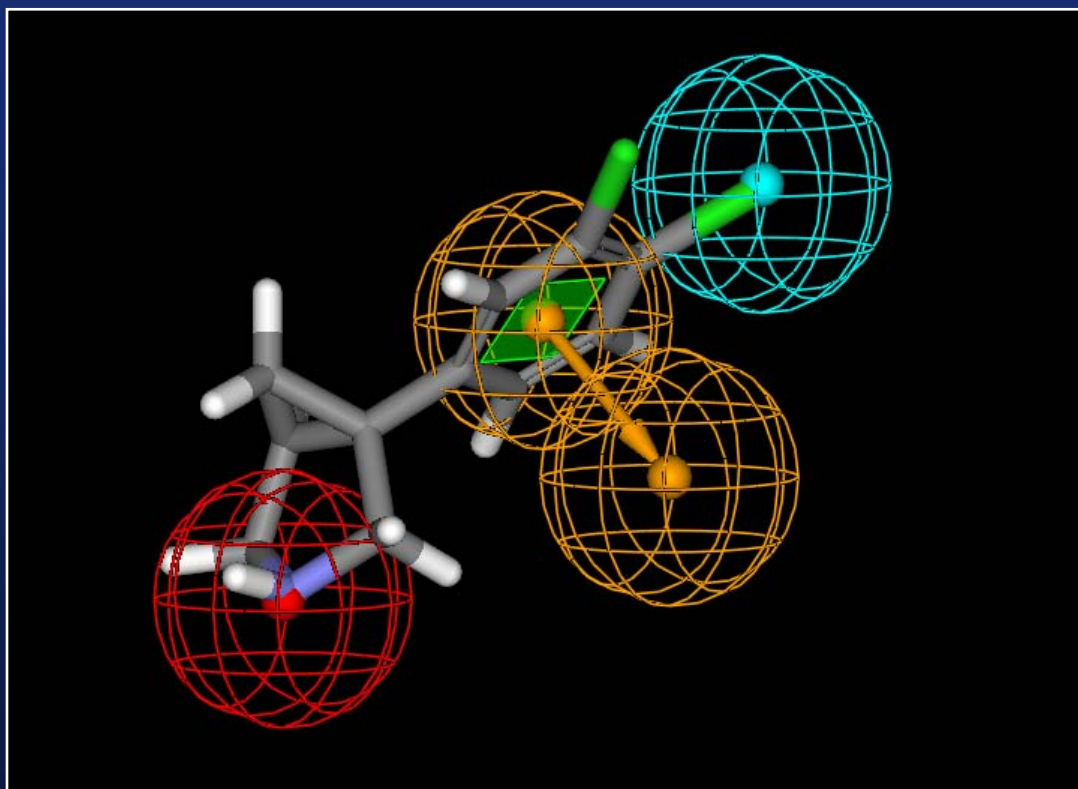
-  Antidepressant type
-  Affinities
-  Clinical indications

TRIP

Serotonin, Norepinephrine and Dopamine Reuptake Inhibitor



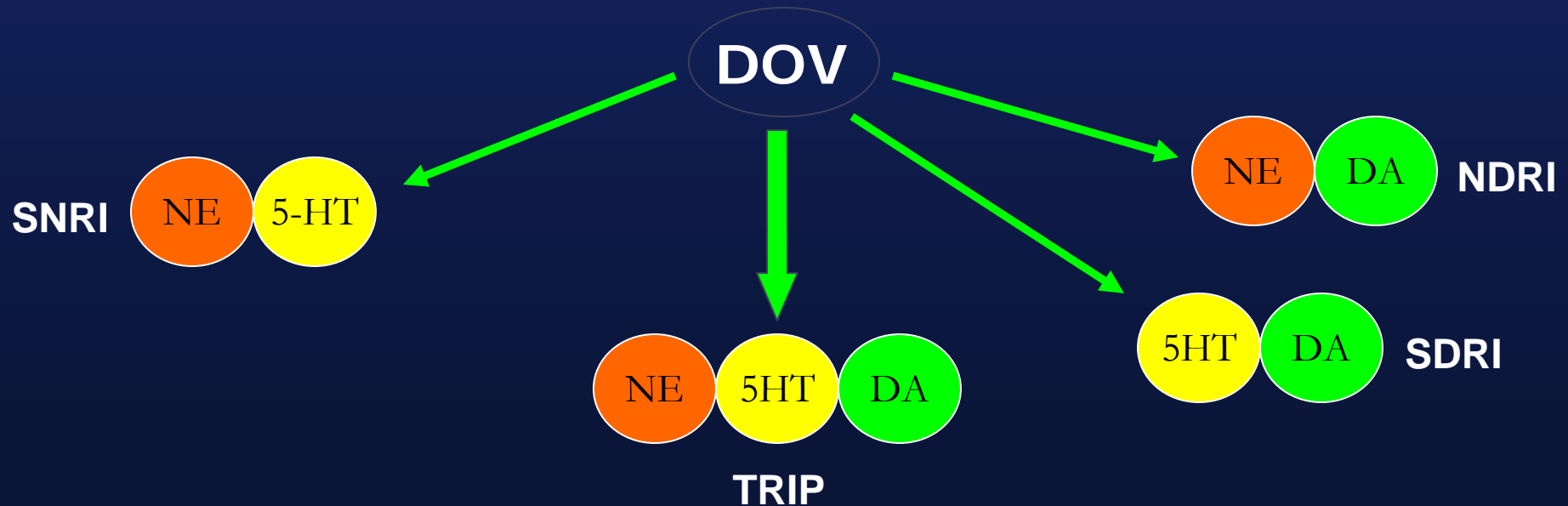
DOV 21,947



-  Hydrophobic Region
-  Positive Ionizable Region
-  Aromatic Ring

Therapeutic Versatility of Uptake Inhibitors

	MDD	GAD	Pain	Alcohol Abuse	PMDD	Phobia	Smoking	ADHD	Obesity
NE	X	X	X	X		X	X	X	X
5-HT	X	X	X	X	X	X			X
DA	X		X	X	X		X	X	X

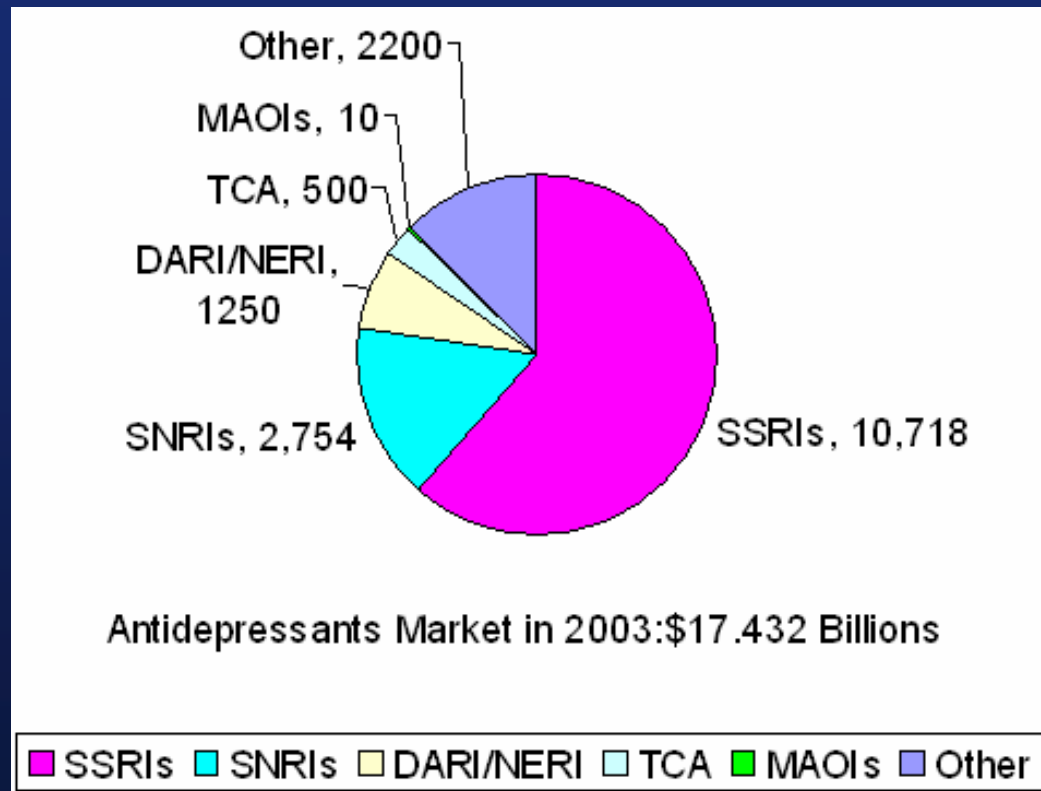


Program Status

Product	Mechanism of Action	Lead Identification	Lead Optimization	Candidate Selection	IND Activity	Phase 1	Phase 2
DOV 21,947	TRIP	Depression					
DOV 102,677	TRIP	Alcoholism (alcoholism+comorbid depression)					
DOV DC	TRIP	Depression, Obesity, Pain					
DOV DC	NED	ADHD, Pain					
DOV DC	SAD	Depression, SA, PMDD					
DOV DC	SNRI	Pain, Depression					
DOV DC	GABA _A R Modulator	Anxiety, Epilepsy, Insomnia					

The Antidepressant Drug Market

(Bear Market Prediction)



Top10 Antidepressants in 2005

Drug Name	Patent Expiration Date
Fluoxetine	Expired
Paroxetine	Expired
Bupropion	Expired
Citalopram	Expired
Sertraline	Expired
Paxil CR	2009
Wellbutrin XL	2018
Cymbalta	2008
Lexapro	2009
Effexor XR	2008

- The world market for antidepressants will decline to yield a revenues of **\$ 7 billions in 2010** due to the patent expirations.

Acknowledgement

- Drs. Skolnick, Koustova, Basile, Yang, Krieter, Tizanno, Epstein, and many more....

Thank You!