Psychotropic Medications: Overview Seminar by Dr. Cummings

Editors: Mikyla Cho, David Puder, M.D.

DEFINITIONS:

Psychotropic medication – An ion or compound used primarily to treat the signs and symptoms of mental diseases, defects, or disorders. By historical convention, anticholinergic medications used to treat acute extra-pyramidal symptoms induced by neuroleptic medications have been included under this definition. Some medications, e.g. antiepileptics, may vary as to whether they fit this definition, depending on the intent of use. For example, valproic acid (Depakene or Depakote) used to treat a partial motor seizure would not be classified as a psychotropic medication, while the same medication used to treat bipolar mood disorder would be classified as a psychotropic medication.

Agonist – An ion or molecule, which when bound to a receptor, produces an effect on signal transduction similar in direction and degree to the naturally occurring neurotransmitter.

Antagonist – An ion or compound, which when bound to a receptor does not activate the receptor. That is, signal transduction is antagonized. An example of this is the opiate antagonist, naltrexone or antipsychotics such as haloperidol (dopamine antagonist).

Partial agonist – An ion or compound, which when bound to a receptor produces a change in signal transduction which is in the same direction as the natural neurotransmitter, but weaker. An example of this is the second-generation antipsychotic, aripiprazole (dopamine partial agonist).

Inverse agonist – An ion or compound, which when bound to a receptor acts on signal transduction in a manner opposite to that of the naturally occurring neurotransmitter. An example of this is the benzodiazepine inverse agonist flumazenil.

Allosteric modulation – This form of receptor modulation occurs when a medication acts by binding to a secondary site on a receptor protein. An example of this is benzodiazepine binding. Benzodiazepines bind to a secondary site on the alpha subunit of the gamma-aminobutyric acid (GABA) receptor. Benzodiazepine binding alone does nothing. However, if GABA is simultaneously bound to the receptor, the frequency of opening of the chloride channel controlled by the GABA receptor is increased, amplifying the effect of the GABA, e.g. greater sedation. Binding of the antipsychotic, clozapine, to the glycine site on the NMDA receptor also fits this model and accounts for clozapine's capacity to increase glutamate signal transduction.

Binding affinity – This is a measure of the electrostatic (van der Waals forces) between a neurotransmitter or medication and its receptor. Mathematically, this is usually

expressed as one divided by the dissociation constant of the medication. The dissociation constant, in turn, is a measure of the concentration of medication needed to saturate one-half of the receptors present.

Reuptake inhibitor – several neurotransmitters have their signal terminated by being actively transported back into the presynaptic neuron by a reuptake transport molecule located in the cell membrane on the proximal side of the synaptic cleft. A reuptake inhibitor acts by binding to and decreasing the activity of the reuptake transporter. For example, SSRI antidepressants act by inhibiting the reuptake transporter for serotonin, while SNRI and tricyclic antidepressants inhibit the reuptake of both serotonin and norepinephrine.

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GENERAL MECHANISMS OF ACTION:

While a few medications interact with neurons via other mechanisms, e.g. lithium's direct modulation of G-protein coupling, most psychotropic medications alter signs and symptoms of mental disorder in one of two ways:

1. Binding to primary or allosteric sites on ligand-gated ion channels: An example of this type of modulation of neuronal signal transduction would be anxiolysis or sedation with a benzodiazepine. When a benzodiazepine binds to its allosteric site on the GABA-a receptor complex and a GABA molecule is also bound to the primary receptor site, it causes the chloride channel portion of the GABA receptor to open more frequently, increasing the overall influx of negatively charged chloride ions into the neuron. This makes the interior side of the dendritic membrane more negative, i.e. moving it away from firing threshold. This type of interaction with neurons is characterized by an immediate effect as soon as the medication is present at the target receptor. Similarly, the effect abates as soon as the medication is removed. A variant of this mechanism is blockade of voltage-dependent sodium channels by antiepileptics, a common mechanism for several members of this class.

2. Initiation and adaptation: Medications, such as the antidepressants or antipsychotics, which repeatedly perturb neuronal signal transduction, e.g. by blocking neurotransmitter reuptake or catabolism or antagonizing post-synaptic receptors, set in motion an adaptive response in neurons usually involving up or down regulation of receptor numbers, changes in coupling of G-protein receptors to intracellular molecules responsible for increasing or decreasing second messengers, and, finally, modulation of DNA transcription and translation.

Unlike the immediate effects seen at ligand-gated receptors, initiation and adaptation produce changes in neuronal signal transduction which typically require weeks to months to occur and which do not depend on the continuous presence of the medication at the receptor or reuptake transporter.

Interestingly, in this context, psychotropic medications and psychotherapies appear to behave similarly. Baxter et al. demonstrated that either an SSRI antidepressant taken for six weeks or response prevention behavioral therapy produced a diminished activation signal from the nondominant caudate nucleus and an enhanced inhibitory signal from the orbital cortex to the caudate nuclei via the globus pallidus in individuals with OCD. The changes in the metabolic activity of neurons involved in this disorder adapted identically, whether the repeated perturbation was via medication or response prevention. When combined, the treatments demonstrated additive effects.

Both types of modulation of neuronal signal transduction suggest that mental illness is associated with a distortion of neuronal signal transduction outside normal homeostatic parameters Unfortunately, one of the limitations of both approaches is that the goal is often to favorably perturb DNA transcription and translation remotely (i.e. from the cell surface). Because this requires a cascade of molecular events, effectiveness is often slow and limited.

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FIRST GENERATION ANTIPSYCHOTICS:

Chlorpromazine	Thorazine and Sonazine
Fluphenazine	Prolixin
Haloperidol	Haldol
Loxapine	Loxitane
Perphenazine	Trilafon
Pimozide	Orap
Thiothixene	Navane
Trifluoperazine	Stelazine

- U.S. Pharmacopeia (USP) or generic names appear in the left-hand column of this and subsequent medication tables. Trade or proprietary names appear in the right-hand column.

Although the first-generation (conventional) antipsychotics are derived from a number of chemical classes (i.e. the phenothiazine group with its aliphatic side-chain piperidine and piperazine subclasses, the thioxanthenes, the butyrophenones, some dibenzoxazepines, the dihydroindolones and their derivatives, the diphenylbutylpiperidines, the benzisoxazoles, dibenzodiazepines, dibenzothiazepines, and thienobenzodiazepines) they differ clinically in relation to their affinity for dopamine (D-2) receptors, rather than due to chemical class. That is, while the antipsychotic mechanism and efficacy at equivalent doses is the same across the entire group, side-effect profiles vary in relation to affinity for the dopamine (D-2) receptor. Dopamine (D-2) receptor antagonism and the resulting depolarization blockade of dopamine neurons account for 92% to 93% of the variance in the antipsychotic effects of these medications.

With respect to side-effect profiles –

Low-potency medications (e.g. chlorpromazine) are also robust histamine (H-1), alpha-adrenergic, and muscarinic acetylcholine receptor antagonists. Respectively, these receptor affinities account for sedation, hypotension, and a host of anticholinergic adverse responses.

Conversely, high-potency medications (e.g. fluphenazine and haloperidol) show far less sedation, hypotension, and anticholinergic effects, but are more likely to induce acute dystonia, acute akathisia, or acute pseudo-Parkinsonism due to robust dopamine antagonism in the pars compacta-striatal dopamine circuit.

Mid-potency medications (e.g. thiothixene) show adverse effects in all the cited areas, but typically in attenuated form.

Importantly, all the first-generation antipsychotics induce tardive dyskinesia at an incidence rate of about 3% to 5% per year of exposure and up to about 60% prevalence. Luckily, tardive dyskinesia is mild and non-progressive in about 94% of cases. This condition results from chronic antagonism of post-synaptic receptors in the basal ganglia. Two mechanisms are known to underlie this condition, which are denervation sensitivity and oxidative damage of dopamine (D-2) receptors. Chronic antagonism causes an increase in the number of receptors expressed, while antipsychotic receptor occupancy slows receptor turnover, exposing the receptors to oxidative damage, cross-linking amino acids, and inducing conformational change. An important outcome is loss of plasticity. That is, once tardive dyskinesia is well-established, withdrawal of the offending agent does not typically result in a return of the nigrostriatal pathway to baseline signal transduction, i.e. movements tend to persist.

Lastly, the first-generation antipsychotic medications, especially high-potency medications, may rarely induce neuroleptic malignant syndrome (NMS). This syndrome is characterized by delirium, muscle rigidity, rhabdomyolysis, extreme fever, febrile seizures, and renal failure due to myoglobinuria. The mortality rate is about 15% in well-managed cases.

SECOND GENERATION ANTIPSYCHOTICS:

Aripiprazole	Abilify, Abilify Maintena, Aristada
Asenapine	Saphris
Brexpiprazole	Rexulti
Cariprazine	Vraylar
Clozapine	Clozaril and FazaClo
Iloperidone	Fanapt
Lurasidone	Latuda
Olanzapine	Zyprexa, Zydis, and Zyprexa Relprevv
Paliperidone	Invega, Invega Sustenna, Invega Trinza
Quetiapine	Seroquel and Seroquel XR
Risperidone	Risperdal and Risperdal Consta
Ziprasidone	Geodon

- Note that risperidone is metabolized to 9-hydroxy-risperidone and that depot risperidone (Consta), paliperidone, and paliperidone palmitate (Invega Sustenna/Trinza) are all in the end 9-hydroxy-risperidone. These medication products vary only with respect to the vehicle by which they are delivered.

Clozapine, the first of the second-generation antipsychotics, was synthesized in 1958, only eight years after chlorpromazine, the initial first-generation antipsychotic. It was missed, however, as a potential antipsychotic because it did not produce neurolepsis and cataplexy in mice.

Presently, the second-generation antipsychotics can be divided into three groups based on structural similarity. The clozapine family is comprised of asenapine, clozapine, olanzapine, and quetiapine. The risperidone family is comprised of iloperidone, lurasidone, paliperidone, risperidone, and ziprasidone. Finally, the partial dopamine agonists include aripiprazole, brexpiprazole, and cariprazine.

To date, the second-generation antipsychotics have demonstrated superiority over the first-generation medications only in the cases of clozapine, olanzapine, and risperidone. Of these, clozapine is clearly superior, producing substantial improvement in positive, negative, and cognitive domains in circa 50% of individuals refractory to at least two prior adequate antipsychotic trials (with a therapeutic dose for a minimum of six weeks). Clozapine also has been shown to specifically reduce criminal behavior, violence, and suicide among individuals suffering from schizophrenia spectrum disorders, independently of its antipsychotic effects. The other first and second-generation antipsychotics produce similar results in only 9% to 14% of such refractorily ill individuals. Moreover, antipsychotics other than clozapine are much better at improving positive symptoms compared to the negative and cognitive symptom domains.

With respect to adverse effects, the second-generation antipsychotics are about ten-fold less likely to induce EPS or tardive dyskinesia. This appears to be based on more rapid dissociation from the dopamine (D-2) receptor, as well as antagonism of serotonin (5-HT2A) receptors. This latter effect increases dopamine release in the meso-cortical, nigrostriatal, and infundibular-pituitary dopamine circuits, but not in the meso-limbic circuit, as the pre-synaptic dopamine neurons of this circuit lack 5-HT2A receptors.

The second-generation antipsychotics, however, are more likely than the first-generation antipsychotics to induce metabolic syndrome. At the heart of this syndrome is the ability to induce resistance at insulin receptors, thereby creating glucose intolerance and shunting lipids toward central adiposity. Clozapine and olanzapine are the worst offenders, while aripiprazole, asenapine, brexpiprazole, cariprazine, and lurasidone appear to have little or no capacity in this direction. The remaining drugs are intermediate in terms of risk.

Like the first-generation antipsychotics, these medications, excluding aripiprazole, asenapine, brexpiprazole, and cariprazine, also commonly exert histamine (H-1), alpha adrenergic, and muscarinic acetylcholine antagonism, producing sedation, hypotension, and anticholinergic effects, respectively. In addition, the clozapine family of medications carries risks for leukopenia/agranulocytosis, eosinophilic myocarditis (rare), and bowel obstruction.

On the research horizon are antipsychotic medications which do not achieve their effects via modulation of dopamine signaling. These include allosteric modulators of metabotropic glutamate receptors and selective M-2 and M-4 muscarinic receptor antagonists. It is hoped that if a variety of pathways can be used to artificially move signal transduction in the psychotic brain back toward homeostatic functioning, the effects across mechanisms will produce additive benefits. Improved ability to premorbidly identify schizophrenic individuals may make it possible to decrease the onset of overt psychotic illness.

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SSRI ANTIDEPRESSANTS:

Citalopram	Celexa
Escitalopram	Lexapro
Fluoxetine	Prozac
Fluvoxamine	Luvox
Paroxetine	Paxil
Sertraline	Zoloft
Vilazodone	Viibryd
Vortioxetine	Trintellix

- Citalopram and Escitalopram are the racemic and left-handed preparations of the same molecule.

Taken together, the selective serotonin reuptake inhibitor (SSRI) antidepressants account for approximately 70% of all antidepressant prescriptions in the U.S. Their popularity reflects both a broad range of efficacy in mental disorders involving depressed mood, anxiety, obsessions-compulsions, and impulsiveness and greater safety than was possible with the classic tricyclic antidepressants or monoamine oxidase inhibitors (MAOIs).

With respect to major depression, the SSRI antidepressants appear to be as effective as mixed or selective noradrenergic antidepressants. However, in severe or melancholic depression, mixed serotonergic/noradrenergic antidepressants appear to be supeior at least in most studies. Anxiety disorders, which include generalized anxiety disorder, social phobia, OCD, and PTSD, have shown positive responses to SSRI antidepressants. These medications also may reduce dysphoria in other mental disorders or reduce the frequency of impulsive behaviors, such as binge eating.

All of this is not to say that SSRI antidepressants are without risks. They may induce relative amotivation (lack of appropriate anxiety), delayed orgasm or anorgasmia, decreased bone mineralization, decreased fetal growth in the third trimester, premature birth, and rare postpartum pulmonary hypertension in the neonate. Vilazodone and vortioxetine, because they are 5-HT1A partial agonists, have shown fewer sexual side-effects. Paroxetine has been associated with a rate of one per 25 live births of cardiac malformation, usually a ventricular septal defect. Some meta-analyses, however, have failed to find this association.

Notably citalopram, and to a lesser extent, escitalopram, may prolong the QT interval at higher doses.

Finally, if mixed with other medications which exert serotonergic effects, e.g. MAOIs, the SSRI antidepressants may cause serotonin syndrome, characterized by an elevated

metabolic rate, fever, severe nausea, vomiting, diarrhea, seizure, coma, and death due to cardiovascular collapse.

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HETEROCYCLIC ANTIDEPRESSANTS:

Amitriptyline	Elavil
Amoxapine	Asendin
Bupropion	Wellbutrin, Wellbutrin SR, and Wellbutrin XL
Clomipramine	Anafranil
Desipramine	Norpramin, Pertofrane
Desvenlafaxine	Pristiq
Doxepin	Adapin and Sinequan
Duloxetine	Cymbalta
Imipramine	Tofranil
Levomilnacipran	Fetzima
Maprotiline	Ludiomil
Mirtazapine	Remeron
Nortriptyline	Aventyl and Pamelor
Trazodone	Desyrel
Venlafaxine	Effexor and Effexor ER

The tricyclic antidepressants, amitriptyline, nortriptyline, imipramine, and desipramine, are comprised of secondary and tertiary amine molecules, with amitriptyline and imipramine being the tertiary amine or parent compounds of nortriptyline and desipramine. Doxepin also is a classic tricyclic antidepressant. All the tricyclic antidepressant medications show mixed reuptake inhibition of both serotonin and norepinephrine, with the secondary amine drugs being more noradrenergic and the tertiary amine molecules being more serotonergic. The most serotonergic tricyclic is clomipramine (Anafranil), however, this medication is more commonly used to treat refractory OCD rather than depression.

While the tricyclic antidepressants were often highly effective in treating depression and anxiety disorders, their narrow therapeutic index (six to eight times the therapeutic dose can be fatal) has caused them to become largely medications of historical interest. Amoxapine and maprotiline, although less cardiotoxic, also have largely become historic medications. Interestingly, amoxapine gives rise to varying amounts of 7-hydroxyamoxapine (a dopamine antagonist) as a metabolite and may thus cause EPS or TD.

Duloxetine and venlafaxine have become the most commonly prescribed “mixed” mechanism antidepressants. Both are much safer than the tricyclic antidepressants but

may increase blood pressure in sensitive individuals. Duloxetine also is indicated for treatment of diabetic neuropathy. Levomilnacipran is a recent addition and is the most noradrenergic of the newer mixed mechanism antidepressants. Milnacipran, a racemic mixture, is not marketed in the U.S. as an antidepressant and is instead used to treat fibromyalgia.

Trazodone was never highly effective as an antidepressant but is often used as an alternative sedative in combination with an activating antidepressant. Its analog, nefazodone, was withdrawn from active marketing in the U.S. due to hepatotoxicity.

Mirtazapine also is a "mixed" mechanism antidepressant but is unique in inhibiting serotonin at 5-HT2A and 5-HT2C receptors but promoting the release of norepinephrine by the locus ceruleous via antagonism at alpha-adrenergic autoreceptors at higher doses (> 30 mg per day). Some (Stahl et al.) have referred to the combined use of an SSRI antidepressant and mirtazapine as "California rocket fuel." Lastly, mirtazapine at lower doses (15 mg at bedtime) may be more effective than propranolol in treating antipsychotic-induced akathisia.

Finally, bupropion is a monocyclic molecule which strongly resembles amphetamine. When metabolized in the liver, however, it is converted to hydroxy-bupropion, which acts as a norepinephrine reuptake inhibitor. In contrast, the parent compound, like amphetamines, blocks the reuptake of dopamine and promotes the release of dopamine from presynaptic vesicles. In forensic populations, inhaling (snorting) or injection of bupropion is pursued to avoid first-pass liver metabolism to the hydroxy form. Thus, bupropion has become a drug of abuse in some settings.

Overall, about 60% of individuals with major depression show a 50% or more reduction in depression ratings when given an adequate trial of an antidepressant medication. Unfortunately, only about 35% achieve a sustained remission. Augmentation approaches are numerous and include CBT, lithium, triiodothyronine, low dose second-generation antipsychotics, exercise, and stimulants. Non-medication treatments now include ECT, TMS, and VNS. ECT remains the most effective treatment, while data regarding transcranial magnetic stimulation and vagus nerve stimulation remain somewhat mixed.

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MONOAMINE OXIDASE INHIBITORS:

Isocarboxazid	Marplan
Phenelzine	Nardil
Tranylcypromine	Parnate

The monoamine oxidase inhibitors were highly effective in treating atypical depression and panic disorder. They are, however, rarely prescribed due to their risk of hypertensive crisis.

Unlike antidepressant medications which increase synaptic serotonin or norepinephrine by decreasing presynaptic reuptake or promoting release, the monoamine oxidase inhibitors (MAOIs) exert their effects on serotonin and norepinephrine signal transduction by covalently binding to and inactivating monoamine oxidase, thereby inhibiting the catabolism of these neurotransmitters. Antidepressant and anxiolytic effects occur when greater than circa 60% of monoamine oxidase is inactivated. The blockade of catabolism remains until enough of the poisoned enzyme has been replaced by newly synthesized monoamine oxidase.

Unfortunately, in addition to inactivating monoamine oxidase in the brain, these medications poison peripheral monoamine oxidase as well. Thus, if the individual ingests an alpha-adrenergic receptor agonist, e.g. tyramine from food or medications such as pseudoephedrine, Neo-Synephrine, etc., the individual has no way to clear the pressor agent. As a result, blood pressure may rise rapidly and dramatically, sometimes causing stroke or even cardiac and aortic rupture.

Outside the U.S. reversible MAOI medications, e.g. moclobemide, have become available. These drugs differ from the classic drugs in that if enough substrate for the monoamine oxidase is present, it can displace the MAOI, thereby avoiding the risk of hypertensive crisis. To date, however, no reversible monoamine oxidase inhibitors have been approved by the U.S. Food & Drug Administration.

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MOOD STABILIZERS:

Carbamazepine	Equetro and Tegretol
Lamotrigine	Lamictal
Lithium	Eskalith and Lithobid
Topiramate	Topamax
Valproic Acid	Depakene, Depakote, and Depakote ER

Lithium is a cationic metal first used in the 19th century to treat gout and was discovered by Cade in 1949 to exert anti-manic effects. Its interactions with the brain are complex and include the following: desensitizing presynaptic 5-HT1A autoreceptors in the raphe nuclei and thereby increasing serotonin release, decoupling G-protein linked production of second messengers, and directly increasing transcription of fast response genes, e.g. KREB, PHOS, and JUN. Consistent with its complex actions in the brain, its clinical uses cover a broad range including the following: treatment of acute mania and hypomania, augmentation of antidepressants, prophylaxis of mood cycling in bipolar mood disorder (especially type I), reduction of suicide risk, and decrease of impulsively or affectively driven violence. Being an ion, lithium does not undergo metabolism and is not protein bound. It is cleared via the kidneys. Despite being highly effective, lithium is not presently widely used. This is due to lithium's very narrow therapeutic index. Optimal plasma concentrations for the treatment of bipolar mood disorder are 0.8 to 1.2 mEq/L. However, toxic signs and symptoms may begin at concentrations as low as 1.5 mEq/L and serious toxicity with risk of permanent neurological injury may occur at concentrations as low as 2.0 mEq/L.

Until the early 1980s, lithium was the only mood stabilizer. At that point, Post et al. were researching the process of kindling in the limbic system (circuit of Papez) in mice. A subthreshold electrical stimulus of one second initially produced no response in the mice. When repeated each 24 hours, however, the mice began to exhibit complex partial seizures (temporal lobe) after about two weeks. If the stimulation was continued for four weeks, the mice went on to have seizures, even when the electrodes were removed. That is, the neurons of the limbic system displayed kindling of seizure activity. Post and others then made the intuitive leap that mood cycles among bipolar individuals may become more frequent over time and more resistant to treatment because the mood cycles themselves are inducing something akin to kindling.

Based on this leap of logic, Post et al. began studying the effects of carbamazepine (Tegretol) in bipolar individuals. They discovered that this anticonvulsant exerted both acute anti-manic and prophylactic effects on cycling rates. Valproic acid joined soon after and was found to be superior to lithium in type II bipolar illness and in rapid cycling illness. Moreover, the anti-convulsants and lithium showed additive benefits.

More recent anti-seizure medications have shown more mixed results. Lamotrigine shows prophylactic and antidepressant properties but is no better than placebo in treating mania. Topiramate may have prophylactic properties but appears to exert little benefit during acute bipolar depression or mania. Several other antiepileptics have been studied, e.g. oxcarbazepine and levetiracetam, and have shown no benefit. The jury is still out regarding zonisamide.

Unlike the classes of medication discussed previously, neither lithium or the antiepileptics alter brain signal transduction by directly binding to and agonizing or antagonizing receptors or by antagonizing reuptake transporters or by altering neurotransmitter catabolism. Instead, they appear to act by dampening axonal signal transmission and by inhibiting cellular response to excitatory signals. A necessary component of this activity is mediated by partial blockade of voltage-dependent sodium channels. This property alone, however, is not sufficient, as antiepileptics which do not show benefit in bipolar illness also exhibit inhibitory effects at voltage-dependent sodium channels. Antiepileptics that do not block these channels, e.g. gabapentin (Neurontin), however, uniformly are not mood stabilizers. To date, the property best correlated with prophylaxis of mood cycling has been depletion of the second-messenger, triphosphoinositol. Another candidate mechanism is increased guanine synthase kinase, type 3, activity. This enzyme plays a role in modulating both voltage and ligand-gated sodium channels.

It is worth noting that several of the second-generation antipsychotics also exert mood stabilizing properties, e.g. aripiprazole, brexpiprazole, clozapine, olanzapine, and quetiapine. Quetiapine's metabolite, norquetiapine, may be an effective treatment for bipolar depression due to selective norepinephrine reuptake blockade. Lurasidone also has been found to be especially effective for treatment of bipolar depression but may not otherwise stabilize mood.

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ANXIOLYTIC MEDICATIONS:

Alprazolam	Xanax, Xanax XR
Buspirone	Buspar
Clonazepam	Klonopin
Chlorazepate	Tranxene
Chlordiazepoxide	Librium
Diazepam	Valium
Hydroxyzine	Vistaril and Atarax
Lorazepam	Ativan
Oxazepam	Serax

Most of the medications classed as anxiolytics are benzodiazepines. The benzodiazepines all act by augmenting the effect of GABA, as described at the beginning of this handout. That is, they decrease anxiety by increasing the effect of GABA on chloride influx into the dendritic portion of neurons bearing GABA type a receptors. For anxiety signs and symptoms, the anatomic target for reduction of anxiety appears to be the amygdala and anterior temporal lobe, as well as the parahippocampal complex. In mammals and primates, these structures are involved in scanning the environment for threats. Although highly and rapidly effective when used short-term, the benzodiazepines pose several risks if used at higher doses or over a longer time span.

Risks of the benzodiazepines include tolerance and physical dependence, abuse, ataxia, diminished attention, failure of memory consolidation, and withdrawal if discontinued abruptly. An important further note is that if benzodiazepines are given to an individual suffering from acute stress disorder, the probability of conversion to PTSD is roughly doubled. That is, the benzodiazepines interfere with post trauma adaptation. Similarly, exposure therapies tend to not work as well if attempted in the presence of a benzodiazepine.

In contrast to the benzodiazepines, buspirone acts by interfering with presynaptic 5-HT1A auto-receptors in the raphe nuclei. This increases serotonin input to temporal lobe structures and reduces anxiety symptoms over four to six weeks. Buspirone does not induce tolerance or dependence, but also does not act quickly to reduce anxiety. Note that the SSRI antidepressants, which also increase serotonin input to temporal lobe structures are currently the most commonly prescribed anxiolytic treatment.

Finally, hydroxyzine, an antihistamine, reduces anxiety by blocking histamine (H-1) receptors. This results in a general decrease in cortical activation.

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SEDATIVES:

Amobarbital	Amytal
Eszopiclone	Lunesta
Flurazepam	Dalmane
Ramelteon	Rozerem
Suvorexant	Belsomra
Tasimelteon	Hetlioz
Temazepam	Restoril
Triazolam	Halcion
Zaleplon	Sonata
Zolpidem	Ambien and Ambien CR

Many of the medications in this class are, like the previous class, benzodiazepines. In this case, however, the target region of the brain is the brain stem, or more specifically, the GABA type a receptors of the reticular activating system. That is, among the benzodiazepines, some show greater affinity for the subtype of GABA-a receptor found in the brain stem as opposed to limbic structures. It is worth noting, however, that this is a relative differential in affinity. All benzodiazepines are anxiolytic and all are sedating. The differences are simply which effect is more prominent for a given medication. Unfortunately, when used chronically, the benzodiazepines induce almost a 100% tolerance to their sedative effects. Thus, while effective if used intermittently or for short-term trials (less than four weeks), they are of limited benefit in treating chronic insomnia. Further, they may suppress respiratory drive among COPD patients and in individuals with sleep apnea.

Eszopiclone, zaleplon, and zolpidem are not chemically benzodiazepines, but act at the benzodiazepine receptor site on GABA-a/omega receptors located on neurons of the reticular activating system. Because these neurons are critical to supporting wakefulness, decreasing their firing rates rapidly results in drowsiness and sleep. Of note, they are also less disruptive to sleep architecture than are the benzodiazepines. They reduce slow wave sleep (< 4 Hz) less, making the sleep obtained more restful. Because they produce a less robust suppression of neuronal firing in the temporal lobe, individuals may be subject to a dissociative delirium if they take one of these selective sedatives and then try to stay awake or mix the medication with alcohol. Finally, unlike the benzodiazepines, they produce much less tolerance and can be used for chronic insomnia.

Suvorexant antagonizes orexan receptors in the reticular activating system. This receptor is normally stimulated by a peptide produced in the hypothalamus, orexan, which

increases activity in the neurons of the reticular activating system. Loss of orexan neurons in autoimmune illness results in narcolepsey.

Amobarbital is useful for severe insomnia unresponsive to other sedatives. Essentially, it induces a state more akin to surgical coma than sleep. Of note, the barbiturates are the only medication class which can, at sufficient concentrations, induce complete electrical silence in the brain. Benzodiazepines increase the frequency of the chloride channel opening in the presence of GABA, while barbiturates can cause the channel to remain open and can act without GABA being bound.

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STIMULANTS:

Atomoxetine	Strattera
Dextroamphetamine	Dexedrine
Lisdexamfetamine	Vyvanse
Methylphenidate	Ritalin and Concerta
Mixed amphetamine salts	Adderall
Modafinil	Provigil
Armodafinil	Nuvigil

The classic stimulants, amphetamines and methylphenidate, act by increasing dopamine release and/or blocking presynaptic reuptake of dopamine. They have been used to treat attention deficit hyperactivity disorder (ADHD) and narcolepsey. In more minor roles, they also have been used to treat adjunctively anergic depression in the elderly and anergic states in AIDS. With respect to ADHD, they are effective in about 70% of cases.

Problems associated with the classic stimulants include psychomotor agitation, insomnia, inhibition of growth hormone release, appetite suppression, and abuse/diversion. Interestingly, appropriate use in children suffering from ADHD appears to reduce risk of later abuse of methamphetamine. Overall effects on adult height are estimated to average a decrease of one to one and one-half inches.

Atomoxetine is a norepinephrine reuptake inhibitor which acts to increase alertness but is not as effective in treating hyperactive symptoms as are the classic stimulants. Risks are primarily those of increasing blood pressure and heart rate.

Finally, modafinil provides its primary stimulant action by increasing histamine release from the cortical projections of the tuberomammillary nucleus. It also does, however, increase dopamine release. It is highly effective for treating narcolepsey and moderately effective for ADHD. Modafinil does not appear to produce the same degree of performance decline or rebound hypersomnia as seen with the amphetamines. Abuse potential appears to be limited. Armodafinil (Nuvigil) is the dextro enantiomer of modafinil.

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COGNITIVE ENHANCERS:

Donepezil	Aricept
Galantamine	Reminyl
Memantine	Namenda
Rivastigmine	Exelon

In Alzheimer's type dementia, neurons of the nucleus basalis deteriorate and die at an accelerated rate, leaving frontal lobe and temporal lobe structures without adequate acetylcholine input vital to a variety of cognitive and memory functions. Donepezil, galantamine, and rivastigmine act to increase available acetylcholine by inhibiting the activity of acetylcholinesterase and/or butylcholinesterase, the enzymes responsible for the degradation and inactivation of acetylcholine in neuronal synapses. Galantamine also exerts some direct agonism at alpha-7 acetylcholine receptors, however, the clinical importance of this effect is uncertain. Unfortunately, these medications do not alter the underlying loss of cholinergic neurons. Thus, when the cholinergic neurons die, there is no longer acetylcholine to be preserved and clinical efficacy fades. Nevertheless, these medications appear to be able to slow the cognitive and memory decline of Alzheimer's disease by an average of about 44 months. So far efficacy has not been demonstrated in other forms of dementia.

In general, the cholinesterase inhibitors are well tolerated, but may cause nausea, vomiting, cramping, and diarrhea in some individuals, especially if doses are increased rapidly.

Memantine acts by partially blocking N-methyl D-aspartate (NMDA) glutamate receptor calcium channels. This is relevant to degenerative dementias because as these neurons decline, they fail to maintain an adequate transmembrane charge, permitting magnesium ions which usually provide partial blockade of calcium channels to "float" away. This leaves the neurons vulnerable to excessive calcium influx and death by excitotoxicity (apoptosis or programmed cell death).

Memantine differs from the cholinesterase inhibitors in that cell life is somewhat prolonged. In moderate to severe dementia, memantine and the cholinesterase inhibitors have been demonstrated to exert additive effects. Mementine is typically well tolerated and rarely produces side effects. Also, preliminary studies have suggested that memantine may reduce the cognitive deficits common in schizophrenia, i.e. decreased verbal fluency and decreased executive functions.

Psychotropic Medications: Overview Seminar by Dr. Cummings

ADDITIONAL RESOURCES:

Stahl, SN. Essentials of Psychopharmacology, 4th edition.

Edited text. American Psychiatric Press Textbook of Psychopharmacology, 4th edition. (Editors – Schatzberg and Nemeroff)

Neuroscience Educational Institute (NEIGlobal.COM)