



The New Psychotropic Medicines

The list of available psychotropic medications continues to grow, posing a constant challenge to the emergency physician who is confronted with a patient taking a new medication. The emergency physician must be able to identify the risks associated with these medicines and the clinical presentations of patients in the setting of an overdose. The lecturer will review the new drugs and provide an overview of their mechanisms of actions, adverse effects, and potential for abuse, as well as appropriate emergency treatment in the case of an overdose.

- List the new psychotropic drugs and describe their mechanisms of action.
- Recognize the signs and symptoms of overdose with each of these agents.
- Discuss the appropriate treatment in the case of an overdose.

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FACULTY

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THE NEW PSYCHOTROPIC MEDICATIONS

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I. INTRODUCTION

psychotropic (si' ko-trop' ik)

Affecting the psyche, denoting specifically, drugs used in the treatment of mental illnesses

Over the past decade we have learned more about the etiologies of both schizophrenia and depression and we have attempted to target specific regions of the brain and receptors in order to reduce adverse effects and toxicity and to improve efficacy.

This presentation will review how conventional agents work and their toxicity and then focus on the newer agents. Appendix A and B are listings of selected antipsychotics and antidepressants based upon their therapeutic mechanism of action.

II. ANTIPSYCHOTICS

A. Symptoms of schizophrenia

positive symptoms

delusions
hallucinations
excitement
paranoid thinking
hostility
grandiosity

negative symptoms

blunted affect
social withdrawal
poor abstract thinking
stereotyped thinking
apathy
avolition

B. Etiology of schizophrenia

Several neurotransmitter/receptor abnormalities have been noted

1. Increased dopamine activity in the mesolimbic region
2. Decreased activity in dorsolateral prefrontal cortex
responsible for higher cortical function
poor activation correlates with severity of negative symptoms

C. Traditional Antipsychotics

Traditional antipsychotics (neuroleptics) are dopamine antagonists.
Classified by potency of dopamine subtype 2 (D₂) receptor antagonism.
The greater the affinity, the more potent the antipsychotic effect.

low potency

chlorpromazine (Thorazine), chlorprothixene (Taractan),
mesoridazine (Serentil), thioridazine (Mellaril)

medium potency

droperidol (Inapsine), loxapine (Loxitane), molindone (Moban),
perphenazine (Trilafon)

high potency

fluphenazine (Prolixin), haloperidol (Haldol), pimozide (Orap),
trifluoperazine (Stelazine), thiothixene (Navane)

Unfortunately this D₂ antagonism occurs throughout the brain:

Good in mesolimbic system

improves positive symptoms

Bad in nigrostriatal and mesocortical tracts

produces extrapyramidal symptoms (EPS) and tardive
dyskinesia, worsens negative symptoms

D. Adverse effects associated with traditional antipsychotics

1. Extrapyramidal symptoms

dystonia Briefly sustained or fixed abnormal postures including
torticollis, oculogyric crisis, facial grimacing,
opisthotonos, laryngeal spasm
Sense of panic, anxiety, fearfulness

akathisia A state of motor restlessness including pacing, rocking,
shifting from foot to foot, "restless legs"
Feelings of restlessness, irritability, discontent

Parkinsonism Bradykinesia w/ mask-like facies, shuffling gait,
resting tremor, rigidity
Apathy, anhedonia, slow mentation

2. Other adverse effects

tardive dyskinesia Involuntary buccolinguomasticatory
movements including lip smacking,
tongue protrusion, grimacing, chewing

NMS hyperthermia, rigidity, altered mental status,
autonomic instability

3. Time of onset of extrapyramidal symptoms in antipsychotic therapy

| | |
|--------------------------------------|-------------------------|
| early (acute - hours to days) | acute dystonias |
| intermediate (acute - days to weeks) | parkinsonism, akathisia |
| late (chronic - months to years) | dyskinesias |

Therapeutic summary of conventional antipsychotics;
effective at improving positive symptoms of schizophrenia
minimal effect on negative symptoms
significant EPS (limits compliance)
produce tardive dyskinesia (disabling)
relatively ineffective - 25 to 35% of patients respond poorly

E. Newer antipsychotic agents

“balanced antagonism”
potent serotonin (5HT_{2A}) antagonism
less dopamine (D₂) antagonism
other receptors
D₁, D₄, norepinephrine

Serotonin hypothesis of schizophrenia

1943 Hoffman synthesized and “experienced” LSD. 10 yrs later
LSD’s hallucinogenic effect was due to serotonin agonism in the
brain. This led to the postulation that serotonin may play a major role
in schizophrenia.

In schizophrenics, there is increased serotonin activity in the
mesocortical and nigrostriatal or extrapyramidal pathways. Because
serotonin is a major inhibitory neurotransmitter, if this increased activity
could be blocked, it may result in more dopamine effects in these
dopamine deficient regions.

Q: Why doesn’t the serotonin antagonism “reverse” the D₂ receptor
antipsychotic effect as well?

A: ??? No satisfying answer yet - “balance”, multiple other
dopamine receptors involved as well, quantity of specific receptors in
each region

CLOZAPINE (Clozaril®)

1970's large european trials

very effective antipsychotic

little EPS or TD

toxic! - 15/3200 patients developed agranulocytosis, 8 died
- seizures

1988 landmark clozapine study in US by Kane

318 chronic schizophrenics who failed 3 or more neuroleptics

1st phase - high dose haloperidol/benztrapine - 2% responded

2nd phase - clozapine vs. chlorpromazine/benztrapine over 6 wks
effectiveness - clozapine 30% vs. chlorpromazine 4%

1. Mechanism of action (see table 1)

Significant serotonin (5HT_{2A}) antagonism

Limited dopamine (D₂) antagonism

PET scanning reveals only 40 to 60% occupancy of D₂
receptors while haloperidol occupies 70 to 80%

D₄ antagonism

Other receptors antagonized: alpha adrenergic (α_1), histamine (H₁),
muscarinic

2. Therapeutic Efficacy

Effective in some patients who are resistant to traditional neuroleptics

Treats negative as well as positive symptoms

May reduce tardive dyskinesia

3. Adverse Effects (see table 2)

Extensive profile comparable in incidence to chlorpromazine

Some adverse effects unique to clozapine

a. agranulocytosis

1-2% incidence

risk factors - older or female

no relation to dose

80% develop in first 3 months of therapy

WBC drop may be gradual or rapid

stop treatment if:

abrupt drop > 3000 mm³

absolute # below 3000 mm³

treat w/ granulocyte colony stimulating factor

national registry (800) 448-5938 records weekly WBC's, flags
patients that have stopped the medication

mechanism unclear - possible metabolite vs. parent compound
vs. immunologic
if rechallenged, most develop agranulocytosis w/in 1- 4 weeks

b. seizures

reduce seizure threshold by unclear mechanism
1-6% incidence, dose-dependent

c. sialorrhea (hypersalivation)

reported by 1/3 the patients taking clozapine
treat long term w/ anti-muscarinic or clonidine

4. Overdose

Exaggeration of pharmacological effects

Manifestations include:

CNS depression or excitation

agitation, hallucinations, seizure, lethargy, obtundation

increased muscle tone, myoclonic movements

cardiovascular

orthostatic hypotension, tachycardia, nl ECG

sialorrhea

RISPERIDONE (Risperdal®)

1. Mechanism of action (see table 1)

Significant serotonin (5HT_{2a}) antagonism

Dopamine D₂ antagonism

Limited alpha adrenergic antagonism

2. Therapeutic efficacy

Effective in some patients who are resistant to traditional neuroleptics

Treats negative as well as positive symptoms

Patients suffering from significant EPS

Now accepted first line therapy for many patients

3. Adverse effects (see table 2)

EPS seen with higher dosing but not with typical dosing (6 mg/day)

Orthostatic hypotension (alpha blockade)

Much lower risk of developing tardive than traditional neuroleptics

4. Overdose:

Exaggeration of known pharmacologic effects

CNS depression

drowsiness, sedation, coma

dystonia, EPS

cardiovascular
orthostatic hypotension, tachycardia,
nonspecific ECG findings

OLANZAPINE (Zyprexa[®])

1. Mechanism of action

Receptor antagonism profile similar to clozapine
Significant serotonin (5 HT_{2a}) antagonism
Dopamine antagonism (D₁, D₂, D₄)
Other receptor antagonism: alpha adrenergic (α_1), histamine (H₁),
muscarinic

2. Efficacy

Effective in some patients who are resistant to traditional neuroleptics
Treats negative as well as positive symptoms
May reduce tardive dyskinesia
Now considered first line therapy in some patients

3. Adverse Effects

No evidence of agranulocytosis or seizures

4. Overdose - limited experience but probably similar to clonzapine

CNS depression
Anticipate exaggeration of pharmacologic effects

F. Newest Agents

Quetiapine (Seroquel)
Sertindole (Serlect)

G. Treatment of Newer Antipsychotic Overdose

Supportive care
If a person presents with a hx of ingestion but is not manifesting
clinical toxicity, the “standard 4 to 6 hour observation period, in
addition to adequate GI decontamination, an ECG (to screen for
TCA’s), and an APAP level, are sufficient for medical clearance

H. Summary of Atypical Antipsychotics

Demonstrate equal or enhanced efficacy to traditional antipsychotics
Effective for negative symptoms
Little or no EPS
Limited tardive dyskinesia

TABLE 1
Pharmacologic Actions of Selected Antipsychotic Agents

| Receptor antagonism | chlorpromazine | haloperidol | Clozapine | risperidone | olanzapine |
|---|----------------|-------------|-----------|-------------|------------|
| Dopamine D ₂ | + | +++ | + | +++ | ++ |
| Serotonin - 5HT _{2a} | ++ | 0 | ++ | +++ | +++ |
| 5HT _{2a} /D ₂ ratio | ++ | 0 | +++ | +++ | ++ |
| alpha adrenergic | ++ | + | + | ++ | + |
| Muscarinic | ++ | 0 | ++ | 0 | +++ |
| Histamine | ++ | 0 | +++ | 0 | ++ |

TABLE 2
Adverse Effects of Selected Antipsychotic Agents

| Adverse effects | chlorpromazine | haloperidol | Clozapine | risperidone | olanzapine |
|-----------------|----------------|-------------|-----------|----------------|------------|
| EPS | + | +++ | 0 | + _a | 0 |
| TD | +++ | +++ | 0 | + | ? |
| Seizures | + | 0 | +++ | 0 | 0 |
| NMS | + | + | + | + | ? |
| Sedation | +++ | + | +++ | + | ++ |
| Orthostatics | +++ | + | ++ | ++ | + |
| Anticholinergic | +++ | + | +++ | 0/+ | ++ |

a = dose dependent

III. ANTIDEPRESSANTS

A. Traditional Antidepressants

1950's MAOI's used as antituberculous agents and TCA's discovered while synthesizing new antipsychotics

The first effective medical treatment for depression. Used to study the cellular chemical and receptor imbalances of depression

MAOI's - Inhibit monoamine oxidase which metabolizes norepinephrine (NE), serotonin (5-HT), and dopamine (D) throughout the central and peripheral nervous system.

antidepressant effect - enhanced NE, 5-HT, and D release

TCA's - Antagonize many different receptors (see table 3)

antidepressant effect - inhibition of NE and 5-HT reuptake

B. Adverse effects associated with traditional antidepressants

1. MAOI's

Food and drug interactions

a. exaggerated peripheral sympathetic response (NE)

hypertension, tachycardia, diaphoresis, headache

tyramine rich foods, indirect sympathetic amines

(cocaine, amphetamines (MDMA), ephedrine, PPA,

dopamine, antihypertensives (reserpine, methyldopa)

b. exaggerated central serotonergic response (serotonin)

serotonin syndrome - hyperpyrexia, CNS depression,

hypertonicity

TCA's, SSRI's, opioids (meperidine, dextromethorphan)

2. TCA's

Antagonize many receptors not involved in the antidepressant effects

which results in high incidence of adverse effects and toxicity in

overdose (see table 3)

C. Overdose

1. MAOI

delay in onset of toxicity up to 12 hrs

duration of poisoning up to 2 to 3 days

CNS depression ranging from sedation to delirium to

obtundation, myoclonus, autonomic instability w/ wide

fluctuations in BP and HR, CV collapse

2. TCA's (see table 3)

TABLE 3

Pharmacologic Etiologies of Adverse Effects of TCA's

| pharmacologic effects | adverse clinical manifestations | |
|---|---|--|
| | therapeutic | overdose |
| sodium channel blockade or quinidine-like effect | QT prolongation | QRS widening, dysrhythmias, seizures? |
| Antimuscarinic | dry mouth, constipation, blurry vision | anticholinergic toxidrome, seizures |
| α adrenergic antagonism | orthostatic hypotension, dizziness | hypotension |
| Antihistamine | sedation | CNS depression |

B. Newer Antidepressants

No evidence that any antidepressant has superior efficacy

New agents have much more specific receptors targeted resulting in decreased toxicity both therapeutically and in overdose

1. Selective Serotonin Reuptake Inhibitors (SSRI's) (see appendix B)

a. mechanism of action

inhibit serotonin reuptake

all have similar efficacy and toxicity

varying potencies of serotonin reuptake inhibition

| | |
|----------|---------------------|
| greatest | paroxetine (Paxil) |
| | sertraline (Zoloft) |
| | fluvoxamine (Luvox) |
| | citalopram (Celexa) |
| least | fluoxetine (Prozac) |

b. adverse effects

fewest adverse effects of all antidepressants

GI distress, sexual dysfunction

hyponatremia - SIADH

fluoxetine, fluvoxamine - p450 inhibitors

c. overdose - relatively benign

GI distress - nausea, vomiting

mild CNS depression

insignificant cardiotoxicity

2. Venlafaxine (Effexor[®])

a. mechanism of action

Similar mechanism of action to TCA's with serotonin and norepinephrine reuptake inhibition but has little antagonism at the α_1 adrenergic, histamine H₁, or muscarinic receptors.

However much more serotonin effects (5X) than NE effects

b. adverse effects

well tolerated

at higher doses - agitation, tremor, hypertension (NE effects)

serotonin syndrome

c. overdose

sedation, sinus tachycardia, rarely seizures

3. Bupropion (Wellbutrin[®], Zyban[®])

a. mechanism of action
inhibits reuptake of dopamine and to a lesser extent NE

b. adverse effects
similar to SSRI w/ less sexual dysfunction
seizures - dose related

c. overdose
CNS depression
seizures

4. Nefazodone (Serzone[®])

a. mechanism of action
serotonin 2 receptor antagonist
serotonin reuptake inhibitor

b. adverse effects
sedation, dry mouth, constipation, light-headedness
unlike trazodone, no α -adrenergic antagonism; less sedation
and orthostatic hypotension, no priapism

c. overdose - limited experience
CNS depression

5. Mirtazapine (Remeron[®])

a. mechanism of action - unique
alters primarily feedback receptors
 α_2 autoreceptor antagonist (stimulation inhibits NE release)
 α_2 heteroreceptor antagonist (found on serotonergic terminals, stimulation inhibits serotonin release) antagonist
Net effect is increase in NE and serotonin release

b. adverse effects
drowsiness, dry mouth, weight gain

c. overdose
CNS depression
no cardiovascular effects

C. General approach to overdose involving a new antidepressant

IV access, cardiac monitor

GI decontamination - does not appear to be any utility for syrup of ipecac, orogastric lavage, or whole bowel irrigation

Use activated charcoal

Screening ECG, APAP level (as for all overdoses)

Clinical manifestations of poisoning will be an exaggeration of pharmacologic effects. Anticipate CNS depression with much less cardiovascular toxicity than MAOI's or TCA's

None are effectively removed w/ hemodialysis or hemoperfusion

Supportive care typically all that is required

Would be conservative w/ these initially. If any manifestations of toxicity, admit to ICU

TABLE 4
Pharmacologic Actions of Selected Antidepressants

| | TCA's | SSRI's | bupropion | venlafaxine | nefazodone |
|----------------------------|-------|--------|-----------|-------------|----------------|
| <u>reuptake inhibition</u> | | | | | |
| serotonin | + | + | + | + | + _a |
| norepinephrine | + | 0 | 0 | + | 0 |
| dopamine | 0 | 0 | + | 0 | 0 |
| <u>Receptor antagonism</u> | | | | | |
| sodium channel | + | 0 | 0 | 0 | 0 |
| muscarinic | + | 0 | 0 | 0 | 0 |
| alpha-adrenergic | + | 0 | 0 | 0 | 0/+ |
| histamine | + | 0 | 0 | 0 | 0 |

TCA's - tricyclic antidepressants

SSRI's - selective serotonin reuptake inhibitors

a = nefazodone also exhibits significant 5-HT₂ antagonism

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APPENDIX A
**CLASSIFICATION OF ANTIPSYCHOTICS
BASED ON MECHANISM OF ACTION**

D₂ receptor antagonists

low potency

chlorpromazine (Thorazine), chlorprothixene (Taractan)
mesoridazine (Serentil), thioridazine (Mellaril)

medium potency

droperidol (Inapsine), loxapine (Loxitane), molindone (Moban)
perphenazine (Trilafon)

high potency

fluphenazine (Prolixin), haloperidol (Haldol), pimozide (Orap)
trifluoperazine (Stelazine), thiothixene (Navane)

D₂/serotonin receptor antagonists

clozapine (Clozaril)

risperidone (Risperdal)

olanzapine (Zyprexa)

quetiapine (Seroquel)

sertindole (Serlect)

APPENDIX B
**CLASSIFICATION OF ANTIDEPRESSANTS
BASED ON MECHANISM OF ACTION**

Monoamine Oxidase Inhibitors (MAOI's) (serotonin, norepinephrine, dopamine)

phenelzine (Nardil), tranylcypromine (Parnate)

Serotonin-Norepinephrine Reuptake Inhibitors

tricyclics - tertiary amines (primary serotonin)

amitriptyline (Elavil), clomipramine (Anafranil), doxepine (Sinaquan)

imipramine (Tofranil), trimipramine (Surmontil)

tricyclics - secondary amines (primarily norepinephrine)

desipramine (Norpramin), nortriptyline (Pamelor), protriptyline (Vivactil)

tetracyclics (primarily norepinephrine)

amoxapine (Asendin), maprotiline (Ludiomil)

non-tricyclics

venlafaxine (Effexor)

Selective Serotonin Reuptake Inhibitors (SSRI's)

fluoxetine (Prozac), fluvoxamine (Luvox), paroxetine (Paxil)

sertraline (Zoloft), citalopram (Celexa)

Norepinephrine-Dopamine Reuptake Inhibitors

bupropion (Wellbutrin, Zyban)

Serotonin Antagonist and Reuptake Inhibitors

nefazodone (Serzone), trazodone (Desyrel)

Norepinephrine Antagonist and Serotonin Antagonist

mirtazapine (Remeron)