

Mood Disorders (Affective Disorders): Unipolar and Bipolar Depression



Depression

(1) First antidepressant: *iproniazid* for tuberculosis in the 1950s, which was found to be a mood elevator and also found to be a MAO inhibitor

(2) animal studies showed that the combo of reserpine + iproniazid led to hyperactivity and hyperaleness

(3) This led to the use of MAO inhibitors for depression in 1957

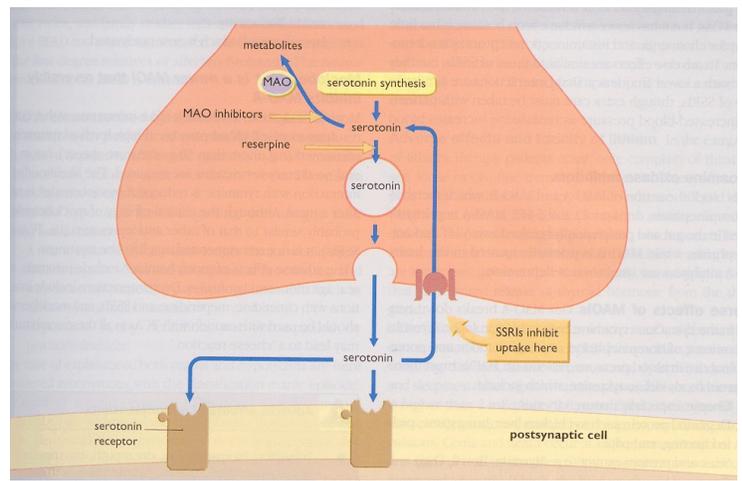


Figure 2 Schematic Representation of a Serotonin (5-HT) Terminal. Selective serotonin reuptake inhibitors (SSRIs) potentiate 5-HT action in the synaptic cleft and are used to treat depression.

TRICYCLIC ANTIDEPRESSANTS.

Roland Kuhn with Klasei in Berne used narcotic sleep treatments on schizophrenic patients and shock treatments (metrazol and ECT) for depressed patients

Geigy gave them an antihistamine (similar in structure to chlorpromazine) to test as a sedative. He also tested it for effects on patients: not effective

A derivative was made with the same side chain as chlorpromazine: the compound made was imipramine (circa 1975) (took the Cl off of chlorpromazine and put in a 7-membered middle ring without sulfur instead of a 6-membered ring). It was found to be effective in certain types of depressed patients--more for lethargic, slow, difficulty in thinking, feelings of heaviness patients as opposed to agitated and guilt-ridden patients. It was also found that several weeks were needed for clinical improvement. This category of compound became known as a *tricyclic antidepressants*.

Actions: Tricyclics *inhibit biogenic amine reuptake*, and depending on their structure can be good inhibitors of NE and/or 5-HT reuptake. Most are *not* good inhibitors of DA reuptake. Secondary amines (desipramine) are more effective for NE neurons. Tertiary amines (amitriptyline) are more effective for 5-HT neurons. This is consistent with theories of amine function and mood, although these

compounds do not cause mood elevation in non-depressed subjects

Side effects: antimuscarinic effects, α_1 blockade: postural hypotension, can produce a “switch” to mania in bipolars (manic-depressives).

SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs)

Fluoxetine (*Prozac*) is selective for 5-HT (IC_{50} for 5-HT = 70 nM, IC_{50} for NE = 10,000 nM). The main advantage may lie in reduced side effects compared to classical tricyclics. But SSRIs can produce nausea, vomiting, headache and sexual dysfunction for both males and females

MAO INHIBITORS

examples: tranylcypromine, phenelzine

These are used when tricyclics (and/or SSRIs) are ineffective. One must be careful with the *wine and cheese effect* (\uparrow in blood pressure due to *tyramine* in the food). Shorter acting MAO inhibitors such as *moclobemide* appear less prone to blood pressure increase caused by tyramine-containing foods

ECT

First used in 1930s for schizophrenia, this was found to be more effective for depression. It is used in conjunction with a muscle relaxant (e.g., *succinylcholine*) to avoid fractures. The mechanism not known. It has been suggested that down regulation of beta receptors in the CNS is a common feature of most antidepressant treatments; it has also been suggest that down regulation of α_2 presynaptic receptors occurs, which would increase NE release receptor (or other protein) alterations, and would fit better with the time dependency for clinical effect

Mania

(See respective chapter for phenomenology).

Pharmacological aspects of mania:

- MHPG levels during mania are normal
- blockade of NE synthesis with fusaric acid doesn't decrease mania
- alpha-methyltyrosine does decrease mania
- L-DOPA* can *cause* hypomania
- Antipsychotics* can *reduce* mania (drugs of choice before lithium)
- physostigmine* can also *decrease* mania
- has been suggested that mania can result from DA overactivity relative to

acetylcholine

LITHIUM

was first used in 1949 by John Cade following lethargy production in guinea pigs at ca. 1 mM (which is clinical level needed). Lithium inhibits PI turnover, inhibits myo-inositol-1-phosphatase, which converts inositol-1-phosphate to inositol and CNS can't make use of plasma inositol: needs inositol from cycle which is blocked by lithium

therefore lithium may dampen this 2nd messenger system and cause behavioral "stabilization?"

Lithium is used for long-term (prophylactic) bipolar treatment. Antipsychotics (also called neuroleptics) can be used for acute treatment for rapid effects. Lithium may also prove useful for recurring unipolar depression.

side effects:

At therapeutic doses: inflammatory response in the kidney. The effects on kidney function uncertain at toxic doses (which may not be too much higher than therapeutic dose!).

nausea, vomiting, abdominal pain, diarrhea, tremor, coma, death associated with increasing toxicity.

ADDITIONAL DRUGS

Drugs used as anti-epileptic agents have had some success in treating mania.

Carbamazepine, a sodium channel blocker slows the rate of recovery from the inactivated state. **Valproate** (valproic acid) may be similar in action to carbamazepine.

ANXIOLYTIC AGENTS

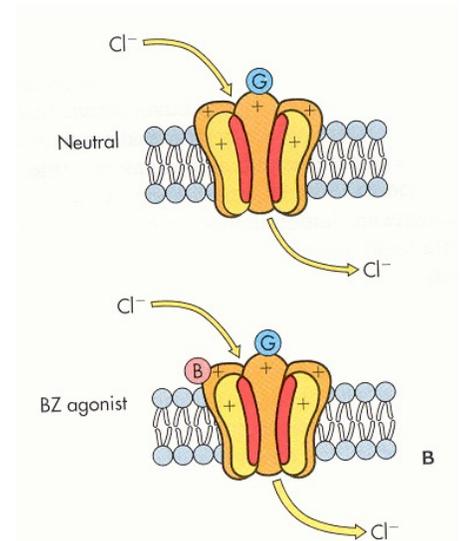


Figure 3. Benzodiazepines (BZ), such as valium, that are used to treat anxiety, enhance the ability of GABA to stimulate chloride influx (B) and thereby inhibit neuronal firing.

Animal Models: use *conflict tests* to evaluate anxiolytic drugs such as diminishing a behavior that normally gets rewarded by adding a negative stimulus (e.g., shock) following a warning. One is asking the question: will the test drug produce a response that indicates the subject is ignoring the warning?

Example: fear-potentiated startle paradigm

1. light before shock
2. sound-induced startle in dark
3. sound-induced startle after light

There is a bigger startle than in dark. One can test to see if an agent can reduce this response as a prediction for possible anti-anxiety effect in humans

CATEGORIES OF ANXIOLYTIC DRUGS

BENZODIAZEPINES

SELECTIVE SEROTONIN REUPTAKE INHIBITORS

5-HT_{1A} AGONISTS

B ANTAGONISTS

BARBITURATES (HISTORICAL IN THIS CONTEXT: SUPPLANTED BY OTHER DRUGS)

BENZODIAZEPINES

examples:

1. *chlordiazepoxide* (Librium)
2. *diazepam* (Valium)
3. *lorazepam* (Ativan)
4. *alprazolam* (Xanax)

PROPERTIES: CLINICAL APPLICATION

1. anxiolytic: *anxiety*
2. anticonvulsant: *epilepsy*
3. muscle relaxant: *spasticity* (multiple sclerosis and cerebral palsy)
4. sedating: *sleep induction*

MECHANISM OF ACTION

Potentiation of GABA action at GABA_A receptors in the CNS. It increases the affinity of GABA for its receptor, and can potentiate the increase in chloride permeability (and hyperpolarization) of the target neurons normally produced by GABA

SIDE EFFECTS

1. can impair motor coordination
2. don't have the acute toxic effects of barbiturates (respiratory depression)
 - a. but *can* produce respiratory depression if combined with alcohol
 1. acute effects can be antagonized by *flumazenil* (competitive antagonist)
3. withdrawal (anxiety, insomnia) can occur, especially with short-acting benzodiazepines such as *triazolam*

5-HT AGONISTS

Buspirone (Buspar) is a 5-HT_{1A} agonist. But it is not known how this would explain anxiolytic effects. It does not cause sedation or hamper motor coordination.

BETA ANTAGONISTS

Ex. *propranolol*, especially for physical symptoms such as tremor and tachycardia. (Note: epinephrine can cause *skeletal muscle twitch* via b₂ agonist effects; this would be blocked by propranolol). Competitive target shooters (gun, archery) sometimes try to use b₂ blockers to steady their aim: use banned in the Olympics.

NEWER APPROACHES

Clinical trials are ongoing with a drug that stimulates a sub-class of glutamate receptors (metabotropic glutamate receptors, or mGlu). This can act pre-synaptically on the glutamate terminals to reduce glutamate release. This drug (called LY354740 at the moment) is reported to be as effective as benzodiazepams with regard to anti-anxiety effects, with with less motor incoordination problems.

Mechanism of action of drugs use to treat anxiety		
Drug	Mechanism of action	Use
Anxiolytics		
Benzodiazepines (diazepam, alprazolam)	Act on GABA receptors	Short-term treatment of anxiety
Buspirone	Acts on 5-HT _{1A} receptor	? Effective in generalized anxiety disorder
Autonomic suppression		
Propranolol	Acts by inhibiting β adrenoceptors	Useful for some social/performance anxiety disorders
Antidepressants		
Imipramine	Tricyclic antidepressant	Most studied biologic treatment in panic disorder
Phenelzine, meclobemide*	MAOIs	Useful for social phobia and panic, may also be useful for PTSD
Fluoxetine, sertraline	SSRIs	Proven efficacy in OCD and panic disorder