Antidepressant Drugs

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SLIDE 1: Our focus today is on antidepressant drugs. Before we begin talking about them, I'd like to talk about major affective disorders.

SLIDE 2:
-I should also point out that the SSRI antidepressants (like fluoxetine) and SNRI antidepressants (like venlafaxine), which I covered earlier, are also first line treatment for most anxiety disorders.

We'll consider 3 disorders where antidepressant drugs are used. These are: Major or Unipolar Depression, Dysthymia (now Persistent Depressive Disorder), and Bipolar Disorder. These disorders represent a lot of suffering and lost manpower hours in the US. It is estimated that $43 billion per year is spent in treatment, job absenteeism, and reduced job productivity.

-In addition depression complicates the treatment and therefore increases the health risk for a number of conditions including cardiovascular disease, diabetes, cancer, and so forth.

SLIDE 3: Major depression or unipolar depression is a prolonged period of depressed mood or loss of interest or pleasure. A diagnosis is made if other causes have been ruled out: such as underlying disease states, drug induced depression, or depression as a symptom of another psychiatric disorder.

In major depression:

- the patient feels depressed most of the day, generally every day. In Addition to losing interest in all or almost all daily activities (anhedonia),
- the patient is likely to lose weight.
-Insomnia or hypersomnia occur daily.
-tend to experience fatigue or loss of energy daily.
-experience pyschomotor agitation or retardation.
-experience feelings of worthlessness and excessive guilt.
-Preoccupation with death and thoughts or plans of committing suicide are common.
-Reduced ability to think or concentrate is also a complaint.

Major depression typically lasts for weeks to months and remits. It may recur. If it recurs once or twice, pharmacotherapy may be in order. This disorder affects *up to 25% of females and 12% of males in the US.*

SLIDE 4:*Dysthymia* (dis-thee-mea) or Persistent Depressive Disorder is persistent depressed mood that lasts for 2 years or longer.

The same types of symptoms that are present in major depression occur in dysthymic disorder (READ SLIDE).

The major difference is the time course and in some cases the intensity of the symptoms. A dysthymic patient is depressed all the time but may not be as depressed as a patient who is experiencing major depression. To be diagnosed with dysthymia, the patient cannot have an episode of major depression occurring during the 1st two years of his persistent depression. Also, other causes both physiological and psychological must be ruled out before the diagnosis can be made.
~ 6% of the population is affected.

SLIDE 5: Some patients have a double dose of depression. That is they have a baseline of dysthymia with intermittent bouts of major depression. So, they are feeling depressed every day, but periodically they have periods of 2 weeks or more where they are severely depressed.

SLIDE 6: Although our focus is pharmacological, I want to stress that counseling and cognitive behavioral therapy is very important for some of these patients whose depression may be secondary to a personality disorder or other psychological disorder.

Secondly, one alternative to antidrepressant drug therapy is electroconvulsive therapy (ECT). Given the controversy surrounding this type of treatment as well as the cost, it is generally reserved for patients that do not respond to drug therapy. None the less it is very effective (80-90%) and has minimal side-effects. The most significant SE being that there is temporary retrograde memory loss.

-A milder form of electrical stimulation called repetitive transcranial magnetic stimulation or TMS is also available although its effectiveness is significantly less than ECT and is very expensive.

SLIDE 7: Bipolar disorder is characterized by intermittent bouts of depression and mania or hypomania. Bipolar disorder has also been called manic depressive disorder in the past. It affects ~ 0.4- 1.6% of the population, and there is a strong hereditary component.

There are several subtypes of bipolar disorder that we will not delve into that vary in length of phases and rapidity of cycling between phases and the degree of symptomology.

In the depressive phase, there are varying degrees of depressed mood and related symptoms that we talked about with Major Depression and dysthymia.

SLIDE 8: The manic phase of bipolar disorder is characterized by an inflated self esteem and grandiose ideas. Usually there is a decreased need for sleep, and the patient may sleep as little as 3 hours per night. The individual will be extremely talkative and have flights of ideas. Psychomotor agitation is common. The person will be easily distracted by extraneous stimuli.

On the other hand, the person may tend to have an increase in goal-directed activity- that is become very preoccupied with performing tasks or doing schoolwork. Another feature is that the individual may become excessively preoccupied with pleasurable activities that may have risk for painful consequences such as unrestrained buying sprees, indiscriminate sex, or foolish business investments.

SLIDE 9: The manic phase can be broken down in severity in 3 stages, with stage 3 being the worst. Stage 1 mania is milder and the patient is still in control. In Stage 2, the symptoms that we talked about in the last slide are exacerbated. In stage 3, the patient is out of control and incoherent, panic stricken, desperate, and experiencing looseness of associations. Bizarre psychomotor activity occurs and he may hallucinate.

Some forms of bipolar disorder are characterized by a milder form of mania called hypomania, where the symptoms that we have discussed in the previous slide are present but to a lesser extent.

SLIDE 10: Of all of the affective disorders, individuals with bipolar disorder are more likely to have co morbid psychiatric disorders. Substance abuse is common. In a random sampling of individuals in alcohol treatment programs, 2-4% were found to be bipolar. In a random sampling of individuals in cocaine treatment programs, 4-30% of patients were found to be bipolar. Other common comorbid conditions are OCD, panic disorder, and bulimia.

SLIDE 11: (Cartoon showing depressive/manic phases)

SLIDE 12: Now we will switch to the treatment of these disorders and begin with major depression and dysthymia. I'd like to first point out that similar pharmacological treatments are used for major/unipolar depression and dysthymia, so I when I speak of treatment of depression, I'm speaking of both.

SLIDE 13: MAO inhibitors were the first antidepressants marketed. They act by inhibiting MAO A and B, although selective A and B inhibitors have since been developed.

Mechanism of Action: Their blockade of monoamine oxidase, decreases the breakdown of neurotransmitter and leads to packaging of more neurotransmitter into synaptic vesicles and therefore increases amount of NE, DA, and 5-HT in the synapse.

◆While MAO inhibition is seen immediately, the therapeutic effects take weeks (at least 2 weeks) to develop, this is a common feature of all antidepressant drugs and speaks to a more complex underlying mechanism of action. I will return to this shortly

Tranylcypromine is one of the older MAO inhibitors still marketed today. MAO inhibitors are not used as frequently as they were previously because of their potential for producing toxicity. Drug interactions and tryramine containing food interactions can lead to

hypertensive crisis. In addition, MAO inhibitors inhibit metabolism of other drugs such as meperidine.

Tranylcypromine (parnate) and Selegiline (eldepryl) are two MAO inhibitors approved still approved for treatement of depression, although they are typically reserved for patients that do not respond to SSRI which I will take about in a few minutes.

SLIDE 14: The TCAs were the second class of antidepressants to be introduced and were the main stay of treatment from the 1960's to the early 1990's . They get their name because of their basic 3 ring structure (see structure). Substitutions at R1, R2, R3 account for the different congeners that are on the market. They are inhibitors of NE, 5-HT and to a lesser extent DA uptake. They inhibit the transporters that remove these NTs from the synaptic cleft.

Mechanism of Action: Inhibition of the transporters occurs immediately. However, there is a time delay of several weeks for their therapeutic action.

◆The bottom line is that we don't know exactly why there is a delay in the therapeutic action, but there are several theories:

We do know that consistent with the delay in therapeutic effect for all antidepressant drugs, - we know that neuroadaptive processes are involved that lead to increase neurotransmission. Currently we believe that three key processes are involved:

(1) At the postsynaptic membrane – there is increased adrenergic or serotonerigic receptor density and/or sensitivity as well as increased G-protein coupling.
(2) There is increased neurogenesis (and presumably synaptic contacts)
(3) Downregulation of the transporters for serotonin (SERT) , norepinephrine (NET) etc..and therefore increased neurotransmitter in synapse.

So bottom line is that the initial treatment with antidepressant drug results in immediate inhibition of NT transporter with a modest increase in neurotransmission, but over time there are adaptive changes that result in a far more robust increase in the level of neurotransmission and this then has a therapeutic benefit.

.Now the question that remains is the 'defect' in how much NT is released? Or is the postsynaptic receptor or signal pathway defective and therefore to restore equilibrium you need to increase amount of NT that will activate postsynaptic receptor?

SLIDE 15: There is a range of selectivity of inhibition of NE vs 5-HT transporters, which I've drawn on the board. The tertiary amines exhibit roughly equal inhibition of NE and 5-HT transporters (**imipramine**). In contrast, the secondary amines preferentially inhibit NE over 5-HT transporters (**Amoxapine**).

That either an increase in NE or in 5-HT is therapeutics suggests that there are subsets of depression in which there is a defect in either system.

SLIDE 16: Given that demethylation of tertiary amines occurs metabolically, administration of a tertiary amine will result in the patient having both parent drug and active metabolite producing antidepressant action.

SLIDE 17: Some of the side effects associated with TCAs are sedation, which may be due to blockade of Histamine H1 receptors located in the CNS. TCAs have very degrees of anticholinergic activity depending upon the specific drug. Blockade of muscarinic receptors results in a whole host of side effects including (READ SLIDE).

Because of these side effects, there are many conditions where TCAs are contraindicated such as glaucoma, prostatic hypertrophy, or dementia. These drugs probably should not be prescribed in the elderly unless absolutely necessary because they are particularly sensitive to the anticholinergic effects.

SLIDE 18: Cardiovascular effects occur at therapeutic concentrations. Orthostatic hypotension is due to blockade of α1 adrenergic receptors. Quinidine-like effects occur on the heart muscle and are concentration dependent. EKG changes include flattening of the T wave or T wave inversion, myocardial depression, and arrhythmias at high concentrations.

SLIDE 19: A number of drug interactions occur. TCAs inhibit many isoforms of P450 enzymes and thus alter the metabolism of many drugs. The antihypertensive actions of guanethidine, α-methyl dopa, and clonidine are reduced. TCAs reduce the seizure threshold and are not good drugs for treatment of patients with seizure disorders. In some cases, they can produce seizures at therapeutic concentrations in patients who have not had a previous diagnosis of a seizure disorder. Because they are sedating they have additive effects with other sedatives such as alcohol. They act synergistically with other anticholinergic drugs. They should never be given with MAO inhibitors because a hyperpyretic crisis, including convulsions, coma can result.

SLIDE 20: Tricyclic antidepressants have a very narrow therapeutic window. Taking 20 or more tablets could be lethal, therefore, RX amounts should be limited. Overdose results in an exacerbation of the SE that we already considered. Hypotension, shock, and renal failure can occur. Grand mal seizures and hyperpyrexia and coma may occur. Conduction disturbances can result in fatal arrhythmias.

SLIDE 21: To treat overdose, supportive measures are indicated: support renal, cardiac, and resp function. Although no specific antidote exists, physostigmine can reverse much of the anticholinergic action. Gastric lavage and/or activated charcoal to remove as much of the ingested dose as possible. Cooling of the core body temperature for hyperpyrexia and fluid expanders for shock. The patient should be monitored in the CCU for at least 72 hours, because arrhythmias may occur after the crisis has appeared to pass.

SLIDE 22: Other uses of TCAs.

SLIDE 23: The third generation of antidepressants that we will discuss today includes some miscellaneous drugs and the SSRIS.

SLIDE 24: The heterocyclics have the TCA backbone, but also have an additional ring. Interestingly, **amoxapine** is a nonselective transporter blocker, but **maprotilene** is more selective at the NE transporter. Depressed patients with lethargy have been reported to respond better to maprotilene.

Trazadone is an **atypical antidepressant** in a class by itself. It is a 5-HTR antagonist and weak selective reuptake inhibitor and has no

antichol effects. It is extremely sedating and is associated with sexual dysfunction in males.

Bupropion (Wellbutrin; Zyban for smoking cessation) **atypical antidepressant** is a DA selective reuptake inhibitor, and it is a good antidepressant in some patients. Given its effect on DA levels it is useful in controlling the craving for nicotine (Zyban; smoking cessation). For similar reasons it is effective in ADHD.

Note: **Typical Antidepressants** like SSRI's, TCAs, SNRI's, MAO inhibitors effect serotonin and/or NE levels

Atypical Antidpressants like Buproprion and Trazadone either effect other neurotransmitters or act on postsynaptic receptors.

SLIDE 25: (NE/SERT Selectivity Chart)

SLIDE 26: **Selective Serotonin Reuptake Inhibitors or SSRI's** were developed in the early 1970's and have become the treatment of choice since the early 1990's. The principal reason being that these agents are safer!

Mechanism of Action: Inhibition of the SERT transporter occurs immediately. However, there is a time delay of several weeks for their therapeutic action (see detailed explanation in TCA section)

SSRIs are indeed more selective and therefore have less side-effects: 1) they don't interact with H1 receptors in CNS or cholinergic receptors and therefore are non-sedating and the lack of cholinergic activity eliminates the serious side-effects associated with TCAs, seizures, cardiac effects, hypotension, etc.

SLIDE 27: **Fluoxetine (Prozac),** is the most prescribed antidepressant, and is used in the treatment of major depression, but also for, OCD, bulimia, PMS, panic disorder, etc.

- SSRIs Like Fluoxetine are often used on or off-label for treating anxiety disorders, in adults and children.

Increased serotonin in the synapse that results from transport inhibition will activate a number of different serotonin receptors and therefore the SSRI's have there own set of side-effects: Headache, Insomonia, restlessness, nausea (likely 5-HT_3R mediated), anorexia, and sexual dysfunction, which includes: erectile dysfunction, delayed ejaculation in males and anorgasmia. While these side-effects are usually temporary…they are the major cause for discontinuation of use.

Fluoxetine is a first line antidepressant approved for treatment of major depression in children (Sertaline approved for OCD in children).

SLIDE 28: There is a weak statistical link of SSRI's treatment and increased risk for suicide in children, leading to an FDA warning in 2004 (**Black Box warning**). While additional studies have not really shed additional light on this risk- this warning has not resulted in a significant barrier to prescribing SSRI's for treatment of major depression in adolescents.

Serotonin Syndrome: All SSRI's can as a result of interactions with MAO inhibitors case the serotonin syndrome: a rare but potentially life-threatening condition characterized by altered mental status, fever, agitation, tremor, etc.

SLIDE 29 **Sertaline (Zoloft)** is another widely used SSRI. Treatment of Major Depression, OCD, panic disorder.

Similar constellation of side-effects: Nausea, Dyspepsia, dizziness, insomonia, sexual dysfunction.

SLIDE 30: **Paroxetine (Paxil**)…..Major depression, OCD, panic disorder.

June 28, 2013- FDA approved use of paroxetine (Brisdelle) for menopausal hot flashes (first non-hormonal treatment)

Side effects: Nausea, insomonia, headache, sexual dysfunction, etc.

SLIDE 31: Other SSRI's include: **Citalopram (Celexa**) and **Escitalopram (Lexapro**) which is just the S-enantiomer of Citalopram.
-just FDA approved in 2011 ***Vilazodone (Viibryd****)*
SNRI: -Other newer agents the are grouped as SNRI's, that is serotonin and norepinephrine selective agents, include **Venlafaxine (Effexor** and **duloxetine (Cymbalta).**

SLIDE 32: Criteria for choosing an antidepressant: see slide.

SLIDE 33: Since the 1970's **lithium carbonate** has been the treatment for bipolar disorder. At therapeutic levels, Lithium has a mood-stabilizing effect, hence its value for treating bipolar disorder (~70% of patients respond) The mechanism of action is really not understood yet.

Unfortunately the therapeutic window for lithium is very small; the SE include: memory problems, weight gain, tremor, poluria, drowsiness, hypothyroidism, cardiac effects,etc

The therapeutic index is 2-3 and acute intoxication can cause vomiting, profuse diarrhea, ataxia, coma, and convulsions.

Treatment is mostly supportive and dialysis.

Often- in addition to lithium, and antidepressant is sometimes prescribed during depression phase. An antidrepessant is never prescribed alone because it can elicit what is called a switch- that it is it can trigger a manic episode.

SLIDE 34: Because of the low therapeutic index for lithium in recent years there has been increased use of alternative mood-stabilizing agents: these include several of the anticonvulsant agents, including **valproic acid**, **carbamezepine, lamotrignine**, etc.

These anticonvulsants are nearly as effective as lithium and are far safer. How they stabilize mood is also not understood at all.

Prior to starting treatment with lithium or **carbamazepine**, often an antipsychotic like haloperidol will be given to stabilize the patient.

Finally atypical antipsychotic (dopamine receptor partial agonist) such as **aripiprazole(Abilify)** are sometimes given as add on agents to help manage bipolar disorder and are also prescribed as add-on treatment for major depression, particularly for patients that don't respond well to an SSRI..

Option 1: **Mood Stabilizer** (lithium/valproic acid/carbamazepine) ***+/-***

.. during depressive phase- add **SSRI antidepressant** (e.g. fluoxetine)

… during manic phase- add **Atypical antipsychotic (**e.g. aripiprazole)

Option 2: **Olanzapine** (Pyrexia) + **Fluoxetine** (Prozac) [combination Symbax].. *paradoxical-SSRI combined with 5-HTR blocker?*

SLIDE 35: Study guide, drug list (those drugs listed in lecture script and ppt)…. First Aid Basic Sciences Organ Systems, 2nd Edition: Chapters 6 and 7.