# Effective use of psychotropic drugs

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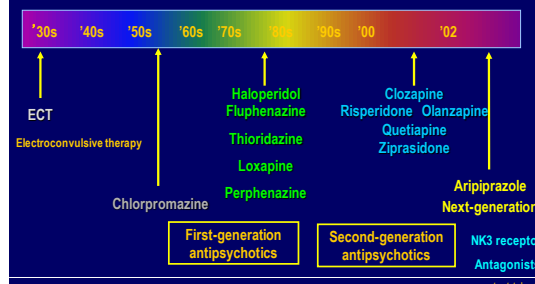
# The 6 rights

- 1. Right drug
- 2. Right individual
- 3. Right dose
- 4. Right time
- 5. Right route
- 6. Right indication.

# Psychotropic drugs

- Antipsychotic drugs
- Antidepressant drugs
- Mood stabilizing drugs
- Antianxiety or anxiolytic drugs

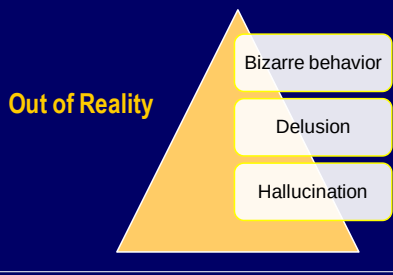
# Developments in Medical Treatments for Psychotic Disorders



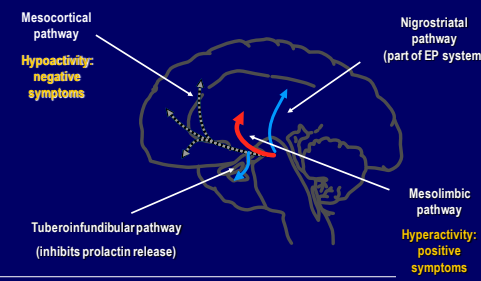

Kapur and Remington. *Ann Rev Med.* 2001;52:503.

Worrel et al. *Am J Health Syst Pharm.* 2000;57:238.

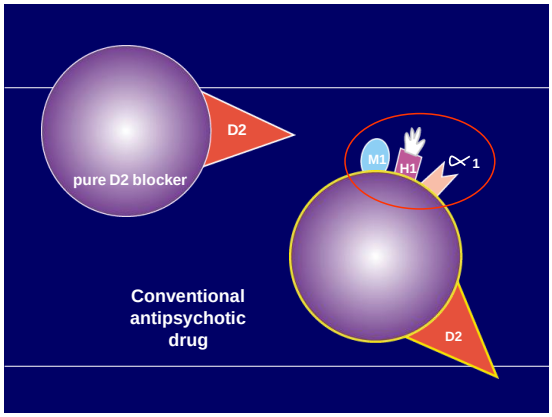
# Psychotic



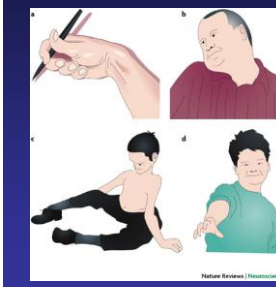

# Dopamine Hypothesis of Schizophrenia




Adapted from Inoue and Nakata. *Jpn J Pharmacol.* 2001;86:376.



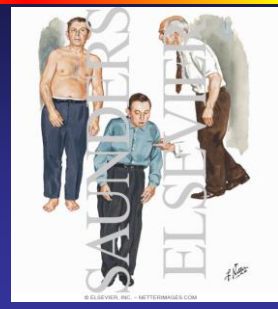

## EPS- Acute dystonia



- ***Symptoms may include***:
  - *Blepharospasm [eye closing]*
  - *Torticolis [neck muscle contraction –pulling head to side]*
  - *Oculogyric Crisis [severe upward deviation of eyeballs]*
  - *Opisthotonos [severe dorsal arching of neck and back]*
  - *Larngospasm/involve-ment of tongue [dysphasia- difficulty swallowing]*

## EPS –Parkinsonism symptoms

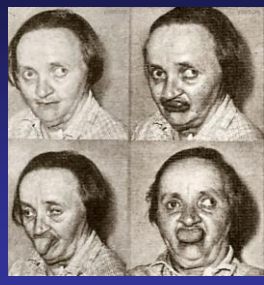
- Tremors
- Bradykinesia/akinesia [slowness, absence of movement]
- Cogwheel rigidity[slow regular muscular jerks]
- Postural instability
- Stooped/hunched posture
- Shuffling gait
- Restricted movements
- Masked face[loss of mobility in facial muscles]
- Hypersalivation &drooling



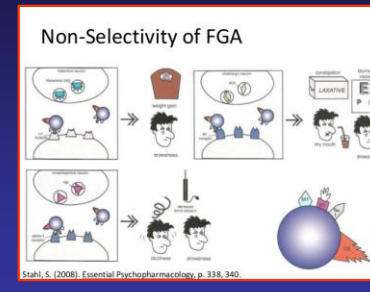

## EPS – Akathesia symptoms

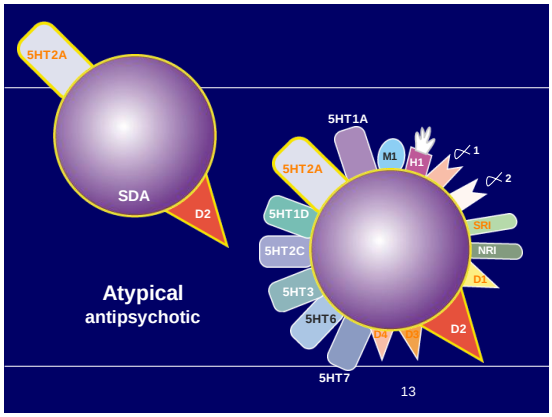
- AKATHISIA – “not sitting”
  - Pacing, Motor restlessness,Rocking, Foot taping
  - Subjective c/o inner restlessness, irritability, inability to sit still or lie down.
  - Need to differentiate between Akathisia and psychomotor agitation or restlessness

## TARDIVE DYSKINESIA
## ( late occurring abnormal movements)



- **Effects 4% of persons taking antipsychotics**
  - Choreoathetoid movements may occur anywhere in the body – *arms,feet,legs,trunk*
  - *Classic description— oral,buccal, lingual,& masticatory movements[ tongue thrusting,lip pursing & smacking,facial grimaces and chewing movements.*






## Tolerability profiles of Atypical Antipsychotics

| Events | CLZ | OLZ | RIS | QTP | ZPD | ARI |
|---|---|---|---|---|---|---|
| ***Metabolic*** | | | | | | |
| Weight gain | ++++ | +++ | ++ | ++ | +/0 | +/0 |
| Dyslipidemia | ++ | +++ | + | + | 0 | 0 |
| Glucose dysregulation | ++ | ++ | + | + | 0 | 0 |
| ***Neurologic*** | | | | | | |
| Somnolence/Sedation | ++++ | +++ | ++ | +++ | + | + |
| EPS | 0 | + | ++ | 0 | + | + |
| ***Cardiovascular*** | | | | | | |
| Myocarditis/Myopathy | +/0 | 0 | 0 | 0 | 0 | 0 |
| QTc prolongation | +/0 | +/0 | +/0 | + | + | 0 |
| ***Hormonal*** | | | | | | |
| Prolactin | 0 | +/0 | ++ | 0 | 0 | 0 |

*Mcintyle et al. J Clin Psychiatry, 2005.*

## Atypical Antipsychotic and Wt gain risk

| Highest risk | Moderate risk | Minimal risk |
|---|---|---|
| | | |

Adapted from Newcomer JW *CNS Drugs.2005*;19(suppl 1): 1-93

## Long-acting injectable antipsychotics

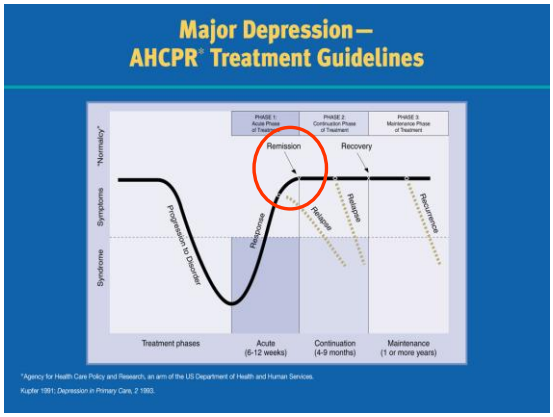
First Generation Antipsychotic long-acting injections : suggested doses and frequencies

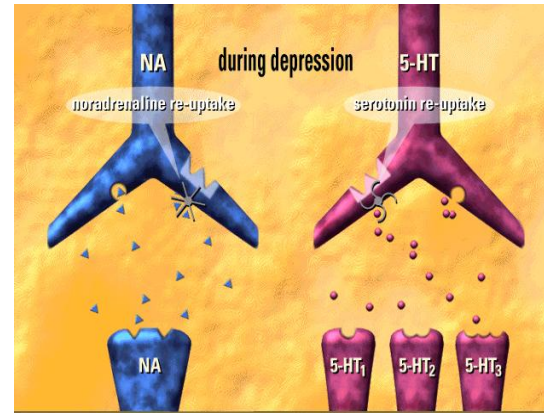
| Drug | Licensed injection site | Test dose (mg) | Dose range (mg/week) | Dosing Interval (weeks) | Comments |
|---|---|---|---|---|---|
| Flupentixol decanoate | Gluteal or thigh | 20 | 12.5-400 | 2-4 | Maximum licensed dose is very high relative to other LAIs |
| Fluphenazine decanoate | Gluteal | 12.5 | 6.25-50 | 2-5 | High EPS |
| Haloperidol Decanoate | Gluteal | 25 | 12.5-75 | 4 | High EPS |
| Pipothiazine palmitate | Gluteal | 25 | 12.5-50 | 4 | ? Lower incidence of EPS (unproven) |
| Zuclopenthixol decanoate | Gluteal or thigh | 100 | 100-600 | 2-4 | ? Slightly higher efficacy |

## Long-acting atypical antipsychotics

- Risperidone microspheres,
- Olanzapine pamoate,
- Paliperidone palmitate
- Abilify Maintenna

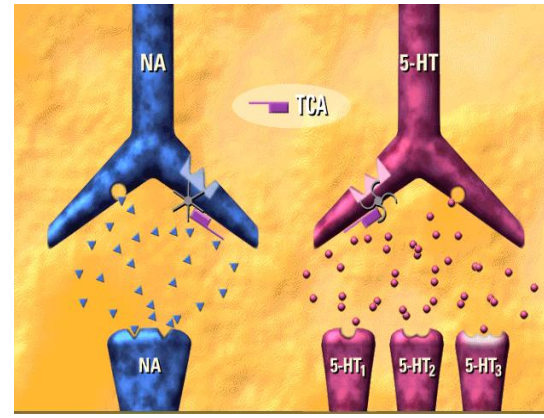
## Antidepressant drugs



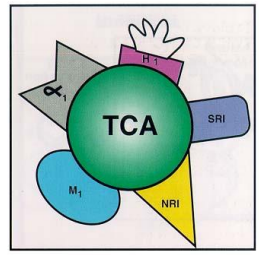

## กลไกการออกฤทธิ์

- ยาแก้เศร้ากลุ่ม tricyclic ออกฤทธิ์โดยการยับยั้ง reuptake ของ monoamine กลับสู่ presynaptic neuron ทำให้ปริมาณของ norepinephrine และ serotonin เพิ่มขึ้นที่บริเวณ synapse
- ก่อให้เกิด Down regulation ที่ post synnaptic site




*กลไกการออกฤทธิ์ของ **TCAs***

- *ที่ให้ **therapeutic effects** คือ **block reuptake** ของ **5HT** และ**NE***
- *ที่ให้ **side effect** คือ การ จับกับ**H1 , M1 , alpha 1 receptors***




***TCA***

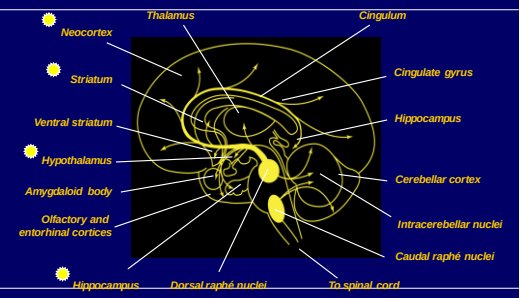
## ข้อห้ามและภาวะที่ควรระวังในการใช้ TCA

- 1) Narrow angle glaucoma
  2) Recent myocardial infarction, มี conduction abnormality โดยเฉพาะ AV-Block grade III, bundle branch block หรือ prolong QT interval
  3) Delirium
  4) Benign prostate hypertrophy
  5) ผู้ป่วยตั้งครรภ์และให้นมบุตร เนื่องจากยาผ่านรกและน้ำนมได้ดี

## Selective Serotonin Reuptake Inhibitors (SSRI)

- Fluoxetine, Fluvoxamine, Paroxetine, Citalopam, Sertraline , Escitalopam

## Serotonergic innervation of the CNS

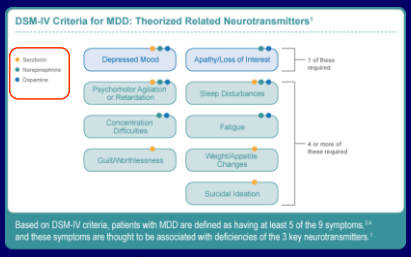



Kaplan & Sadok. In: Synopsis of Psychiatry, Behavioral Sciences, Clinical Psychiatry, 6th ed. Revised. 1991.

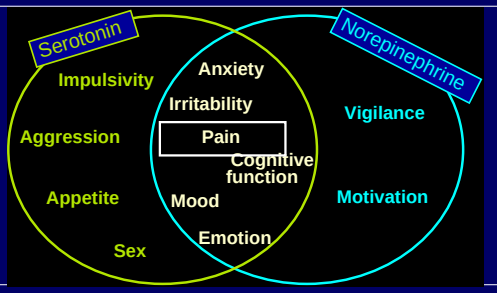
## SSRIs pharmacological ( therapeutic ) profile :

- 1. From midbrain raphe to **prefrontal cortex**
  ( antidepressant )
- 2. From midbrain raphe to **basal ganglia**
  ( anti-OCD )
- 3. From midbrain raphe to **limbic cortex & hippocampus**
  ( anti-panic )
- 4. From midbrain raphe to **hypothalamus**
  ( anti-bulimia )

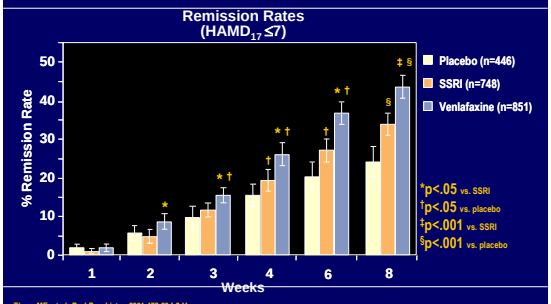
## The relationship between neurotransmitters and symptoms in MDD




## Functional Domains of Serotonin and Norepinephrine[1-5]




## Remission Rates: SNRI vs. SSRI

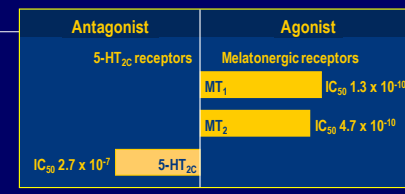



Thase ME, et al. *Br J Psychiatry.* 2001;178:234-241.

## Therapeutic implications of circadian rhythms in depressed patients

- Sleep deprivation therapy
- Bright light therapy
- Interpersonal and social rhythm therapy (IPSRT)
- Sleep phase advance therapy

## Receptor profile of Agomelatine




- Negligible affinity for other receptors or transporters
- No down regulation of $5HT_{1A}$ receptors
- No influence on extracellular serotonin levels

Millan et al, 2003; Hanoun et al, 2004; Audinot et al, 2003

## Agomelatine, a unique receptor profile: $MT_1/MT_2$ agonist and $5\text{-}HT_{2C}$ antagonist

| | Melatonergic | | Serotonergic | | | | | Noradrenergic | | | Dopaminergic | ACh | Histaminergic |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | $MT_1$ | $MT_2$ | $5HT_{1A}$ | $5\text{-}HT_{2A}$ | $5\text{-}HT_{2C}$ | $5\text{-}HT_3$ | Reuptake inhibition | $\alpha_1$ | $\alpha_2$ | Reuptake Inhibition | Reuptake Inhibition | $M_1$ | $H_1$ |
| TCA | | | ↓ | A– | A– | | + | A– | A– | + | | A– | A– |
| fluoxetine | | | ↓ | | (weak) | | + | | | | | | |
| paroxetine | | | ↓ | | | | + | | A– | + | | A– | |
| escitalopram | | | ↓ | | | | + | | | | | | |
| venlafaxin | | | ↓ | | | | + | | | + | | | |
| duloxetine | | | ↓ | | | | + | | | + | + | | |
| mirtazapine | | | | A– | A– | A– | | | A– | | | | A– |
| Agomelatine | A+ | A+ | | | A– | | | | | | | | |

A+: agonist A–: antagonist ↓: desensitization +: reuptake inhibition

Adapted from Racagni and Popoli, In press

## Cytochrome P450 and psychotropics

- Cytochrome P450 enzymes ที่ตับใช้ในการ metabolize ยาต่าง ๆ
- ที่สำคัญ 4 ชนิด
  - CYP 1 A 2
  - CYP 2 D 6
  - CYP 3 A 3,4
  - CYP 2 C19

Drug Drug interaction

## Drug Interactions at Usual Effective Doses

Inhibitory effect of select antidepressants on specific cytochrome P450 isoenzymes

| | 1A2 | 2C9/10 | 2C19 | 2D6 | 3A3/4 |
|---|---|---|---|---|---|
| Citalopram* | • | • | • | + | • |
| Escitalopram† | • | • | • | ++ | • |
| Fluoxetine* | • | +++ | ++ | +++ | + |
| Nefazodone* | • | • | • | • | +++ |
| Paroxetine* | • | • | • | +++ | • |
| Venlafaxine* | • | • | • | + | • |
| Sertraline* | • | • | • | + | • |

• no or minimal effect (<20%)‡ + mild effect (20%-50%)‡ ++ moderate effect (50%-150%)‡ +++ substantial effect (>150%)‡

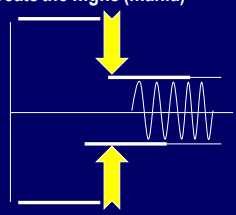
Sertraline has the potential for clinically important 2D6 inhibition. Consequently, concomitant use of a drug metabolized by P450 2D6 with sertraline may require lower dose than usually prescribed for the other drug. Furthermore, whenever sertraline is withdrawn from coherapy, an increased dose of the coadministered drug may be required.

Preskorn 1999; Manufacturers' product information 2003.

## Mood stabilizing drugs

## Treatment of Bipolar Disorder

Treats the highs (mania)



Helps prevent the highs and lows (maintenance)

Helps manage the lows (depression)

## Treatment Options for Bipolar Disorder

- Lithium
- Divalproex
- Lamotrigine
- Carbamazepine and other anticonvulsants
- Typical antipsychotics
  - Haloperidol
  - Chlorpromazine

- Atypical antipsychotics
  - Aripiprazole
  - Clozapine
  - Olanzapine
  - Quetiapine
  - Risperidone
  - Ziprasidone
  - Other atypicals
- Antidepressants

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## Acute Mania: Aims of Treatment

- Acute tranquilization, sedation
- Improve manic symptoms
- Improve psychosis
- Improve depressive symptoms
- Avoid subsequent depression

## WHY WE MIGHT CHOOSE THIS MEDICATION?

**LITHIUM**

| Pros | Cons |
|---|---|
| Gold standard treatment | Suicidal risk is a concerns |
| Long term experienced & widely accepted on guidelines | Required closely monitoring serum lithium level |
| Effective in both acute bipolar mania & depress | High risk of lithium toxicity |
| Very inexpensive | Risk of hypothyroidism |

## Signs & symptoms of lithium toxicity:

- Fine hand tremors that progress of coarse tremors
- Mild GI upset progressing to persistent upset
- Slurred speech and muscle weakness progressing to mental confusion
- **Severe Toxicity**:
  - decrease level of consciousness to stupor and finally coma
  - Seizures, severe hypotension, severe polyuria with dilute urine

**VALPROATE**

| Pros | Cons |
|---|---|
| Widely accepted as 1st line in all updated guidelines | Limited value in Bipolar depression, particularly as monotherapy |
| Strong efficacy in acute Bipolar mania | Increased appetite and weight gain |
| Probably prevent manic and depressive relapse | Pregnancy concerned |
| Rapid onset of action within 3-4 days | |
| Wide spectrum of responders | |
| Superior tolerability to LI | |

## LAMOTRIGINE

| Pros | Cons |
|---|---|
| Strongly accepted as 1st line in Bipolar Depression | Slow escalation of dose essential |
| Shown efficacy in rapid cycling | Rash: especially if dose escalation rapid, particularly if added to VPA |


## SEROQUEL

| Pros | Cons |
|---|---|
| Strong antidepressant effects | Risk of weight gain |
| Effective in both Bipolar mania & depression | High incidence of dry mouth |
| Prevents both manic and depressive relapse | Expensive |
| Lower risk of diabetes & EPS than other AAPs | |


## ZYPREXA

| Pros | Cons |
|---|---|
| Long term experienced | Largest increased on weight |
| Proven efficacy in Bipolar mania | Diabetes risk |

## RISPERIDONE

| | |
|---|---|
| Prevents only manic relapse | Can cause some muscle problems (EPS) |
| No diabetes risk & change on cholesterol levels | EPS side effect limits how high one you can push the dose |

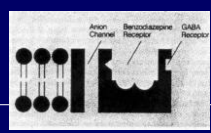
## ARIPRIPAZOLE

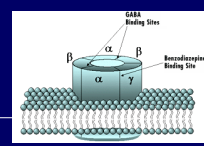
| | |
|---|---|
| Prevents only manic relapse | No efficacy in Bipolar depression |
| No diabetes risk & change on cholesterol levels | |

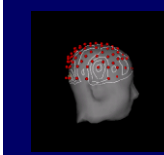
# Antianxiety or anxiolytic drugs

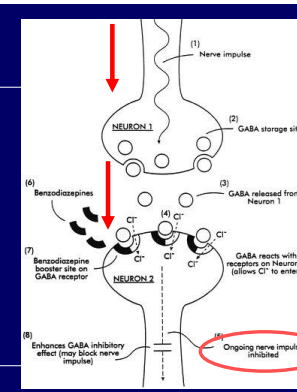
## Biologic Basis of anxiety Disorder

- GABA Inhibitory neurotransmitter system
- GABA and benzodiazepine receptors complex



## ข้อมูลทั่วไปของ benzodiazepine ชนิดต่างๆ

| Drug | Dosage | rate absorb | half life | duration of action | dosage range |
|---|---|---|---|---|---|
| Alprazolam | 0.25, 0.5, 1.0 | medium | 12 | short | 0.5-6 |
| Chlordiazepoxide | 5, 10, 25 | medium | 100 | very long | 15-100 |
| Clonazepam | 0.5, 2 | medium | 34 | long | 0.5-10 |
| Clorazepate | 5, 10 | rapid | 100 | very long | 7.5-60 |
| Diazepam | 2, 5, 10 | rapid | 100 | very long | 2-60 |
| Flurazepam | 15, 30 | rapid | 100 | very long | 15-30 |
| Lorazepam | 0.5, 1, 2 | medium | 15 | short | 2-6 |
| Midazolam | 15 | rapid | 2.5 | very short | 15 |
| Oxazepam | 15 | slow | 8 | short | 30-120 |
| Prazepam | 10 | slow | 100 | very long | 20-60 |
| Temazepam | 15, 30, 20 | medium | 11 | short | 15-30 |
| Triazolam | 0.125, 0.25 | rapid | 2 | very short | 0.125-0.25 |

## Benzodiazepine Therapy Advantages

### Efficacy

- Broad range of therapeutic choices
- Rapid onset of therapeutic action
- Safe
- Few adverse drug interactions
- Favorable sleep profile

## Disadvantages of Benzodiazepines

- Potential for physiologic/psychologic dependency.
- Some potential for abuse.
- CNS side effects.
- Additive CNS depression.
- Active metabolites can accumulate in elderly or ill patients.

## Principles of effective use of psychotropics

1. Diagnostic assessment
2. Risk-to-benefit ratio
3. Prior personal history of response
4. Target specific symptoms
5. Adverse effects assessment
6. Psychopharmacotherapy alone is insufficient