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Antidepressants: The Lay of the Land

ANTIDEPRESSANTS: THE LAY OF THE LAND

Regardless of your specialty, Prozac, Zoloft, and Paxil have become commonly used and familiar medications. What others should we know? You are listening to ReachMD, The Channel for Medical Professionals. Welcome to the Clinician's Roundtable. I am Dr. Leslie Lundt, your host, and with me today is Dr. Stephen M Stahl. Dr. Stahl is Adjunct Professor of Psychiatry at the University of California in San Diego. He is an internationally recognized clinician, researcher, and teacher in psychopharmacology and he has authored more than 350 articles and chapters. His latest book is the third edition of Stahl's Essential Psychopharmacology.

DR. LESLIE LUNDT:

Welcome to ReachMD, Dr. Stahl.

DR. STEPHEN M. STAHL:

My pleasure to be here.

DR. LESLIE LUNDT:

How do you currently explain how antidepressants work in the brain. We have all seen these little commercials put out by the pharma companies with a little blob. I am wondering if that's really how they work?

DR. STEPHEN M. STAHL:

Well, I think that we know where the antidepressants bind, but I am not sure that that means we know how they work. Certainly, if the blobs are monoamines that's probably the best bet we have to explain these drugs right now. The monoamines particularly serotonin is the most famous and norepinephrine it's sister, but even dopamine. These 3 monoamines sometimes called trimonoamines are the targets of every known antidepressant, and in fact it's only in research that we have ever identified a non-monoaminergic kind of mechanism that ever worked for depression. So, the current antidepressants someway or another we think boost monoamine neurotransmission and that's how they are thought to work in the brain.

DR. LESLIE LUNDT:

Boost monoamine transmission, but what kind of timeframe, clearly they don't work right away.

DR. STEPHEN M. STAHL:

That's good question. Indeed they do not work right away. It turns out that if you block a monoamine transporter that is an inactivator of a monoamine, it will cause a buildup of the monoamines, but not a very big one even though it's a very sudden one. In fact, it probably makes them buildup sufficiently to cause a side effect, but not a therapeutic effect. So what's happening? Well, if you sustain the buildup of the monoamines, the neuron will react by down regulating certain receptors. Those receptors are mostly, if you will, bricks, they turn off the release of monoamines. So if you down regulate them or you cut the brick cable, boom, you get a big amount of monoamines being released, so we think what happens is that the antidepressants suddenly block transporters, which then causes the monoamines to indirectly decrease, down regulate the bricks of the neuron, which then 70 days later something like that will cause a much more profound increase of the monoamines, so it's thought that that increase of the monoamines with a delay is what's necessary in order to exert an antidepressant effect.

DR. LESLIE LUNDT:

Besides the basic SSRIs as I mentioned sertraline, fluoxetine, paroxetine, what other antidepressants are important for our listeners to know?

DR. STEPHEN M. STAHL:

Well, they certainly are the SNRIs or serotonin-norepinephrine reuptake inhibitors also called dual action drugs and of course there are 3 almost 4 of them. The 3 that are out there are Effexor (venlafaxine) is the branded name and unbranded name, then there is (duloxetine) Cymbalta, but you also have the new one Pristiq, which is desvenlafaxine and one that's imminent to be approved at the FDA, but not for depression, but perhaps for fibromyalgia called milnacipram. Those are SNRIs. We also have Wellbutrin, which is kind of in a class by itself also called bupropion and it's a dopamine and norepinephrine reuptake inhibitor or NDRI if you will. Of course, you have got old-fashioned trazodone, you got the tricyclics, you got the old MAO inhibitors. I will put a little plug in here. If the listeners are psychopharmacologists of any sophistication is one of the secret weapons in the armamentarium for treatment resistance, but almost nobody prescribes them anymore. So they are the major classes. The mirtazapine is a interesting drug. Remeron is in kind of a class by itself. It has alpha-2 antagonist properties, but it's not a reuptake blocker.

DR. LESLIE LUNDT:

Now you mentioned the newest one on the market is desvenlafaxine or Pristiq. What do we need to know about that, that's probably the one people are least familiar with?

DR. STEPHEN M. STAHL:

Well, it is active metabolite of one that the listeners probably do know very well venlafaxine. It turns out that Effexor or venlafaxine is actually metabolized into desvenlafaxine just sort of like its name sound like. The main difference is that when you take desvenlafaxine itself, you are not dependent on their conversion of the parent compound into it and that makes the net action more noradrenergic. In

other words, venlafaxine is a little less noradrenergic at the end of the SNRI than is desvenlafaxine. So it's a little more noradrenergic, it's a little more predictable. It has perhaps fewer drug interactions, but it is very similar to venlafaxine.

DR. LESLIE LUNDT:

So, may be a bit more like Cymbalta than Effexor, is that one way to think about it?

DR. STEPHEN M. STAHL:

Well yes, in terms of its pharmacology, both Cymbalta and Pristiq are more noradrenergic. Their so called claim to fame of Pristiq, which will require marketing for a while to see if it's true is that it seems to be able to be used without much titration at least for the first line treatment of the easier patients. Mostly, Cymbalta and Effexor require some titration. Whether that will be true or whether it will be an advantage is really what we will have to find out if the drug is used in the early months.

DR. LESLIE LUNDT:

Now if you are just joining our discussion, you are listening to the Clinician's Roundtable on ReachMD, The Channel for Medical Professionals. I am Dr. Leslie Lundt, your host, and with me today is Dr. Stephen M. Stahl. We are discussing the latest in antidepressant treatment.

Dr. Stahl in your book, you have talked about the TMM, that was the new one for me. What are they?

DR. STEPHEN M. STAHL:

Well, it's a trimonoamine modulator and what I mean by that were trimonoamines, they are serotonin, norepinephrine, and dopamine, and what is a modulator, it's something that may act either indirectly on monoamines or work if you will more better in the presence of an antidepressant that directly changes monoamines. What I mean by that it's a number of hormones like estrogen, like thyroid. These agents in themselves possibly have a little bit of antidepressant effect that's controversial and certainly not established, but certainly in combination with antidepressants can boost or modulate the trimonoamines that the antidepressant is already boosting or modulating and so give you a further efficacy boost to the antidepressant action. Another one is lithium, by itself at least in unipolar depression is not that good of a antidepressant, but can boost regular antidepressants and modulate monoamines while it's doing that and the new kid on the block is the L-methylfolate, which is the centrally active form of the vitamin folate. It's sister product would be S-adenosyl-methionine or SAMe and other natural products that could fall in this category include things as varied as testosterone, vitamin D, and omega-3 fatty acids, so these things are not as well investigated, none of them are approved as a monotherapy, but by various mechanisms, which we could discuss, but they all do have a way of boosting monoamines and helping antidepressants boost them if you will more better.

DR. LESLIE LUNDT:

Certainly, these "natural" treatments have a huge appeal with our patients. I note for me SAMe you know had some great press about 10 years or so ago, we tried it, and I can't say I ever noticed anything from SAMe, but now L-methylfolate and omega-3 fatty acids are sort of the rage. Is there any downside to at least trying them?

DR. STEPHEN M. STAHL:

I don't think so. Some people are cynical and say that the mechanism of action of these agents is that they bind to money receptors.

DR. LESLIE LUNDT:

(laughs)

DR. STEPHEN M. STAHL:

They may do that, but actually the one that I am kind of interested in <_____> now is L-methylfolate. It turns out that L-methylfolate is a precursor for a co-factor that makes monoamine synthesis called biopterin and by doing that it can make more serotonin, norepinephrine, and dopamine. If you don't have folate, you can become depressed and people, who are folate deficient tend to have high levels of homocysteine, and if you give L-methylfolate, the homocysteine level will come down and particularly if you haven't responded to an antidepressant, those are excellent candidates to give L-methylfolate for. The other thing that has happened is that there are different genes for the enzymes that converts the folate that you eat into L-methylfolate in your body, and if you have a low level of that enzyme, you become functionally L-methylfolate deficient in your brain. Also, drugs can interfere with that like anticonvulsants, Depakote can interfere with absorption of folate and actually Lamictal interferes with the formation of L-methylfolate. So there may be mysterious ways to identify the people, who could respond to this. It will be very nice to know who they are, but empirically, I have seen responders to this in my practice, but it's been in the minority and it's been unpredictable, but this can be very sudden and very profound and I was a little bit skeptical about it until I actually saw a couple of cases. I don't think we know who to give what to though.

DR. LESLIE LUNDT:

How do you dose L-methylfolate?

DR. STEPHEN M. STAHL:

Well, it's available I think only in one commercial form called Deplin and it comes in the standard 7.5 mg. To signal what that is, the folate you take in from your diet might be a tenth or two-tenths of a mg, that's also the amount in multivitamins. A pregnant woman would take 1 mg of folate. L-methylfolate is more potent, so actually 7.5 mg of L-methylfolate is more comparable to like 52 mg of folate itself. So, it's a real blast of it and it's a pharmacological dose. You can't get it from a food store. It's actually a prescription you have to get it from.

DR. LESLIE LUNDT:

Now, real quick, let's look in your Stahl crystal ball. What do we have to look forward to in antidepressant treatment?

DR. STEPHEN M. STAHL:

Well, there are a couple of new monoamine mechanisms and there are couple of new and for the first time non-monoamine

mechanisms. I think the thing that will happen even before them is that we may very well have a treatment that is approved for both unipolar and bipolar depression. Quetiapine is heading in that direction. Even drugs like aripiprazole, they could be expensive, but since antidepressants in a bipolar patient can make you manic, it would be sure nice to have something that worked for both. I think we will see that such approvals are already pending, but in addition to that in terms of new molecules, there is a beta 3-agonist called Amibegron, which is out there that has preliminary signs of efficacy. There is a D3 partial agonist though that could be used called Cariprazine. There is even an NK2, a neurokinin-2 antagonist if you care, it's a sister, but not the same. It is a substance P, which is NK1, which was tried with greater pomp and then crashed. It didn't work. It's called <_____>. It's actually been showing preliminary signs of efficacy in depressed patients and finally is the (CRF) corticotropin releasing factor 1 receptor antagonist for the listeners who care. I actually have an article in CNS Spectrums this month on that and its sister would be a vasopressin 1B antagonist. Vasopressin 1B receptors also regulate HPA access, so these are new possibilities for antidepressants that don't even work by monoamines for the first time.

DR. LESLIE LUNDT:

Thanks so much for sharing all this new information with us today.

DR. STEPHEN M. STAHL:

My pleasure.

DR. LESLIE LUNDT:

We have been speaking with Dr. Stephen Stahl about what's new in antidepressants. His latest book is the third edition of Stahl's Essential Psychopharmacology. I am Dr. Leslie Lundt and you have been listening to the Clinicians Roundtable on ReachMD, The Channel for Medical Professionals. To listen to our on-demand library, visit us at reachmd.com. If you register with the promo code radio, you will receive 6 months of free streaming to your home or your office. If you have comments or suggestions, give us a call at (888 MD XM157). Thank you for listening.

Good day, I am Dr. Trevor Duke from the Center for International Child Health in Melbourne, Australia. You are listening to the first national radio channel created specifically for medical professionals, ReachMD XM160.