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When to Treat with Antipsychotic Combinations

### LACK OF WISDOM OF COMBINING ANTIPSYCHOTICS

In an ideal world evidenced based medicine and thoughtful clinical research might guide our every treatment decision. Of course, this is not the way it often works. Treating psychotic patients poses extraordinary challenges. When is it logical to combine antipsychotics.

Welcome to the Clinician's Roundtable. I am Dr. Leslie Lundt, your host, and with me today is Dr. Aaron Gibson. Dr. Gibson is assistant professor in the College Of Pharmacy at the University of New Mexico.

**Dr. LESLIE LUNDT:**

Welcome to ReachMD, Aaron.

**DR. AARON GIBSON:**

Thank you Dr. Lundt. It is a pleasure to be on the show with you today.

**Dr. LESLIE LUNDT:**

What does the research tells about combining antipsychotics?

**DR. AARON GIBSON:**

Unfortunately, very little. The body of data that is available with respect to combining antipsychotics in the treatment of schizophrenia is actually really pretty sparse. There are actually only 4 randomized double-blind controlled studies and all 4 of those were with clozapine and risperidone. And so, the fact of the matter is that most clinicians don't have relative data to refer to whom we are discussing antipsychotic polypharmacy.

**DR. LESLIE LUNDT:**

But, it seems like we do it all the time.

**DR. AARON GIBSON:**

We do and in fact there is up to 25% of outpatients and up to 50% of inpatients actually are on some sort of whether a short-term or a long-term antipsychotic polypharmacy. So, even though the data isn't there to support the practice, it is something that is seen quite routinely and pretty frequently.

**DR. LESLIE LUNDT:**

Can it be dangerous to combine antipsychotics?

**DR. AARON GIBSON:**

It certainly can and I think there are 3 kind of major areas that you really need to focus on when we are combining antipsychotics, and the first would be the metabolic effects of these agents, particularly the atypical antipsychotics. What we have noticed with these newer agents is that we have seen quite a bit of weight gain and glucose dysregulation and hyperlipidemia with these, and we do not know if we combine these agents if there is an additive effect to that so we might be giving these patients a double whammy by combining those. Second area would be tardive dyskinesia, which is a movement disorder that can be seen and we don't know much about this adverse event at all, and the bottom line is we don't know if there is an additive risk. So, if we are combining an older agent with a newer agent are we going to actually increase the risk for tardive dyskinesia than if we were just using 1 agent and we don't know the answer to that question. And, the last thing would be cardiac effects. Most of the antipsychotics, if not all of them, are going to cause an increase in the QTC prolongation and 1 drug in particular ziprasidone as a name brand Geodon tends to be the worst of the atypical antipsychotics with this, and so if you have a patient with history of cardiac problems or even a patient without that it might be dangerous to combine these medications simply because we could be increasing the risk for causing arrhythmias because of this QTC prolongation.

**DR. LESLIE LUNDT:**

Or even I am thinking one of the older antipsychotics, Mellaril.

**DR. AARON GIBSON:**

Oh! Certainty, certainly and it has a \_\_\_\_\_ warning for that effect. So, even if we dip into the typical agents or the older agents that is certainly a very big concern as well.

**DR. LESLIE LUNDT:**

So, when it is reasonable considering really the lack of knowledge that we do have in the research about combining antipsychotics. When is it reasonable to consider doing it?

**DR. AARON GIBSON:**

I think the most reasonable time to consider doing it is when you really have a treatment-resistant population and you'll see that term thrown out quite a bit in the literature and in clinical practices as well. But, when you have a treatment-resistant population, I think that's when you should start to think about doing something that is outside the box and outside of the body of literature that we currently have. What I would recommend is always assessing compliance. I teach the medication education class to the patients on the inpatient unit and most of the time they claim that it's "well, I stopped taking my medications and that's why I am back in the hospital." So, I think it is really important for clinicians to assess the fact is the patient taking the medication or they are not taking it, and if they are not taking it is that the reason that you are not seeing a response that you should see because it does not really make a lot of sense to add another medication to a regimen that the patient is not taking anyway. I would also think about inpatients who have failed trials of both typical and atypical antipsychotics. What I would caution with this is that making sure that you give the patient an adequate dose and an adequate duration of the antipsychotic medication before you consider it a failure. I think what happens a lot of time is clinicians aren't seeing an effect within 7 to 10 days and/or the patient's family want something to be done now and really that is not enough time to see an effect with the antipsychotics and so what you'll see is that maybe this is truly not a treatment-resistant patient. We just needed to give the medication more time. So, those are some of the criteria that I would look at. I would also look at making sure that the patient has at least had a trial of clozapine and the reason I say that is because we have very good data that shows that clozapine is very effective in the treatment-resistant population, and so if you have a patient, who has failed maybe a typical antipsychotic or 1 or 2 atypical, I would really give strong consideration to giving a trial with clozapine because it has shown to be effective in that patient population. If you have gone through that list of criteria, you have made sure that the patient is taking the medication, they failed adequate trials of other medications, they can't tolerate or they failed clozapine, then I would certainly think about looking into the possibility of a combination of antipsychotics.

**DR. LESLIE LUNDT:**

But, Aaron, don't you feel like most clinicians are afraid of clozapine.

**DR. AARON GIBSON:**

Most of them are and some of that is probably very warranted and some of them may not be, and I think the reason that they might be afraid of clozapine is because of the very significant monitoring parameter burden to see and not only on the clinicians, but also the patient because when you initially start the drug, you have to come in for weekly blood draws and then there is the fear of agranulocytosis, and if you have ever seen that in a patient, it is something that not only scary, but it is a reminder of that we are dealing with medications that are very dangerous as well.

**DR. LESLIE LUNDT:**

If you are just joining us, you are listening to the Clinician's Round Table on ReachMD professional. I am Dr. Leslie Lundt, your host, and with me today is Dr. Aaron Gibson. We are discussing the wisdom or maybe lack of wisdom of combining antipsychotics.

Aaron, what logic can we then use to determine whether an antipsychotic combination is reasonable or not.

**DR. AARON GIBSON:**

There are a couple of things that you can look at. The first one that I would look at would really be to look at the mechanisms of the

antipsychotics. You obviously don't want to duplicate what you are doing with 1 antipsychotic by adding another antipsychotic that has very similar mechanism. An example of this would be if you were to give the patient 2 high potency typical antipsychotics or older agents because they have virtually the same mechanism that's really not going to do much good. So, when you are considering an antipsychotic combination, I would recommend that you at least try and mix and match the mechanisms so that you are doing something a little differently. So, that would be the first step that I would do is look at the mechanisms and make sure that you are combining 2 agents that are going to be doing the same thing with respect to mechanisms. The second thing that I would look at would be the adverse event profile. We know that you can see an increase in metabolic problems with the atypical antipsychotics, and so obviously clozapine and olanzapine are 2 of the worst offenders and so that's going to be a very strong consideration if you are wanting to think about combining those 2 agents, you have to be really concerned about the potential additive effect for the metabolic problems that these 2 agents can cause on their own, and if you put them together, it might exacerbate that. So, I think that that's the big thing with respect to adverse event profile because you want to make sure that you are really careful with that and not giving 2 agents that are really going to compound each other and make things worse for whatever adverse events that you are looking at.

**DR. LESLIE LUNDT:**

So, on the flip side of that could you give us some examples of theoretically beneficial antipsychotic combinations?

**DR. AARON GIBSON:**

One combination that I think would make sense from a lot of different standpoints would be combining quetiapine and aripiprazole and when you look at the mechanism, they have very different D2 binding profiles, and so I think that that makes that a logical step in considering that quetiapine has a very fast on, fast off binding profile with respect to the D2 receptors and aripiprazole differs from that completely. So, I think from a mechanism standpoint, that would be a reasonable combination, and when you move to the adverse event or adverse profile effect of these 2 agents, there is really not a lot of overlap there. You are going to have a very low risk of increasing extrapyramidal symptoms with these 2 agents. You are also going to have a low risk of metabolic concerns other than beyond which you would expect with each individual agent and there is a low risk of additive sedation as well. The drawback I would say would be cost because these agents are extremely expensive, but from a mechanism standpoint and from an adverse effect standpoint, this combination certainly makes a lot of sense to me.

**DR. LESLIE LUNDT:**

You mentioned quetiapine or Seroquel is the brand name. Don't you see that being added a lot to other antipsychotics mainly for its use in as a sedative as sleeper if you will?

**DR. AARON GIBSON:**

Exactly, we see a lot of that practice, not only in the inpatient unit, but also as an outpatient as well because Seroquel is very sedating. What we will notice is patients will have Seroquel combined with another antipsychotic, but the dose of the Seroquel would be very low, probably anywhere from 50 mg to 200 mg and it's usually given in the evening and so it is used for a sedative properties as well and when you think about that, that tends to be a very expensive medication or sleeping medication if you will and so that's one of the more common combinations that we see and it's really generally used for sleep.

**DR. LESLIE LUNDT:**

So, again, that may not be entirely rationale.

**DR. AARON GIBSON:**

It may not be entirely rationale, exactly, and I am not saying that that's not a combination that is not effective, but it is certainly something that you are going to look out from a cost standpoint and maybe trying other agents for sleep first before you jump to using Seroquel in combination with another antipsychotic.

**DR. LESLIE LUNDT:**

Let's talk more about the cost. Has anybody elected the pharmacoeconomics of combining antipsychotics?

**DR. AARON GIBSON:**

From my knowledge, there isn't any data available with respect to combining these antipsychotics and based on the prohibitive cost of these agents, I don't know that that data will ever become available simply because it is going to be something very difficult to capture. I would think that it's going to be very difficult to show a benefit with combining these agents simply because they are so expensive.

**Dr. LESLIE LUNDT:**

I have seen data from Medi-Cal, which is the California State Medicaid Program and the dollars spent from the City California on antipsychotics dwarf pretty much any other medication class. It's really amazing the billions dollars that are spent every year.

**DR. AARON GIBSON:**

That is exactly the case here in the Mexico as well. I serve in the P&T committee for the medicaid distributor here in Mexico and the same is very true here in the Mexico as well. So, it is quite mind boggling to see how much is spent on these agents on a yearly basis by our state medicaid system.

**DR. LESLIE LUNDT:**

At least, in the literature, it seems like there is somewhat of a backlash now reevaluating the older conventional antipsychotics like haloperidol. Thank God, you know these meds really any different in terms of efficacy than the newer much more expensive medicines. You have any opinion about that?

**DR. AARON GIBSON:**

Certainly, and I think that that is something the CATIE trial really brought into the forefront as clinicians and really had clinicians revisit their thinking on using these agents and are we really getting enough bang for our buck out of the newer atypical antipsychotic agents and I think that's a very valid question. I would be cautious in interpreting that though and we do know that the typical agents tend to

have a higher risk of tardive dyskinesia and I think that that's one thing that really didn't shine out with respect to the CATIE trial on other literature because of the long-term side effect and so I think it's something very valid to consider maybe going back to a lot of the older typical agents, but it is something that I would do with caution.

**DR. LESLIE LUNDT:**

Yeah. You know it is amazing just today as a matter of fact I had a student in the office and she didn't even know how to examine someone for tardive dyskinesia. I mean it's really kind of fallen off the map.

**DR. AARON GIBSON:**

Exactly, exactly, so I think it's maybe a forgotten side effect and so everybody is up in arms with the cost of these agents and saying well if the older agents are just as effective, why aren't we using those, and I think we need to be cautious with that. I do think that there is a place for that discussion, but I think we need to quantify that and make sure that we are being smart about that discussion.

**DR. LESLIE LUNDT:**

Absolutely good words. Thank you so much for being on our show today.

**DR. AARON GIBSON:**

Certainly, thank you for your time and I enjoyed it.

**DR. LESLIE LUNDT:**

We have been speaking with Dr. Aaron Gibson about combining antipsychotics. I am Dr. Leslie Lundt. You are listening to ReachMD, The Channel For Medical Professionals. For a complete program guide and downloadable podcast visit our website at [www.reachmd.com](http://www.reachmd.com).

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