Psychiatric Pearls:
An Overview of Medications and Treatment Options for Managing Depression when Initial Treatment in Adults isn't Working Well

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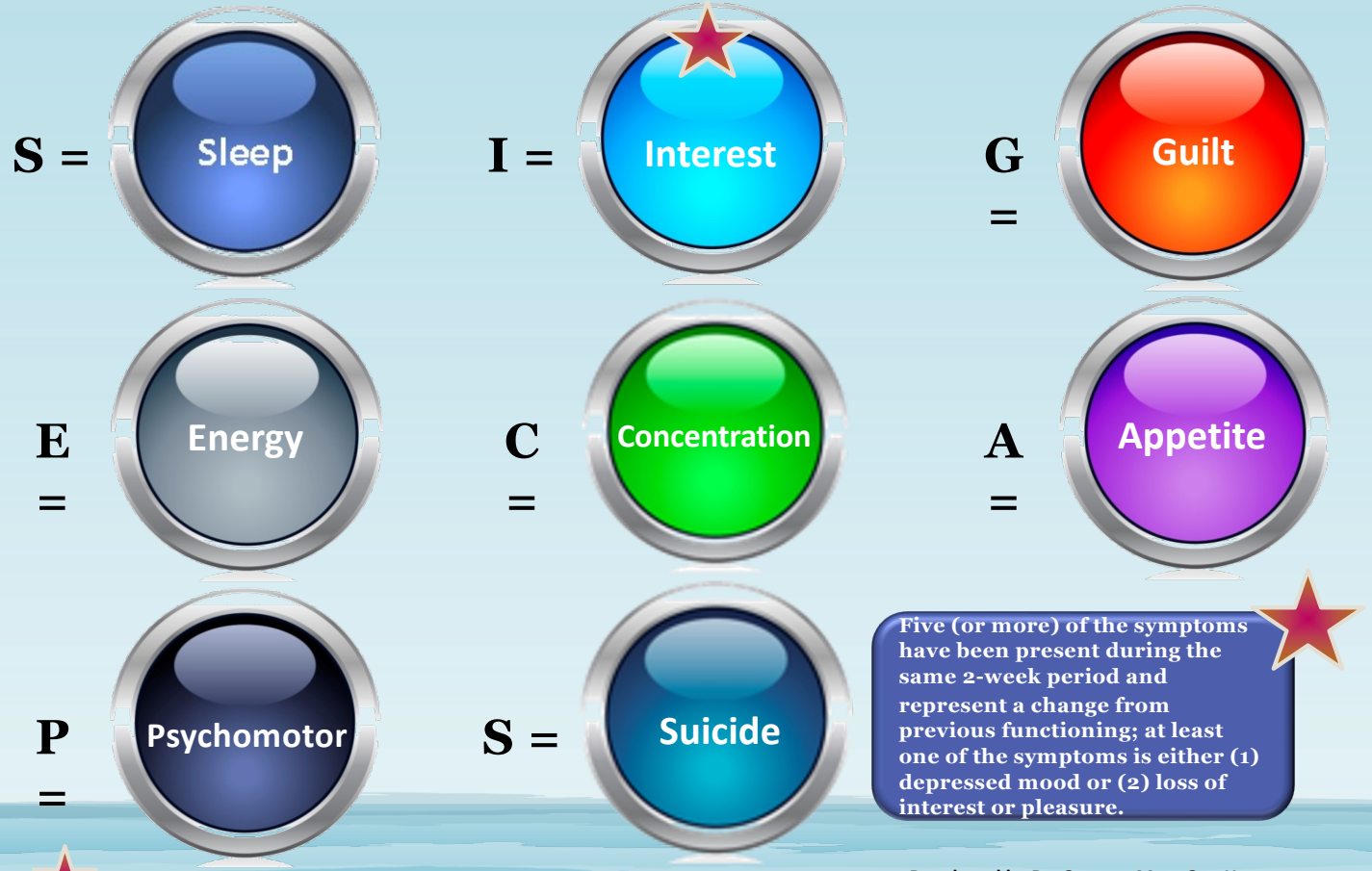
Objectives

- Have a better understanding of the importance of accurately diagnosing major depressive disorder (MDD), with the mention of the PHQ-9
- Have a better understanding of patient and treatment factors in selecting initial pharmacotherapy for patients with MDD
- Understand various therapeutic approaches for patients with non-response and incomplete response to initial antidepressant
- At the conclusion of this presentation, participants will enhance their ability to proficiently navigate and adjust antidepressant strategies following an initial treatment that proves ineffective, thereby demonstrating improved competency in managing cases of inadequate response to the first drug treatment.

Depression

A QUICK OVERVIEW

Approaches to Diagnosis - SIG: E CAPS



Developed by Dr. Gross at Mass Gen Hosp;
Carlat. *Am Fam Physician* 1998;58:1617-24

Helping recognize depressive disorders: Quick Screen

If a physician is considering the possibility of depression, use the quick "2-Question Screen":

"In the past month, have you been bothered by little interest or pleasure in doing things?"
"In the last month, have you been feeling down, depressed or hopeless?"

An answer of 'yes' to either question requires a more detailed assessment and consideration of other possible causes of depressive symptoms.

Arroll B, et al. *BMJ* 2003; 327(7424): 1144-6.

Patient Health Questionnaire 9 (PHQ-9)

Over the past 2 weeks, how often have you been bothered by any of the following problems?	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed or hopeless	0	1	2	3
3. Trouble falling asleep, staying asleep, os sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself – or that you're a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking slowly that other people could have noticed. Or, the opposite – being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or hurting yourself in some way	0	1	2	3
ADD COLUMNS				
TOTAL SCORE				
10. If you checked off any problems, how difficult have those problems made it for you to do your work, take care of things at home, or get along with other people				
□ Not difficult at all □ Somewhat difficult □ Very difficult □ Extremely difficult				

Download: PHQ-9 at www.depression-primarycare.org.
Centre for Quality Assessment and Improvement in Mental Health. *The Patient Health Questionnaire (PHQ-9) – Overview*. Available at: http://www.cqaimh.org/pdf/tool_phq9.pdf. Accessed: November 11, 2013.

PHQ-9 Scoring

PHQ9 Score	Provisional Diagnosis	Treatment Recommendation
0 - 4	Not depressed	
5 - 9	Minimal symptoms*	Support, educate to call if worse, return in 1 month
10 - 14	Minor depression ++ Dysthymia* Major depression, mild	Support Antidepressant or psychotherapy Antidepressant or psychotherapy
15 - 19	Major depression, moderately severe	Antidepressant or psychotherapy
≥ 20	Major depression, severe	Antidepressant and psychotherapy (especially if not improved on monotherapy)

*** If symptoms present ≥ two years, then probable chronic depression that warrants antidepressants or psychotherapy**
(ask, "in the past 2 years have you felt depressed or sad most days, even if you felt okay sometimes?").
++ If symptoms present ≥ one month or severe functional impairment, consider active treatment.

The Patient Health Questionnaire (PHQ-9) – Overview. Available at: http://www.cqaimh.org/pdf/tool_phq9.pdf. Accessed 11 November, 2013.

What Outcome Are Patients Trying to Achieve? Remission: Patient Perspective

1. Absence of symptoms of depression
2. Presence of positive mental health
   - e.g. optimism, vigour, self-confidence
3. Feeling like your usual, normal self
4. Return to usual level of functioning at work, home, or school
5. Feeling in emotional control
6. Participating in, and enjoying, relationships with family and friends

Zimmerman et al. *Am J Psych* 2006;163:148-50

Multiple Mechanism of Action

- **Serotonin Transporter Blockade**
  - SSRIs (i.e. fluoxetine, sertraline, escitalopram)
- **Serotonin/Norepinephrine Transporter Blockade**
  - SNRIs (venlafaxine, duloxetine)
- **Norepinephrine Transporter Blockade**
  - Nortriptyline, atomoxetine
- **Receptor Effects**
  - Aripiprazole (partial D2 agonism, partial agonism 5HT1A, antagonism 5HT2A)
  - Quetiapine (D2 antagonism, antagonism 5HT2A, blockade of NE transporter by metabolite)
  - Mirtazepine (alpha 2 presynaptic blockade, blocks 5HT2A, 5HT2C and 5HT3)
  - Moclobemide (blocks MAO-A)
  - Bupropion (NE and DA transporter blockade)
  - Trazodone (5HT2A receptor antagonism, weak 5HT transporter blockade)
  - Fluoxetine (5HT2C antagonism, 5HT transporter blockade)

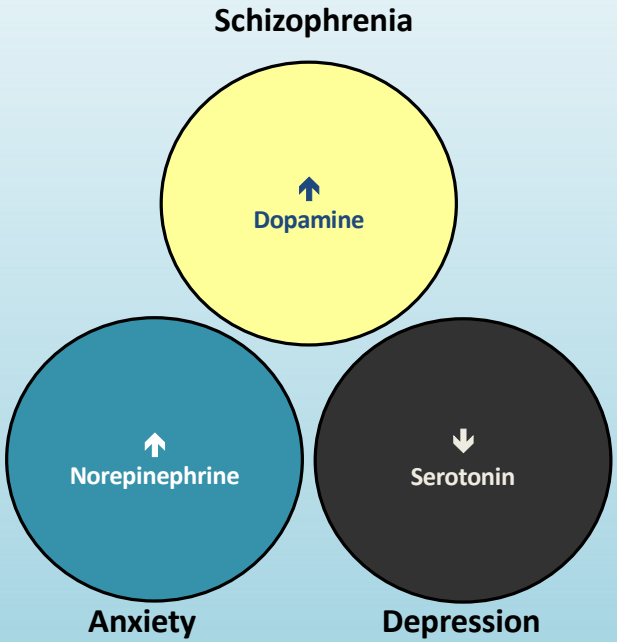
NE – Norepinephrine
DA – Dopamine
5HT – Serotonin

Note: The mode of action of bupropion remains somewhat unclear. Not all suspected modes of action are included here

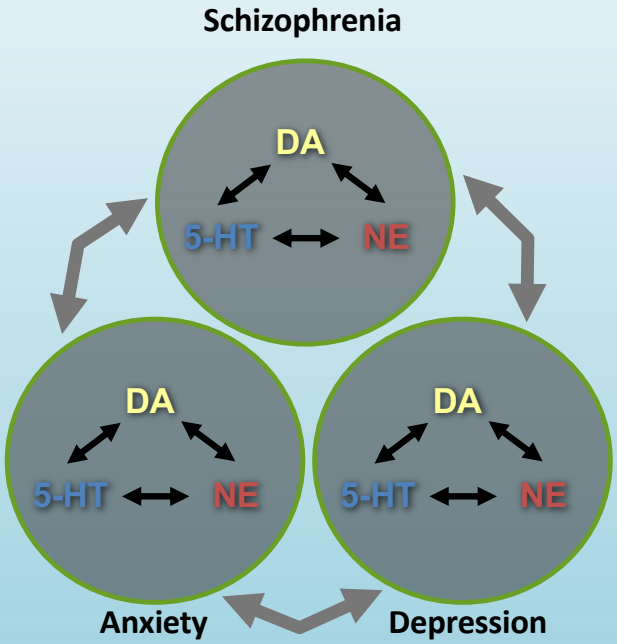
Stahl, S., Essential Psychopharmacology: The Prescriber's Guide, 2005

Complex Alterations in Neurotransmitter Levels in Psychiatric Disorders

Traditional concept



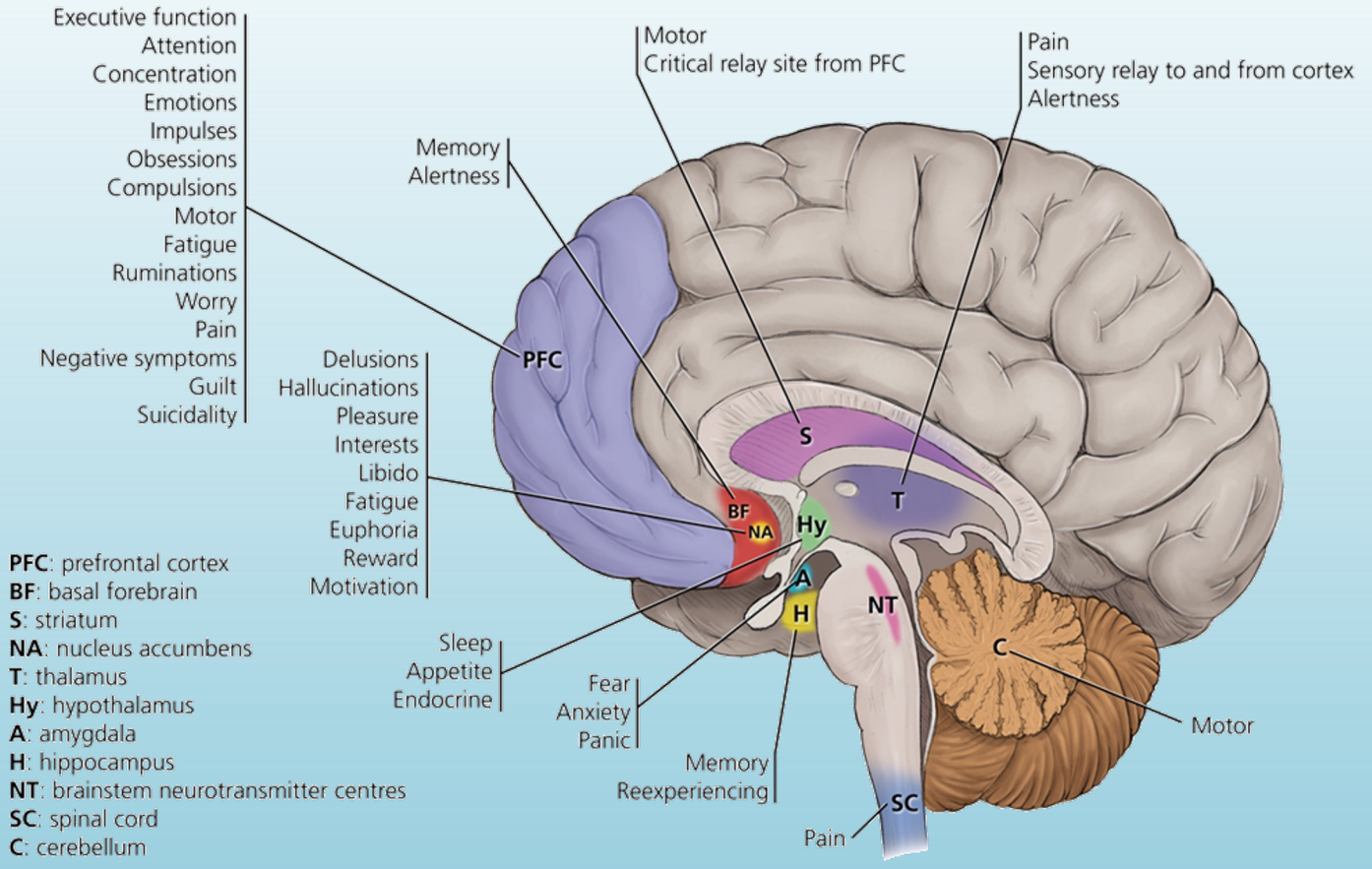
Modern concept



5-HT :serotonin; NE: norepinephrine; DA: dopamine

Adpated from Millan. *Eur J Pharmacol* 2004;500:371-84

Key Behaviours Hypothetically Linked to Specific Brain Regions



Adapted from Stahl. *Essential Psychopharmacology* 2008, 3rd ed

The "Anatomy" of Depression: Linking Symptoms to the Brain

	Linking Symptoms to Neurotransmitters → 5HT, NE, DA	Potential Brain Regions Involved
	Depressed mood → 5HT, NE, DA	ii, xii
S	Sleep → 5HT, NE, DA	i, v, vi, vii
I	interest, apathy → NE, DA	i, vi, ix
G	guilt, worthlessness → 5HT	ii, xii
E	energy → NE, DA	i, vii, ix
C	concentration, function → NE, DA	iii
A	appetite, weight → 5HT	vi
P	psychomotor → 5HT, NE, DA	i, ix, x, xi
S	suicide → 5HT	ii, iv, xii

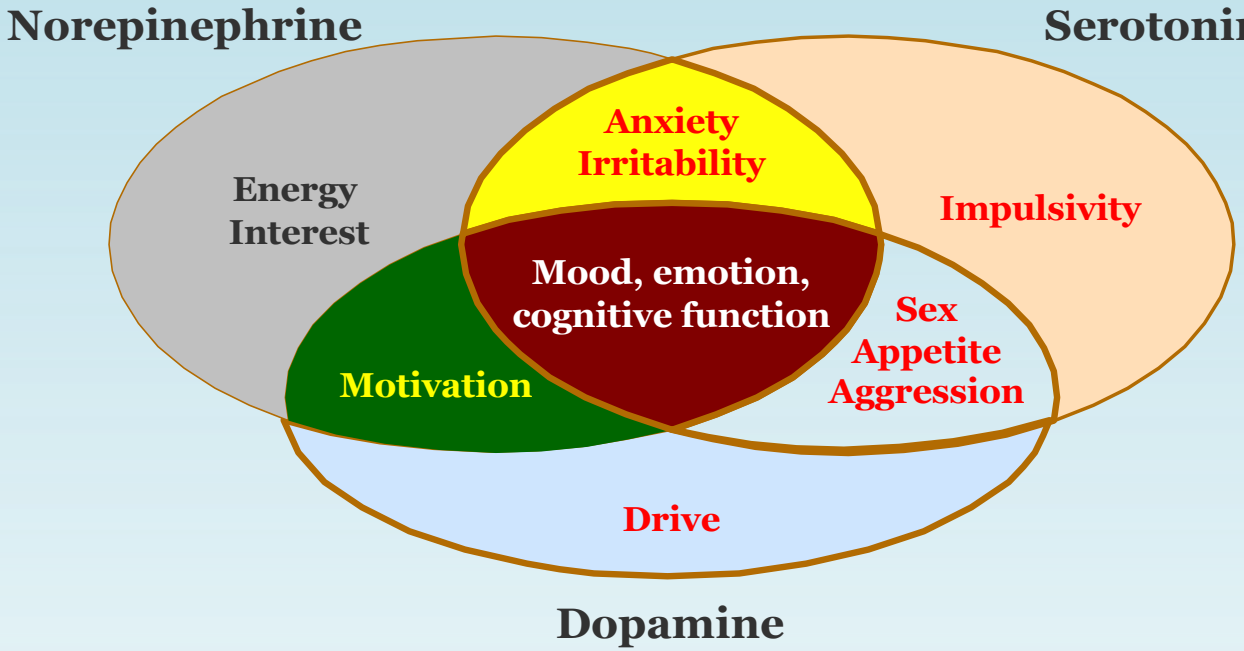
Continued Research Involving Brain Regions

i. Prefrontal Cortex (PFC)
ii. VentroMedial (VMPFC)
iii. DorsoLateral (DLPFC)
iv. Orbital (OFC)
v. Basal Forebrain (BF)
vi. Hypothalmus (Hy)
vii. Thalmus (Th)
viii. Spinal Cord (SC)
ix. Nucleus Accumbens (NA)
x. Striatum (S)
xi. Cerebellum (C)
xii. Amygdala (A)

Main Clinical Point: There is some evidence to support the fact that various brain regions and neurotransmitters may be responsible for the symptoms of depression.

Stahl. *Essential Psychopharmacology* 2008, 3rd ed

Neurotransmitters Involved in Regulating Mood



Adapted from Stahl SM. Essential Psychopharmacology: Neuroscientific Basis and Practical Applications. 2nd ed. Cambridge, UK: Cambridge University Press; 2000:152.

Summary Recommendations for Antidepressants

Kennedy et al CANMAT Guidelines 2016 CanJourPsychiatry 2016: vol 61, no 9;pp 540 -560

Factors to Consider in Selecting an Antidepressant

Patient Factors

- Clinical Features and dimensions
- Comorbid conditions
- Response and side effects during previous use of antidepressants
- Patient preference

Medication Factors

- Comparative efficacy
- Comparative tolerability (potential side effects)
- Potential interactions with other medications
- Simplicity of use
- Cost and availability

A Case for us to Consider

- Female, 52 yrs
- Prior MDD diagnosis, 5 years ago
  - Treated successfully with SSRI, discontinued after several years of treatment
- Divorced 6 months ago, father died 3 months ago
- Current symptoms
  - Depressed mood
  - Feelings of worthlessness
  - No interest in daily activities
- ***How would you proceed?***

Ten Simple Tips for Improving the Care of Patients with Depression

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Antidepressants: 5 first-line options

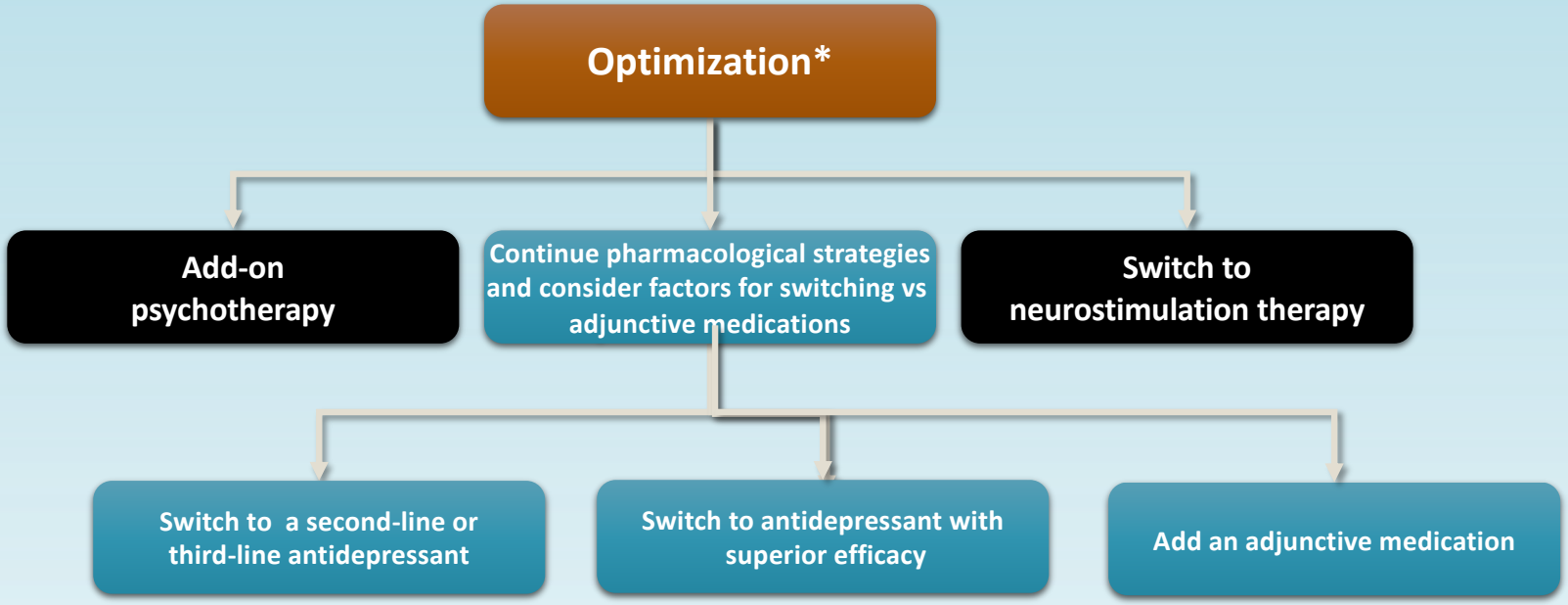
Drug	Start	Increase to	Advantages	Side effects / disadvantage
Sertraline	50mg OD	200mg OD	Good efficacy-tolerability balance, good for OCD	Nausea, sexual dysfunction
Escitalopram	10mg OD	20mg OD	Good efficacy-tolerability balance, good for OCD	Nausea, sexual dysfunction, May prolong QT interval
Vortioxetine	10mg OD	20mg OD	New, good experience so far	Nausea++
Fluoxetine	20mg OD	No point increasing	Safe in adolescents and young adults, less withdrawal effects	Nausea Drug-drug interactions (e.g. warfarine)
Bupropione	150mg	450mg	No sexual dysfunction, no weight gain, may shorten QC interval	Dry mouth, agitation; Not effective for OCD

Antidepressants: *5* good alternatives

Drug	Start	Increase to	Advantages	Side effects / disadvantage
Levomilnacipran	40mg OD	120mg OD	Good for fatigue, cognitive slowing	May increase hart rate and blood pressure
Desvenlafaxine	50mg OD	100mg OD	Easy to use, less withdrawal effects than venlafaxine	Nausea, weight gain
Clomipramine	25mg OD	150mg OD	Good for obsessive compulsive disorder	Dry mouth, constipation
Nortriptyline	25mg QH	125mg QH	Good for chronic pain, sleep, prevents migraine	Dry mouth, constipation
Moclobemide	150mg BD	300mg BD *450mg BD	Efficacy in atypical cases, easy to tolerate	May interact with tyramine-rich foods; requires wash-out from SSRI antidepressants

*off-label

Management Strategies After Inadequate Response



- Monitor outcomes and ensure compliance.
- Consider using PHQ-9

Kennedy et al CANMAT Guidelines 2016 CanJourPsychiatry 2016: vol 61, no 9;pp 540 -560

Antidepressants with Evidence for Superior Efficacy Based on Meta-Analysis

- Escitalopram (Level 1)
- Mirtazapine (Level 1)
- Sertraline (Level 1)
- Venlafaxine (Level 1)
- Agomelatine (Level 2)
- Citalopram (Level 2)

How to add-on treatments and what to add-on?

Recommendations for Adjunctive Medications for Nonresponse or Partial Response to an Antidepressant*

First Line	**Adjunctive Agent**	Aripiprazole 2-15mg Quetiapine 150-300mg Risperidone 1-3mg
		All these agents above have Level 1 evidence which is new since the 2009 CANMAT guidelines

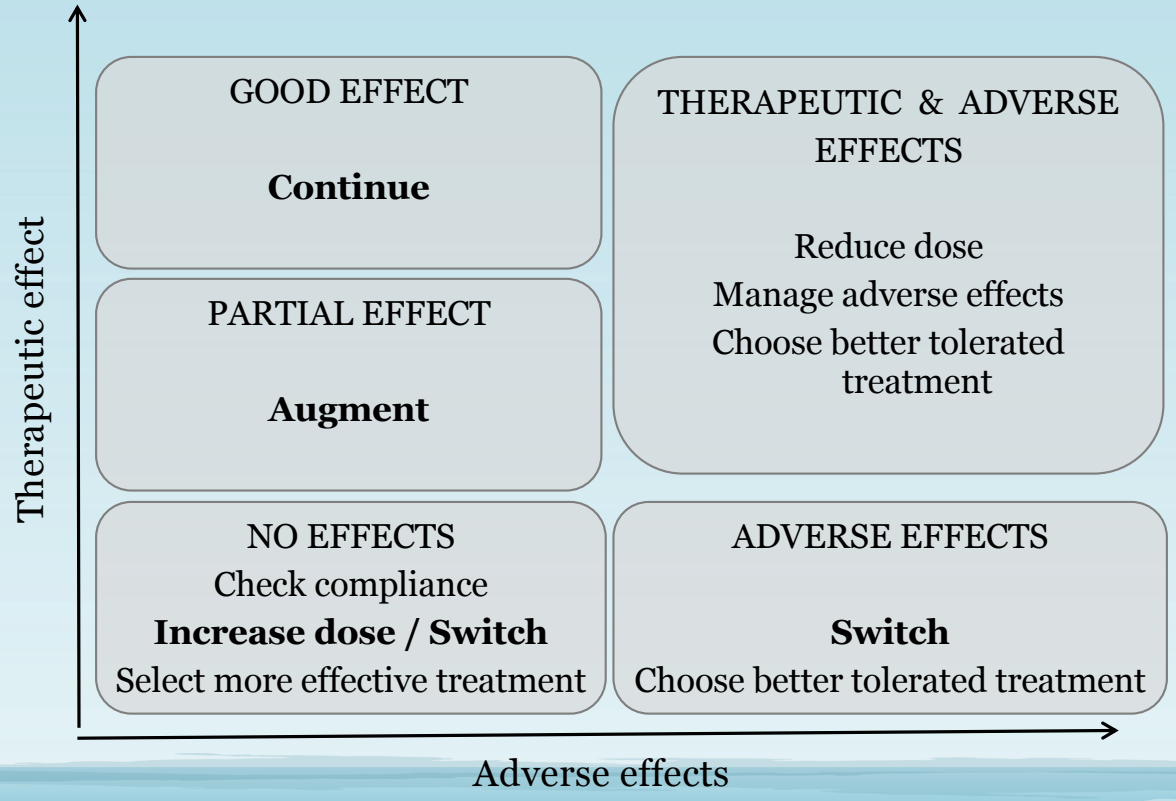
* After dose optimization.

Kennedy et al CANMAT Guidelines 2016 CanJourPsychiatry 2016: vol 61, no 9;pp 540 -560

Recommendations for Adjunctive Medications for Nonresponse or Partial Response to an Antidepressant

Second Line	**Adjunctive Agent**	• Brexpiprazole 1-3mg (Level 1) • Bupropion 150-300mg (Level 2) • Lithium 600-1200mg therapeutic serum levels (Level 2) • Mirtazapine/ Mianserin 30-60mg (Level 2) • Modafinil 100-400mg (Level 2) • Olanzapine 2.5-10mg (Level 1) • Triiodothyronine 25-50 mcg (Level 2)
Third Line	**Adjunctive Agent**	• Other Antidepressants (Level 3) • Other stimulants eg Methylphenidate (Level 3) • TCA (eg desipramine) (Level 2) • Ziprasidone 20-80mg bid (Level 3)

Kennedy et al CANMAT Guidelines 2016 CanJourPsychiatry 2016: vol 61, no 9;pp 540 -560


GOOD EFFECT
Continue
PARTIAL EFFECT
Augment
THERAPEUTIC & ADVERSE EFFECTS
Reduce dose
Manage adverse effects
Choose better tolerated treatment
NO EFFECTS
Check compliance
Increase dose / Switch
Select more effective treatment
ADVERSE EFFECTS
Switch
Choose better tolerated treatment
Therapeutic effect
Adverse effects

Antidepressants: good augmentation agents

Drug	Start	Increase to	Advantages	Side effects / disadvantage
Bupropione	150mg	450mg	May improve sexual dysfunction, may shorten QC interval	Dry mouth, agitation;
Mirtazapine	15mg QH	45mg QH	Improves sleep	Increases appetite, weight gain!
Aripiprazole	2mg OD	5mg OD	Effective for residual anhedonia, works quickly	Agitation, akathisia Remains in system for weeks
Bexpiprazole	0.5mg OD	2mg OD	Effective for residual anhedonia, works quickly	Agitation, akathisia Remains in system for weeks
Lamotrigine*	25mg	300mg	Easy to tolerate	Rash (monitor!, discontinue if rash appears!) Headache
Lithium	300mg	Blood level 0.6mMol/L	Reduces suicide risk, long-term preventive efficacy	Thyroid, kidney, parathormone, NSIAD int. Requires monitoring
Pramipexol*	0.25mg QH	2.5mg QH	Effective in treatment-resistant cases, improves tremor, anhedonia	Nausea, oedemas, gambling

*off-label use

Psychological interventions are effective

- CBT is rigorously evidence based
- CANMAT depression guidelines states that CBT is as effective for mild and moderate depression as antidepressant medications, and
- Combined psychopharmacology and CBT is superior to either modality alone (1)
- For major mental illnesses, CBT is very effective, with low numbers needed to treat (2):
  - GAD: 2.3
  - PTSD: 1.7
  - Depression: 4.4

Cannabis, anxiety and depression

- Anxiety and insomnia are common reasons to use cannabis
- Cannabis often relieves anxiety for several hours
- Cannabis often helps to go to sleep initially
- Continued use of cannabis associated in deterioration in anxiety
- Continued use of cannabis associated with worse prognosis of depression and bipolar disorder
- Discontinuation of cannabis use associated with improvement in depression and anxiety

GAD-7

GAD-7

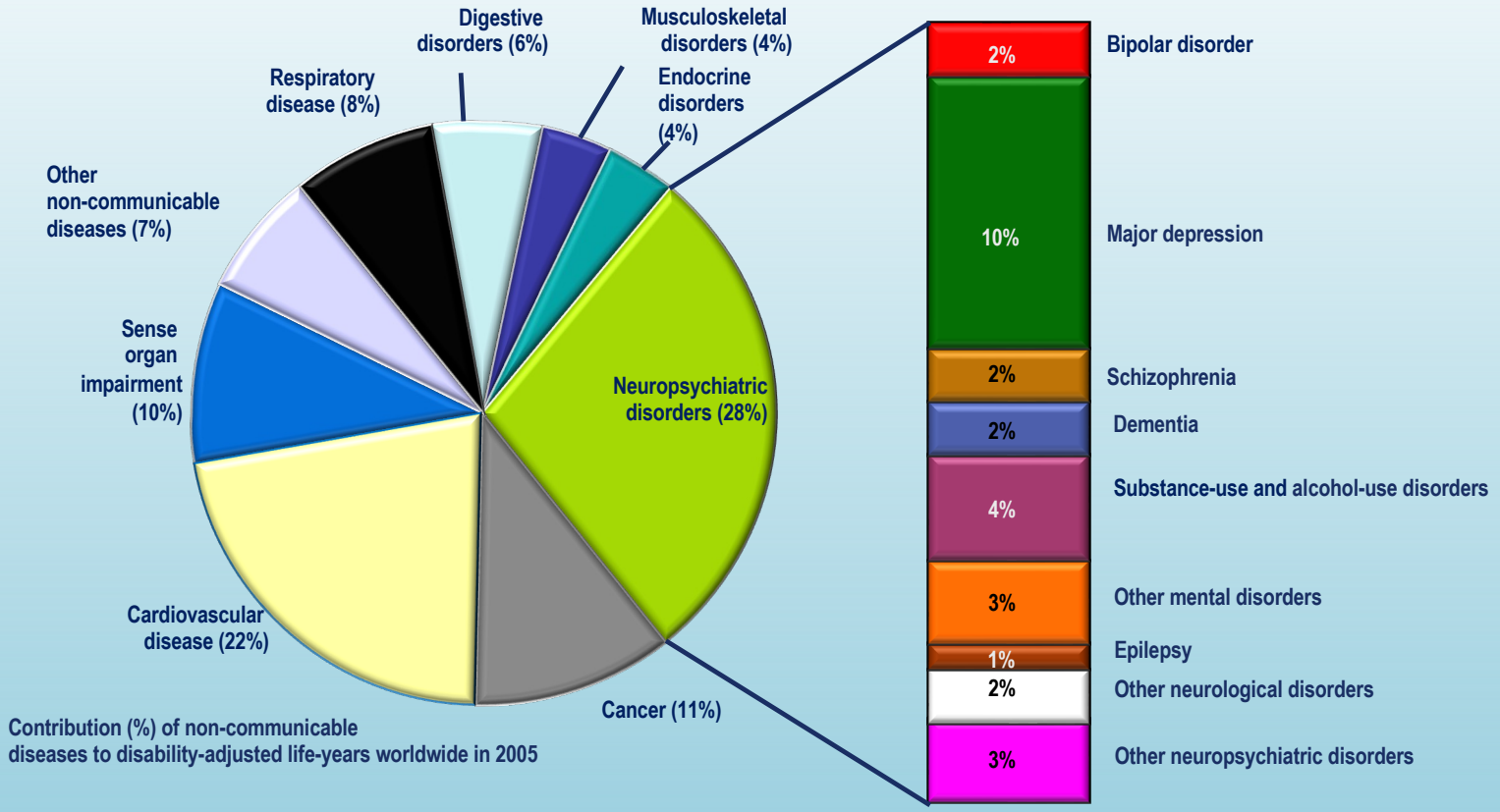
Over the last 2 weeks, how often have you been bothered by the following problems?	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it is hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3

Total Score ___ = Add Columns ___ + ___ + ___

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

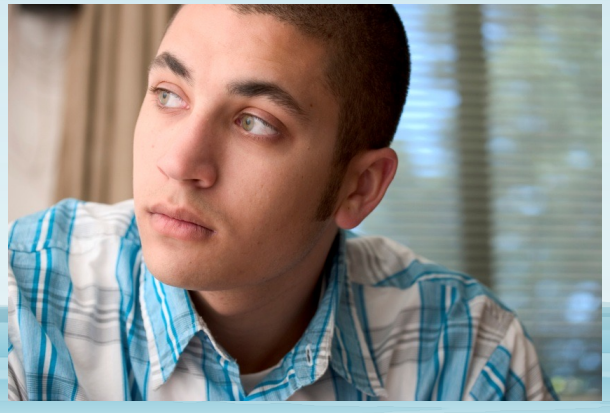
Psychiatric Disorders: Underestimated and Disabling Conditions

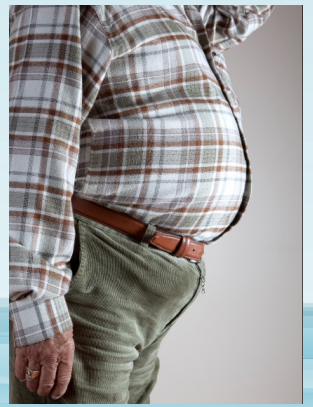


Prince et al. *Lancet*. 2007;370(9590):859-877.

Which Drug for Which Patient?

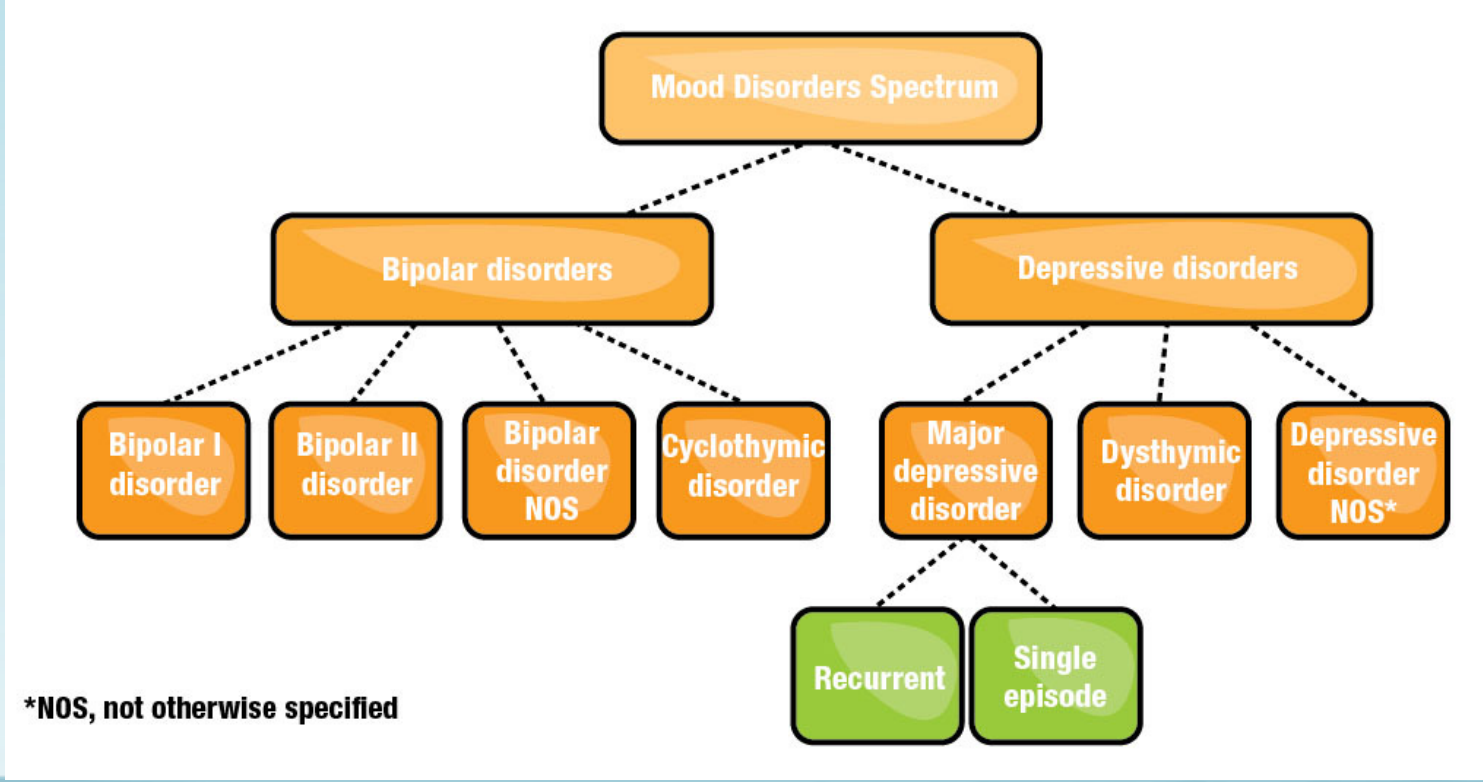
- Patient symptom profile
- Clinician comfort
  - Understanding of efficacy/indications
  - Understanding of drug attributes (e.g., sedating, activating)
  - Knowledge of side effects
  - Experience/comfort using the drug
- Choose with the future in mind





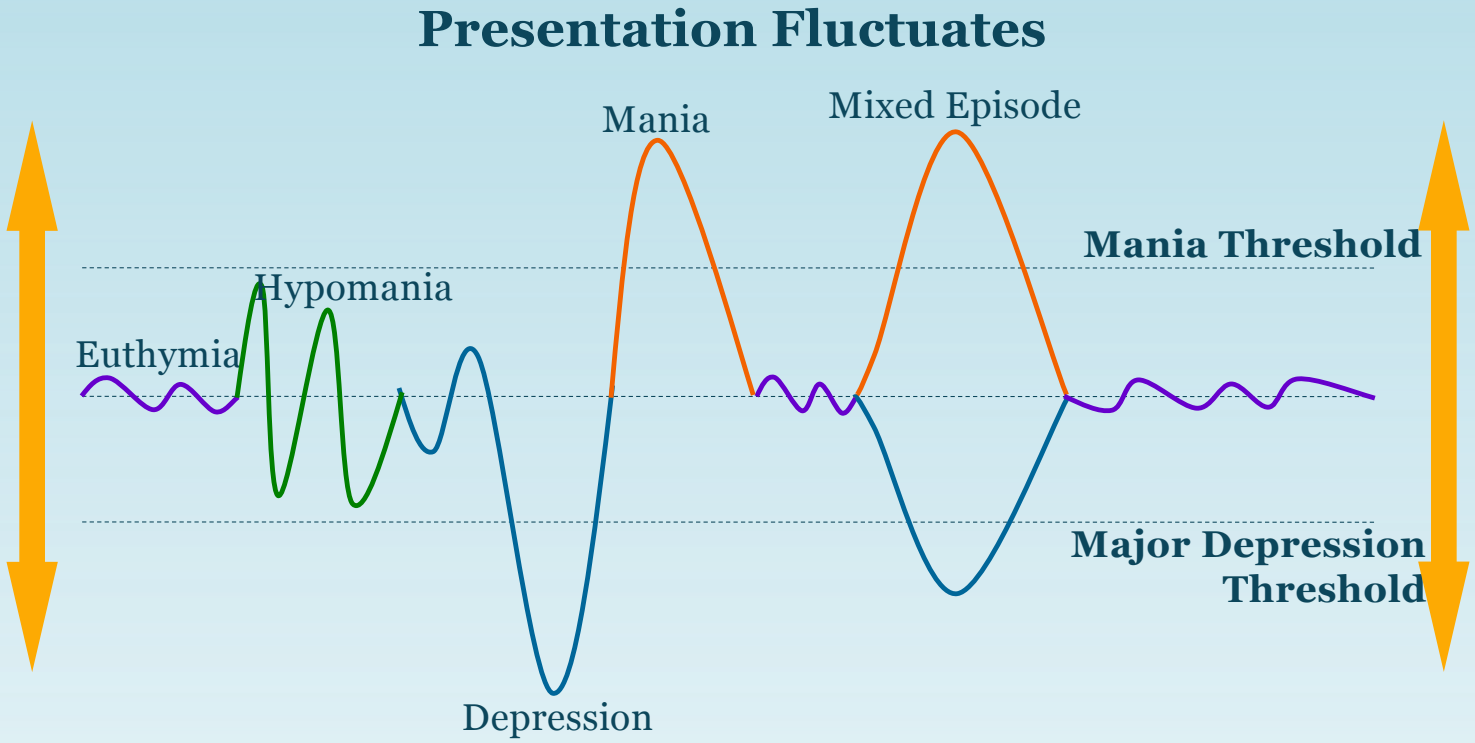
Bipolar Mood Disorder

Making the Diagnosis: DSM-IV



American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders DSM-IV-TR*, 2000.

Bipolar Subtypes



Adapted from: Manning JS et al. *Prim Care Companion J Clin Psychiatry*. 2002;4(4):142-150.

Today's Clinical Pearls

- Many patients fail to achieve remission with initial antidepressant therapy
  - Early response (i.e., 2 weeks) may be a powerful predictor of remission at 6-8 weeks
  - Non-response (<20% improvement from baseline) at 2 weeks is a powerful negative predictor of future remission[1]
- Measurement-based assessment can help decide whether the clinical response is adequate or if a change in therapy is warranted
- Medication decisions must be individualized based on patient profiles and severity of symptoms

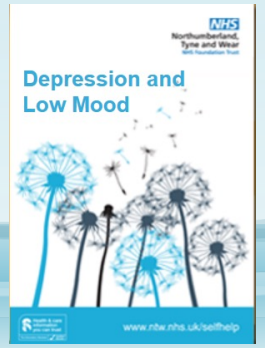
Resources on-line

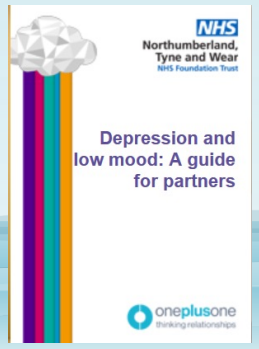
- Depression treatment guidelines:

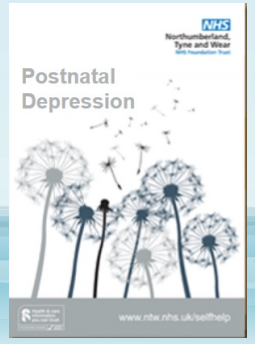
  CANMAT http://www.canmat.org

  NICE https://pathways.nice.org.uk/pathways/depression

- CBT booklets /audio free on-line:
  https://web.ntw.nhs.uk/selfhelp/







Thank you!

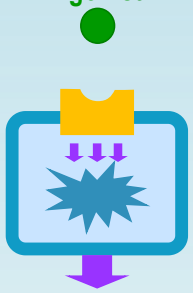
Questions?
Thoughts?

How are these drugs different?

Agonist, Antagonist, Partial Agonist

An agonist interacts with the receptor and initiates a physiologic response[2,3]

Agonist

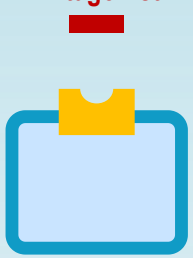


Full activation

An antagonist interacts with the receptor and blocks receptor stimulation by an agonist[2,3]

(No physiological response)

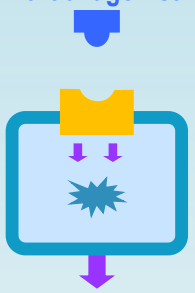
Antagonist



No activation

A partial agonist interacts with the receptor and initiates a partial response without fully inhibiting receptor activity[2,3]

Partial agonist



Partial activation

Higher affinity drugs require lower concentrations to effect change in a receptor

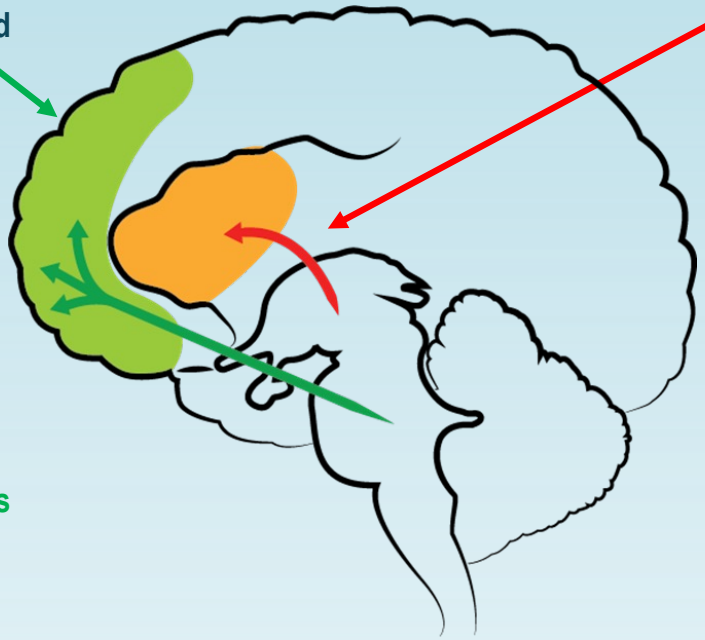
[1] Adapted from Inoue A et al. *Jpn J Pharmacol*. 2001;86(4):376-380.
[2] Adapted from Tamminga CA. *J Neural Transm*. 2002;109(3):411-420.
[3] Gründer G et al. *Arch Gen Psychiatry*. 2003;60(10):974-977.

Rationale for Dopamine Partial Agonism

Mesocortical Pathway[1,2]

Dopamine Deficit Associated With Negative Symptoms

- Alogia
- Affective flattening
- Avolition



Mesolimbic Pathway[1,2]

Dopamine Excess Associated With Positive Symptoms

- Delusions
- Hallucinations
- Disorganized speech/ thinking
- Disorganized or catatonic behaviour

Partial D_2 Agonist Increases Dopaminergic Activity

Partial D_2 Agonist Decreases Dopaminergic Activity

[1] Kandel ER et al. *Principles of Neural Science*, 1991.

[2] Stahl SM. *Essential Psychopharmacology: Neuroscientific Basis and Practical Applications*, 2000.

(Information from regional product monographs)

Indications in Adults by Drug and by Country

Antipsychotic	Indications by country	
	United States	Canada
Aripiprazole	• Schizophrenia • Bipolar I disorder: - acute manic and mixed episodes - maintenance for BPI • Adjunctive treatment for MDD • Injection used for acute treatment of agitation in schizophrenia and BPI	• Schizophrenia • Bipolar I disorder: acute manic and mixed episodes – monotherapy or cotherapy with lithium/valproate •Maintenance cotherapy with lithium/valproate – mixed or manic episodes
Olanzapine	• Schizophrenia • Bipolar I disorder (manic or mixed episodes) with or without lithium or valproate • Agitation associated with schizophrenia and bipolar I mania • Depressive episodes associated with bipolar disorder (in combination with fluoxetine) • Treatment-resistant depression (in combination with fluoxetine)	• Schizophrenia • Bipolar I disorder (acute and maintenance)
Quetiapine	• Schizophrenia • Bipolar I disorder (acute and maintenance) • Depressive episodes associated with bipolar I disorder • Major depressive disorder (XR only)	• Schizophrenia • Bipolar disorders (acute) • Depressive episodes associated with bipolar disorders (acute) • Major depressive disorder (XR only)
Risperidone	• Schizophrenia • Bipolar I disorder	• Schizophrenia • Bipolar I disorder
Ziprasidone	• Schizophrenia • Bipolar I disorder (acute and maintenance)	• Schizophrenia • Bipolar I disorder (acute)

THOUGHTS?
COMMENTS?
QUESTIONS?

Thank you!