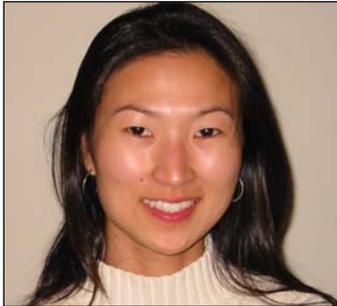


Overview and Update on Current Psychopharmacological Medications, Including New Medications in Clinical Trials

Summarized by Thomas T. Thomas

New psychotropic medications are coming on the market all the time and more are entering clinical trials. The newer medications often work better than the older ones, usually with fewer side effects.



ALICE MYONG, PHARM D

Many of the new medications target different neurotransmitter chemicals in the brain. Our May 26 speaker, **Alice Myong, PharmD**, clinical pharmacologist with Alameda County Behavioral Health Care Services, has been in the position since last December, replacing Dr. Mark Watanabe, a previous speaker to NAMI-East Bay. She offered insights from her clinical experience into the various classes of medications, gave her reasons for prescribing them, and updated our members on new drugs in the research pipeline.

Antipsychotic medications, she said, are divided into the conventional, or typical, medications and the novel, or atypical. The first of the conventional medications were used in the 1960s, and these drugs have heavier side effects, including movement disorders (akathisia), muscle spasms (atonia), and involuntary facial twitching (tardive dyskinesia). “All of these are deterrents toward compliance with medication,” she said.

In the early 1990s the first of the novel medications, clozapine, was introduced in Europe. It presents the risk of a drop in the white blood cell count (agranular cytosis), and so the patient needs weekly blood tests during the first six months of taking the drug and then less frequently. Clozapine was followed by risperidone,

Antipsychotics	
Conventional	Novel
chlorpromazine (Thorazine)	clozapine (Clozaril)
thioridazine (Mellaril)	risperidone (Risperdal)
mesoridazine (Serentil)	olanzapine (Zyprexa)
perphenazine (Trilafon)	quetiapine (Seroquel)
trifluoperazine (Stelazine)	ziprasidone (Geodon)
thiothixene (Navane)	aripiprazole (Abilify)
molindone (Moban)	
loxapine (Loxitane)	
fluphenazine (Prolixin)	
haloperidol (Haldol)	
pimozide (Orap)	

which has no blood cell problem but can cause an increase in prolactin, a brain hormone associated with breast milk and menstruation.

The more recent novel antipsychotics have fewer movement problems but some can cause metabolic problems, including an increase in appetite and weight gain. Some can cause diabetes—particularly in recent reports with Zyprexa. Now there are label warnings for metabolic problems with all the novel antipsychotics, even Geodon and Abilify, which have not shown these problems—although we have less experience with them to date.

Abilify has a different mechanism than the other novels, being a partial dopamine agonist. Where the others are dopamine blockers, Abilify blocks where dopamine is too active in the brain and increases it where needed. “It’s a push-pull, give-and-take mechanism,” Dr. Myong said.

“However, Abilify has not been used much because it was not covered by Medi-Cal until the beginning of this month. The doctors say it is useful for people who don’t respond to the other medications.” Abilify does have some akathisia problems.

Q: What about adding these drugs together?

A: Normally, you mix antipsychotics and antidepressants, but you wouldn’t mix two novel antipsychotics. But, if you’ve given one a complete trial and are reaching a dosage where the side effects are becoming intolerable, you could back off on the dosage and supplement it with another medication.

Q: Are all the novel antipsychotics taken orally?

A: All of them are available orally and some intramuscularly. Risperdal has a long-acting injectable form that starts with one shot every two weeks instead of one pill a day. However, it’s very costly. A one-month treatment costs as much as Zyprexa, which is comparatively expensive.

Q: Are all novel antipsychotics covered by Medi-Cal?

A: Yes, now that Abilify is covered.

Q: How does a doctor choose among these drugs?

A: All are about equally effective, although clozapine is considered good for people who are refractive with the others. The doctor studies the patient’s history, sees what may have failed in the past, and then chooses based on medical conditions, such as diabetes and metabolism.

Q: Do the antipsychotics keep on working? Or can you develop a tolerance to them?

A: Some people can use them for years, although some studies also show the potential for tolerance. So the situation is not clear yet.

Among the antidepressants, SSRIs are “selective serotonin reuptake inhibitors,” which tend to increase the action of the neurotransmitter serotonin, while tricyclics are older and have an effect on the transmitter norepinephrine. Both are about equally effective.

Lexapro is unusual among the SSRIs in that it has only half of the molecule found in Celexa. Thus, it has fewer side effects. In fact, Medi-Cal is no longer covering Celexa in favor of Lexapro.

The tricyclics can have sedation effects and cardiac effects, including altered heartbeat (arrhythmia) and dizziness upon standing up (orthostatic hypotension). Other side effects are dry mouth, constipation, and blurry vision from dry eyes. So this class of medications is not used much.

Antidepressants	
SSRIs	Tricyclic Antidepressants
fluoxetine (Prozac)	amitriptyline (Elavil)
fluvoxamine (Luvox)	nortriptyline (Pamelor)
paroxetine (Paxil)	imipramine (Tofranil)
sertraline (Zoloft)	desipramine (Norpramin)
citalopram (Celexa)	clomipramine (Anafranil)
escitalopram (Lexapro)	doxepin (Sinequan)
Miscellaneous Agents	protriptyline (Vivactil)
bupropion (Wellbutrin)	MAOIs
mirtazapine (Remeron)	phenelzine (Nardil)
venlafaxine (Effexor)	tranylcypromine (Parnate)
trazodone (Desyrel)	
nefazodone (Serzone)	

Other side effects are dry mouth, constipation, and blurry vision from dry eyes. So this class of medications is not used much.

MAOIs, or “monoamine oxidase inhibitors,” are difficult to take because they have interactions with cured foods like wine, cheese, and anything that contains the

amino acid tyramine. This is a precursor to the neurotransmitter that the MAOIs work on, so you can get too much of it. One side effect is high blood pressure (hypertension). MAOIs are moderately effective for atypical depression, where people tend to overeat and oversleep instead of losing appetite and being wakeful.

The miscellaneous agents are in a class by themselves, Dr. Myong said. Wellbutrin works on dopamine. Remeron works on norepinephrine and serotonin, increasing them by negative feedback. Effexor is an SNRI, “serotonin norepinephrine reuptake inhibitor.” Desyrel is used for insomnia. And Serzone is now being pulled from the market because it has been linked to a type of liver toxicity (hepatotoxicity) that, while low risk, doesn’t show up in tests and occurs without warning.

Q: What about upset stomach?

A: All of these antidepressants can have this effect—the SSRIs and Effexor more than the others—although everyone reacts differently to medications. Theoretically, Remeron causes less nausea, but it can stimulate the appetite at lower doses. So it is often prescribed for elderly people who are depressed and not eating.

Q: Could these antidepressants be used for bipolar syndrome?

A: You could use Remeron, which is less likely to tip the patient into mania. You would also use it with a mood stabilizer.

Q: What is the toxicity with antidepressants?

A: This has not been shown, except for Serzone’s hepatotoxicity. Behavioral Health Care Services does not require blood work with antidepressants.

Among the mood stabilizers, lithium has proven very effective. Most of the others are for people with a mixed presentation (e.g., mania with depression) or are rapid cycling (i.e., four or more manic episodes within a year). With mood stabilizers it is more the norm to add agents. For example, Lamictal can keep people from relapsing into depression from a manic state.

Mood Stabilizers and Anti-Manic Agents	
lithium (Lithobid, Eskalith)	risperidone (Risperdal)
divalproex sodium (Depakote)	olanzapine (Zyprexa)
valproic acid (Depakene)	quetiapine (Seroquel)
carbamazepine (Tegretol)	aripiprazole (Abilify)
lamotrigine (Lamictal)	

Mood stabilizers do not work on a neurotransmitter. In fact, we don’t know exactly how they work. One theory is that they stabilize the channeling of sodium ions into neurons. As shown on the table above, several of the antipsychotics are also used as anti-manic agents in treating bipolar syndrome.

Most of the mood stabilizers require blood tests. With lithium, you take blood levels on a yearly basis because it can be toxic at too high a dosage, can cause kidney problems (renal function), and can increase white blood cell counts. With Depakote and Depakene, you test liver function and do a platelet count. With Tegretol, you want a complete blood cell count.

Q: How long for the mood stabilizers to take effect?

A: All of them need one to two weeks to start showing an effect, and three to four weeks for maximum benefit. So you need at least four weeks on the medication to reach a stable level.

Q: What’s the incidence of acne with lithium?

A: Some people may get it, although this could also be a matter of hygiene. The solution is to take the patient off lithium.

Q: What about the drug Topamax?

A: Topamax is not on our prescription list (nonformulary) because there have been no double-blind studies on it. In fact, there is anecdotal evidence that it doesn’t work. But, again, everyone reacts differently.

Q: What are some of the other negative effects of mood stabilizers?

A: Depakote, as well as lithium and Tegretol, can cause hair loss, but taking zinc and selenium seems to help with this. Depakote can also cause wakefulness.

Tegretol can cause a rash and, in interaction with other agents, can cause them to be metabolized in the liver, thus reducing their effectiveness.

Lamictal can cause a fatal rash in which the skin sloughs off (epidermal necrolysis). So you want to start at a low dose and increase it very slowly.

Of the anti-anxiety medications, benzodiazepines are effective right away, within half an hour to an hour of taking. But the body builds up tolerance to them, so you need higher and higher dosage. These medications have the potential for abuse.

Anxiolytics (Anti-Anxiety)	
Benzodiazepines	Miscellaneous
alprazolam (Xanax)	bupirone (Buspar)
lorazepam (Ativan)	venlafaxine (Effexor)
oxazepam (Serax)	fluoxetine (Prozac)
temazepam (Restoril)	fluvoxamine (Luvox)
clonazepam (Klonopin)	paroxetine (Paxil)
diazepam (Valium)	sertraline (Zoloft)

Of the miscellaneous agents, bupirone is effective only for generalized anxiety disorder, not for social anxiety and other specific indications. The other medications are antidepressants, and for anti-anxiety you start with small doses, usually half the amount for depression, and work up to higher levels. They have the same side effects as when used for depression.

Q: What is the half-life of Ativan?

A: Four to six hours. All of the benzodiazepines are for short term. For long-term effect, such as when starting a regimen of SSRI, you would take bupirone to cover the short term until the SSRI becomes effective.

Q: Can you take Klonopin for a while?

A: Some people can take it before a panic attack. But you can build up a tolerance to Klonopin. It is not meant to be taken indefinitely.

Of the hypnotics, or sleeping pills, Ambien and Sonata are considered “non-benzo-benzos.” That is, they are of the benzodiazepine class, but have less potential for abuse and withdrawal symptoms. They have a short half-life, so less of a hangover the next morning, and have no muscle relaxant effect. Restoril is a benzodiazepine and Benadryl can cause dry mouth.

Hypnotics	
zolpidem (Ambien)	temazepam (Restoril)
zaleplon (Sonata)	diphenhydramine (Benadryl)

Q: Can you build a tolerance to these medications?

A: Yes. They are intended for acute, not chronic, sleep disorders.

Of medications for attention deficit hyperactivity disorder, the methylphenidates—Ritalin, Concerta, and so on—all share a common molecule, although Focalin has only half of the molecule, like Lexapro among the SSRIs.

For Attention Deficit Hyperactivity Disorder (ADHD)
methylphenidate (Ritalin, Concerta, Methylin, Focalin)
amphetamines (Adderall, Dexedrine)
atomoxetine (Strattera)

The amphetamines, Adderall and Dexedrine, are controlled substances, and there is controversy about giving them to children. For these medications we require triplicate prescription.

Strattera is not a controlled substance and is pretty effective. This medication is good for a patient who cannot use amphetamines or has a history of substance abuse.

Of the new medications in clinical trials or awaiting approval, a molecule called SPD503 is similar to Strattera for ADHD. A new antidepressant,

duloxetine (Cymbalta), is an SNRI, like Effexor. A couple of other antidepressants are also in early Phase III trials, but they have not yet proven efficacy in the human population. And finally, a new molecule called eszopiclone (Estorra) is being tested in Canada and Europe for chronic insomnia.

Q: Are there any new antipsychotics in the pipeline?

A: Nothing is due out soon, although some drugs may be in early, pre-human testing.