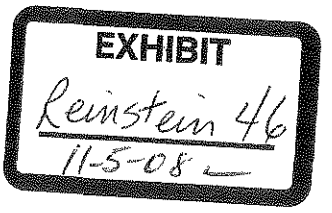

New Developments in Antipsychotic Treatments
Weight Gain and Diabetes

P R O C E E D I N G S

MS. THOMISON: Hello everyone and welcome to today's program. My name is Lynne Thomison and I'm the Director of Continuing Medical Education for the School of Medicine at the University of South Dakota.

We have partnered with the Distance Learning Network and are pleased to be joint sponsors of this videoconference series entitled The Mind Maze.

Packets have been shipped to each site. Inside those packets are your handouts, certificates, evaluation forms, sign-in sheets, and a return envelope.

Please complete the sign-in sheets and the evaluation forms at the conclusion of today's program and return those to us in the envelope provided.

Please keep the certificate for your continuing medical education records.

Your comments and registrations are very important to us. The Distance Learning Network and our office would like to thank AstraZeneca for their educational grant in support of this four-part videoconference series, The Mind Maze.

I would now like to introduce Dr. Henry Narallan, who is Professor of Neurology and Psychiatry at the University of Mississippi Medical Center, as well as Chief Mental Health Services at the V.A. Medical Center in Jackson.

It is now my pleasure to turn the program over to him.

MR. NARALLAN: Welcome to the Distance Learning Network. I'm Dr. Henry Narallan of the University of Mississippi School of Medicine and your host for today's program.

We have Dr. Michael Reinstein with us presenting new developments in antipsychotic treatments, weight gain and diabetes. This is an interactive

program and we encourage you to call us with your questions or comments during our call-in segment at the end of the show.

The toll free number is 1 (800) 494-0655 or you may fax us at (651) 308-0533.

We have over 350 sites today with an audience of over 5,000 people registered for the program which we are very excited about.

Dr. Reinstein is with us on location at Somerset -- Somerset Halfwayhouse in Chicago. And we had a chance to tour this very unique facility and we'd like to share that with you.

UNIDENTIFIED SPEAKER: Today, Distance Learning Network is proud to be broadcasting live from the Somerset Halfway House in Chicago. Once a proud and

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uptown hotel in the '40s, Somerset is now the world's largest facility for the chronically mentally ill. The facility has a census of 424 patients, 200 of which make up the largest psychiatric practice.

Somerset offers a full treatment program for patients ranging from medication management, individual therapy, group therapy, to occupational therapy. Armed with the goal of keeping patients out of hospitals and moving them into independent living, Somerset deals daily with treatment challenges that affect many of us.

MR. NARALLAN: Well, here we are at Somerset Place with Dr. Reinstein. Thanks for joining us, Dr. Reinstein.

What you see behind me are examples of some of the artwork created by the patients at this facility. It's really an interesting place that you work in.

MR. REINSTEIN: Yes. I've been the medical director here for many years. And I've been coming here well over 20 years. And for me it all started in 1962. My college psychology class went to see Chicago Reed, our local state hospital. And at that time Chicago Reed had over 10,000 patients. Right now, it's down to about 200. And virtually all of the patients have been discharged to the uptown area, where we are now. And

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there's a number of facilities like this in the uptown area.

Somerset is -- is the largest and probably the -- the best known. We have approximately 430 residents here. And we -- we get a lot of visitors here. And certainly if the audience ever is in Chicago, we'd love to show you the uptown area or Somerset and they can feel free to call me.

MR. NARALLAN: What I understand, Mike, is that you have the largest Clozapine practice in the country.

MR. REINSTEIN: That's correct. I'm the senior member of a five psychiatrist practice which is here in the uptown area where we have many refractory patients. And we have close to 2,000 active Clozapine patients.

MR. NARALLAN: Well, that's exactly -- that's exactly what we -- what we look forward to hearing from you about, some of the options that you use in treating the difficult, chronic patients.

But tell us, if you could, how the -- how

the developments, the exciting developments in antipsychotic therapy over the last few years has influenced your practice.

MR. REINSTEIN: Yes. When I started practicing here in 1973, the only options were basically the typical antipsychotics. The original one was Chlorpromazine. Of course, there were many others. Our local favorite became Haldol.

Now, the problems we ran into with the typical antipsychotics was essentially twofold.

One, a lot of patients didn't respond even when we knew they were getting their medication and taking their decanoid injections.

And two, even some of the patients who responded would not take the medication because of the severe side effects, the negative symptoms, the movement disorders, and the elevation in prolactin levels associated with sexual dysfunctions and other abnormalities.

MR. NARALLAN: So what will you be covering today?

MR. REINSTEIN: Today we'll talk about new developments with the use of atypical antipsychotics, which is what virtually all of our patients are receiving.

We're going to talk about some issues with weight gain with some of the antipsychotics and the atypicals and some of the ways of coping with that as well as some new data on widening of QTc interval with some atypical antipsychotics.

MR. NARALLAN: I see you already have the first slide showing how it all started.

MR. REINSTEIN: Yeah. We actually had a brief run with Clozapine in 1973. And I was actually using it quite a bit. But unfortunately in 1975 there were 16 cases reported of agranular cytosis or severe lowering of the white count, including eight deaths. So from 1975 to 1990 it was very difficult to use Clozapine. I was able to keep some patients on it on a compassionate basis, but we couldn't start new patients.

Finally, in February of 1990, we were able to start using Clozapine again. And that's what created, since then, this huge interest in atypical antipsychotics.

MR. NARALLAN: Okay. So proceeding from there, you still have patients, though, that -- that do not necessarily respond to Clozapine fully. And we'll talk later about some combinations --

MR. REINSTEIN: Right.

MR. NARALLAN: -- creative combinations you've discovered.

But, please, keep going.

MR. REINSTEIN: Yeah. Essentially we have a choice of five atypical antipsychotics. We're going to talk about all of them. They're considered atypical because they're all serotonin antagonists, although they have differences from each other. They do some dopamine D2 blocking, but the strength of the D2 blocking is not as -- as prominent as with the typicals.

And of course, all during the '60s, the

'70s, and the '80s, we had this theory that psychosis and mania were imbalances of dopamine, thus treated by dopamine blockers. Now, that's certainly been challenged in the last ten years.

The atypicals do present different side effects which obviously present different challenges in the extrapyramidal symptoms and the elevated prolactin level symptoms that we had to deal with previously.

Now, Clozapine, as I said earlier, was the -- the first atypical antipsychotic. It has a unique efficacy. It's considered the gold standard for -- for very refractory patients such as you see here at Somerset and the uptown area.

We still have a lot of patients on Clozapine. Problems we've run into with Clozapine is, one, it's a big hassle factor because of the protocol requiring regular blood draws to monitor for the idiosyncratic effect of the agranular cytosis.

And, two, day to day, Clozapine has a lot

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of side effects: Weight gain, diabetes, elevated lipid profiles, drooling or hypersalivation.

MR. NARALLAN: How about seizures?

MR. REINSTEIN: Seizure thresholds.

MR. NARALLAN: Have you had some patients seize before?

MR. REINSTEIN: Yes. Yes. And as a result of this, most of our Clozapine patients are getting a prolactin -- prophylactic anticonvulsant. We used to use Depakote. We now use a lot of Trileptal.

Then Risperidone came out in 1990 -- '94. We were first going with that for a few years because it had less side effects than the Haldol, although it still had -- had EPS and prolactin level problems.

We had patients who wanted to get pregnant who weren't having menstrual periods. We had people getting enlarged breasts on Risperidone.

Olanzapine came out in 1996. We were initially enthusiastic about Olanzapine. The molecule looked like Clozapine; however, unfortunately, when we tried switching patients from Clozapine to Olanzapine a lot of them had relapses. So it didn't equate at least with positive symptoms with Clozapine.

And unfortunately it had a lot of the same baggage as Clozapine: The weight gain, the elevated

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blood sugars, and the problems with the elevated lipid profiles, particularly very high triglyceride levels.

MR. NARALLAN: That's actually very consistent with what Dr. Connelly mentioned in a previous DLN show. That Olanzapine inherited the -- more of the side effects of Clozapine, but did not inherit this unique effect on the refractory.

MR. REINSTEIN: Right.

MR. NARALLAN: That it is a good drug, like the others, but it's not a Clozapine.

MR. REINSTEIN: Right. We use it for about five percent of our patients. It's actually for the group that needs to gain weight. Most of our patients don't want to gain weight or they're obese. Schizophrenics, in general, tend to be obese and have a higher incidence of diabetes. So for those patients, we tried to avoid Olanzapine.

Quetiapine came out in 1997. It's actually our first line antipsychotic now. I just presented a paper at the APA meeting last month on high dose Quetiapine therapy, 1200 milligrams a day. When the dose of Quetiapine gets very high it starts to work like Clozapine and is very useful with refractory patients.

MR. NARALLAN: But you know -- let me interject here something, Mike. I really regard 800 of Quetiapine as the usual dose for schizophrenics rather than a high dose. But 1200 is on the higher side. But is that the highest you've gone with Quetiapine?

MR. REINSTEIN: No, we've actually had patients on as much as 2,000 a day.

MR. NARALLAN: Okay.

MR. REINSTEIN: It's well tolerated. Patients don't get EPS with the high dosing. They don't get problems with the prolactin levels. They don't get problems with the widening of the QTc interval on EKG and they don't get weight gain. So it's a very well tolerated drug in high dosing.

MR. NARALLAN: Is that why it became your first line drug, the tolerability or the efficacy or both?

MR. REINSTEIN: It's actually both. We were the lead site in the country on the Quest study, which we did in 1997 and I presented at the APA in 1999, which essentially compared Quetiapine to Risperidone. And we were first going with Risperidone before we did the study. Once we did the study we kind of fell in love with Quetiapine and we've used it first line ever since. But we've liked it. It's well tolerated. The patients tell us they like it much better. There is less EPS in placebo and Risperidone, which does have significant EPS.

And actually one of the more striking findings was on the HamD scale. We found that actually there seemed to be an antidepressant quality to Quetiapine.

MR. NARALLAN: Yeah, actually, it might be worth mentioning here that your Quest study showed that Quetiapine was better than Risperidone in antidepressant. Both of them helped depression, but Quetiapine was better. There's a recent study funded with the Stanley foundation that I understand very recent analysis showed the same thing. So there's an independent replication of what you guys found.

MR. REINSTEIN: Yeah. It's very interesting because I think that's one of the reasons why patients really like Quetiapine. And I was analytically trained, so all of my mentors were psychoanalysts so they always talked about how mania was a defense against depression; psychosis, substance abuse. So if you have a drug that has an antipsychotic with an antidepressant quality, it's going to be very well tolerated by the patients.

Now, I'll also just mention Ziprasidone, which is the newest atypical. It was approved less than two months ago. We've used it with a few patients. It seems to help some patients with very refractory-negative symptoms. We haven't been quite as

impressed with it with patients with refractory-positive symptoms. And of course, we're a little concerned about the EKG issue.

MR. NARALLAN: We'll talk about EKG a little later on.

MR. REINSTEIN: Okay. This is actually Dr. Widen's slide which actually shows how our concerns have shifted. It used to be we worried more about EPS as the side effect. And now, as Dr. Widen's slide shows, our concern with the atypicals is more with weight gain, lipid profile problems and diabetes with Clozapine and Olanzapine; and the QTc prolongation with -- with Ziprasidone.

MR. NARALLAN: Those side effects existed before, but the EPS was so important and so disabling to the patients that we really overlooked them. But now the EPS is being controlled by the atypicals, we're beginning to see the health hazards of weight gain, the diabetes and the like.

MR. REINSTEIN: Right.

MR. NARALLAN: Cardiovascular effect.

MR. REINSTEIN: Right. Before we had the atypicals, you know, the illness was so devastating

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actually patients weren't getting better. And also, a lot of times, they would stop their treatment because of the EPS. They complained about shaking or rigidity. And also the prolactin level issues with the sexual dysfunction was a big reason why patients became noncompliant.

But anyway, excessive weight has a lot of concerns and that's why we really want to monitor it with our patients. Again, our patients tend to be obese as it is. There is obviously linkage of schizophrenia and obesity. And our patients often don't have the best diet. They can't afford the right foods. So we don't want to add a drug that will add to the obesity issue.

MR. NARALLAN: Well, actually, obesity is a real disease. I wish -- I wish people would take it more seriously. Because not only does it cause of these cardiovascular effects and diabetes effects and cancer, studies actually showed that -- that if -- that obesity accounts for about 30 to 40 percent of the cancer in this country. And if we controlled obesity, cancer rates will drop down.

MR. REINSTEIN: Right.

MR. NARALLAN: So it's not just diabetes and heart potential side effects. So it's a serious illness.

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MR. REINSTEIN: Yeah. And it also leads to noncompliance with treatment. Patients get concerned about it. And our patients have self-esteem that's -- that's bad enough as it is because of their illness. We don't want to add another factor that will cause them to have low self-esteem.

MR. NARALLAN: Actually, noncompliance was shown in bipolar patients to be about 400 percent higher with weight gain. Bipolar patients particularly resent weight gain.

MR. REINSTEIN: Right.

MR. NARALLAN: Schizophrenic patients sometimes are not aware of it.

MR. REINSTEIN: Yesterday I did a psychiatric evaluation on a lady. She came in the hospital. And she had stopped her medication. Actually, she was on Ziprasidone and Depacon. She claimed on that she'd gained 30 pounds and so she stopped both medications and then her mania relapsed and she had to be rehospitalized. So it's an important factor to look at.

Now, two of the drugs: Clozapine and Olanzapine cause very significant weight gain, particularly during the first two years of treatment; averages about 25 pounds a year, some patients much more

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than this. And it's a big factor why it's hard keeping patients on Clozapine or Olanzapine.

Now, fortunately with Quetiapine and Risperidone and also with Ziprasidone, we're not seeing significant weight gain. In fact, Quetiapine and Ziprasidone seem to be weight neutral. Risperidone we see a little more weight gain, particularly in children and adolescents and young females.

MR. NARALLAN: I think we have some slides about that coming up. This shows that the atypicals are really, like, two classes: Some that increase weight gain; some don't.

MR. REINSTEIN: Yeah, Clozapine and Olanzapine seem to significantly block the 5H2C receptor and that's associated with increased appetite. We've seen just tremendous carbohydrate cravings with the patients on Clozapine and Olanzapine.

Now, this slide shows a comparison of -- of Quetiapine with Olanzapine in terms of weight gain.

Now, with Olanzapine we find the weight gain persists and is progressive. And this -- this goes on pretty steadily for about two years before it seems to level off.

Now, with Quetiapine there's a slight upward in the weight, maybe the first two months of

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therapy. But actually by the first year in this data it actually is -- becomes weight neutral.

MR. NARALLAN: Yeah, this is a new study actually in Europe -- from Europe with monotherapy with Clozapine. So it's striking that if you follow the patients you do have weight trouble. You also have additional data in the next slide showing the relationship to body mass index.

MR. REINSTEIN: Yeah. And what's -- what's also encouraging is the patients who are actually under weight seem to gain a little weight with Quetiapine but actually the group that's more severely obese seems to lose weight. And that's what we've found with people who had gained a lot of weight on Clozapine, which I'll show that data in a couple of minutes.

MR. NARALLAN: And also, the -- correct me if I'm wrong, Mike -- but the weight gain with Clozapine and Olanzapine, the two major offenders in this area, seems to be dose related. The higher the dose, the more the weight gain.

MR. REINSTEIN: Yeah. That's what we've been seeing. But interestingly, with Quetiapine, even with people on very high dosing, like 1200 milligrams a day, we're not seeing weight gain.

Now, this slide is a comparison of
Quetiapine and Ziprasidone. And pretty much they work the same. The patients who are under weight seem to gain a little weight on both drugs. The patients who are overweight seem to lose a little weight. So where obesity is a major issue we think these are the best -- best two drugs to look at.
Again, Risperidone is somewhere in the middle and the two that you would want to avoid, once again, is Clozapine and Olanzapine.
MR. NARALLAN: Yeah, this slide really shows that these two drugs, regardless of dose, they're weight neutral. This one shows the opposite for Olanzapine.
MR. REINSTEIN: Yeah. Olanzapine with high dose therapy, which again is only defined as 15 milligrams a day, and of course, a lot of people go much higher than that, there is this very progressive weight gain. And you even see it a bit with at the low dose Olanzapine, but it's obviously much worse with the high dose Olanzapine.
MR. NARALLAN: Yeah, I have patients on Olanzapine that did not gain a lot of weight. They tend to take lower doses. But clearly, most of my patients take 15 or 20 or higher and they gain a lot of weight.
MR. REINSTEIN: Yeah. Yeah, it seems the higher the dose, the more risk of weight gain.
Now, with children and adolescents it's interesting because about 71 percent have a significant weight gain with Olanzapine. So again, if you want to -- if you're concerned about a child or adolescent, usually if you give it to an adolescent female and she gains a couple of pounds, she'll throw the pills in your face. So Olanzapine is a good drug to avoid.
And for some reason we've seen more weight gain in children and adolescents with Risperidone. Still not as bad as with Olanzapine, but it's more than Quetiapine with the children and adolescents.
MR. NARALLAN: There is another reason why Olanzapine also is not -- is not helpful for -- for adolescents, not just the weight gain is the worse, but a recent study by McConnel showed that prolactin effects of Olanzapine -- prolactin. Hyperprolactinemia causes a lot of sexual dysfunction in adolescents.
MR. REINSTEIN: Yeah.
MR. NARALLAN: Almost like Risperidone. So that's another difference. Quetiapine showed very little effects.
MR. REINSTEIN: You know, and we worried about these long-term implications of elevated prolactin levels with particularly children and adolescents.
MR. NARALLAN: Right.
MR. REINSTEIN: We're afraid it will interfere with their sexual development and even concerns about breast cancer and possibly ovarian cancer being related to elevated prolactin levels.
Anyway, this is our mean weight gain at three months for children and adolescents. It's almost 15 pounds in three months with Olanzapine.
Again, children and adolescents are

naturally growing, but this gets to be a major problem, less with Risperidone and less with Risperidone with Quetiapine.

MR. REINSTEIN: And by the way, Type II diabetes will occur in adolescents if you push their weight up.

MR. REINSTEIN: Yeah. This is actually the next -- the next thing I was going to review with you.

Numerous case reports show diabetes sometimes with ketoacidosis with patients on Clozapine and Olanzapine; not with -- with Quetiapine or Risperidone. And I can remember one patient, no family history of diabetes, not overweight. We started him on Olanzapine. And a week later we got a call from his family. He was very ill. We didn't know what was going on. We had him go to the emergency room. He had a

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blood sugar of over 1200. He was in full blown ketoacidosis. So this is not a benign drug. It can be dangerous for -- for certain patients.

MR. NARALLAN: Well, yeah. We do avoid it. We have an official policy in our institution that patients with preexisting diabetes in themselves or their family, first degree family, will not receive Olanzapine unless you exhaust all other atypicals.

MR. REINSTEIN: Yeah. Yeah. Well, being in the city here, our population is about -- our patient population is at least half African-American and Hispanic. And we've been finding they seem even more sensitive to the -- to the effects of the Olanzapine.

MR. NARALLAN: Very good.

MR. REINSTEIN: Now we're going to talk about some combination strategies with -- with resistant patients.

First of all is Clozapine and Haldol was actually a combination we used to use a lot of. It seemed to work well with patients with very refractory-positive symptoms, such as -- such as we have here at -- at Somerset.

MR. NARALLAN: And they need more dopamine blocking, right?

MR. REINSTEIN: Right. It seems the

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Clozapine by itself did not do it. We'd get maybe about a 40 percent response rate as measured by reduction in hospital days with Clozapine monotherapy as opposed to atypical -- if we had added Haldol, we got a -- we got up to about 80 percent reduction in terms of hospital days.

MR. NARALLAN: Why not use Risperidone instead of Haldol?

MR. REINSTEIN: It's not a bad combination. We -- we actually have a lot of people on Clozapine and Risperidone. And I suppose the only issue is just cost. You can get the same effect with Risperidone and Clozapine as you can with Haldol and Clozapine.

MR. NARALLAN: Okay.

MR. REINSTEIN: Now, lately we've been using much less Clozapine. We've been starting less patients on it. And we, first of all, give a trial of high dose Seroquel. We'll go as high as 1200 or even higher. Most of our patients tolerate it quite well. We tend to give most or all of it at night, so that gets

away from the sedation and the dizziness.
And another combination we use, if the Seroquel itself doesn't totally control the positive symptoms, is a combination of Risperidone and Seroquel. We use that combination quite a bit.

We also use Haldol and Seroquel. So as a result of using either Haldol and Seroquel, again, low doses of Haldol or low dosages of Risperidone with high-dose Seroquel therapy, we've had to go to Clozapine much less. And that avoids all of the hassles and side effects of Clozapine.
Now, for patients who have refractory, irritability, mania, hostility, we use Quetiapine with different anticonvulsants that work as mood stabilizers.
In the '80s we -- we used to use a lot of Tegretol or Carbamazepine. That worked pretty well except we had the concerns about aplastic amenia and some of the other side effects on Tegretol.
In the '90s, we used more of Depakote or Valproic acid. And it wasn't a bad drug, but we had a lot of weight gain with Depakote. We had a lot of elevations of the blood sugars, liver dysfunctions.
MR. NARALLAN: Polycystic ovaries.
MR. REINSTEIN: Polycystic ovaries, lowering of the platelet count. And then we actually had several patients who developed pancreatitis in relation to Depakote. And now, as you know, there's a black box warning for Valproic acid. Right now our favorite mood stabilizer is actually Carbamazepine. It's actually a derivative of Tegretol, but it doesn't

have the risk of aplastic anemia. And that works very well in conjunction with Phytolyn. There seems to be a synergism of the two drugs for some of the more refractory, manic, irritable patients.
We also use SSRIs with -- with Seroquel with people with panic disorders, anxiety. Seroquel seemed to be -- Quetiapine seems to work very well for this population. And we also like Quetiapine with the elderly, because it doesn't cause EPS. We use it a lot in the nursing homes. A lot of the patients are Parkinsonian. We don't have to worry about weight gain. A lot of them are diabetics. So we try and avoid Olanzapine.
MR. NARALLAN: You know, everything you've said about combination is -- is of great interest to clinicians because of a lot of them are using combinations. But one thing that is interesting, is that all of the clinicians are using them but there are very few, if any, control studies.
MR. REINSTEIN: Yes.
MR. NARALLAN: So your experience, of course, is clearly important for you, other clinicians are using those combinations. But there is only one study I know that's published about -- the one you're going to talk about now, which is how you use

combination to improve safety in the patients.
MR. REINSTEIN: Yeah, there's certainly a need for more combination studies. Unfortunately, nobody has been willing to fund them. But we're using a lot more combination therapy than -- than -- than we

used to, particularly for the more refractory patients.
Now, the one combination study that we did do, which -- which is published and I'm going to talk about now. The study that was published in the Journal of Clinical Drug Investigation. And it was actually a Clozapine/Quetiapine combination therapy study. And we -- we actually selected 65 patients who -- who developed weight gain and diabetes during six months of monotherapy with Clozapine. And just to show you how significant the diabetic issue is actually 13 out of the 65 of these patients or 20 percent had developed diabetes while -- while on Clozapine.
Now, the group who -- who had developed diabetes actually gained more weight than -- than the average population. It was actually about 19 pounds. So there was a correlation of -- of Clozapine and weight gain and diabetes. But interestingly, not all of the patients that developed diabetes had gained significant amounts of weight.
So right now our protocol is with Clozapine

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and Olanzapine patients is we get a monthly weight and we're also very regularly getting blood sugars and insulin levels and lipid profiles.
Now, in terms of the weight gain, in this group of 65 or in this six-month period their average weight gain was 14 pounds. Diabetic group was actually 19 pounds, almost.
Now, what we found by gradually tapering the Clozapine to the Quetiapine starting with a 25 percent reduction in Clozapine back on Quetiapine we find it's basically a one for two titration; for every milligram of Clozapine we take away we add 2 milligrams of Quetiapine.
Now, the hypothetical patient who's on 400 of Clozapine, we start by reducing it to 300 and doubling back on the Quetiapine so they'd rather be -- instead of 400 on Seroquel and 300 -- of -- of -- 400 of Clozapine, they go up to 300 Clozapine and 200 of Seroquel.
MR. NARALLAN: Don't you add the Seroquel first and then you withdraw the Clozapine?
MR. REINSTEIN: No, we do it at the same time.
MR. NARALLAN: At the same time?
MR. REINSTEIN: Yeah. And then usually

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after a month we'll withdraw another 25 percent of the Clozapine and double back on the Seroquel. Now, what we found first of all was the -- the weight gain with the Clozapine stopped and you actually start seeing weight loss, which is welcomed by the patients.
In terms of the diabetic issue, there's something about Quetiapine that's actually protective of whatever problem Clozapine is causing with the blood sugar. Because we see normalization of -- of serum glucose levels. Those patients who are getting treatment for diabetes on insulin or -- and/or hypoglycemics that is actually less than it was previously.
MR. NARALLAN: I've had some experience with Olanzapine-induced diabetes. And when I switched the patient to Quetiapine, the diabetes resolved without

the need for anti -- for medication.
MR. REINSTEIN: Right. If you have a patient on Olanzapine who is either gaining weight or -- or creeping into diabetes or has abnormal lipid profiles, you'll find terribly abnormal lipid profiles with both Clozapine and Olanzapine, sometimes triglyceride levels of over 1,000.
MR. NARALLAN: Nobody is looking at them. I wish clinicians would monitor that, because this is a

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health hazard.
MR. REINSTEIN: Actually, when they draw the blood somethings the serum is even labeled lipemic. So -- so it's a big concern with both drugs.
Anyway, during Clozapine therapy in our study we found significant elevations of the hemoglobin 1Ac levels with the patients who are on Clozapine.
And interestingly, as we switched to Quetiapine, this elevation in the hemoglobin 1Ac levels rapidly dropped so there's much less need for insulin and we're able to discontinue insulin and/or the oral hypoglycemics. We found this both with the Clozapine group and we haven't published our data on Olanzapine, but we also do have data on that as well.
Anyway, we're going to switch to another subject now. That's clinicians' concerns about the EKGs which has been publicized quite a bit recently since Ziprasidone was approved.
Now, this is a typical EKG here. Basically we're talking about the QTc interval, which measures ventricular depolarization and then repolarization.
MR. NARALLAN: Now, Mike, this is a legitimate issue because the Pfizer drug, Ziprasidone, was delayed about two and a half years because the FDA asked them to do more safety studies.

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MR. REINSTEIN: Right.
MR. NARALLAN: But frankly, I think the tone of the advertisements -- advertising by some of the companies have magnified the risk. We hope -- we hope to see with the data today what exactly is the story.
MR. REINSTEIN: Yeah, I agree with you. I think there's reasons to be concerned. But I think there's been certain advertisements which may cause overconcern, as well.
Anyway, the data shows that the QTc interval with -- with -- with Thioridazine or Mellaril is increased over -- over 30 milliseconds per beat. Now, as a result of this the FDA has placed a black box warning on -- on Thioridazine that it's not supposed to be used unless you've tried with other agents.
Actually, we don't have anybody left on Thioridazine. We've actually been concerned about this issue for a long time.
Now, Ziprasidone has a bold warning about its effect on -- on the QTc interval. This is less severe than Thioridazine, which has a black box warning. But it still means clinicians should be careful and use some commonsense about using Ziprasidone since it does prolong the QTc interval significantly, although not as significantly as Thioridazine. We personally avoid

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Ziprasidone in those patients which -- which have

significant cardiac disease or they're on other drugs which may also prolong the -- the QTc interval.

MR. NARALLAN: Now, it seems that the Ziprasidone has a relative --

MR. REINSTEIN: That's right.

MR. NARALLAN: But compared to the other atypicals, you know, Olanzapine, Risperidone, Clozapine, they seem to be quite less than -- than the Ziprasidone. But Ziprasidone is not a dangerous drug necessarily in it's own right.

MR. REINSTEIN: No, as long as clinicians are careful with their use and avoid uncertain situations.

MR. NARALLAN: Which we'll talk about in a second.

MR. REINSTEIN: Right.

Now, this is the data on -- on QTc intervals. This is the Pfizer 054 study. Now, the FDA looks at baseline effects. Now, here Thioridazine is over 30, which is very significant. And again, you'd have to be very careful using it. Ziprasidone is 15. It's -- it's a concern but not a terrible concern. And the other drugs, Haloperidol is actually the next at 7.1. That's not terrible. And then it drops down from

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there.

Now, the Bazett's Correction we don't really look at. We think it's flawed by a variance in the cardiac rate. So the one we're looking at is the baseline correction, which is not significant.

MR. NARALLAN: That's what the FDA actually looked at. The baseline correction is the FDA's choice.

MR. REINSTEIN: Right. Right.

MR. NARALLAN: And then they did the metabolic inhibitor study, the 054.

MR. REINSTEIN: Right.

Well, this slide shows that they would use a metabolic inhibitor to raise up the level of each drug. And again, even raising up the level did not significantly widen or prolong the QTc interval.

Thioridazine, again, was still significantly high. And Ziprasidone was -- was not significantly affected by the inhibitor. And again, no major problems, even with the inhibitor with the other atypicals and Haloperidol is somewhere in the middle there.

MR. NARALLAN: I think this is a reassuring study.

MR. REINSTEIN: Yeah. We were reassured by it. You know, there was some effort to tower all of the

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atypicals as drugs that were sort of dangerous. But we don't actually find that. And again, with very high-dose therapy, we don't find significant prolongation of the QTc interval. And again, the last slide just showed the effects on the inhibitor and that prolonged that.

Now, this slide shows the incidence of QTc increase greater than 450 millisecond, which is starting to get into a dangerous territory. And particularly over 500 is an area that clinicians should avoid.

Again, Thioridazine is the one most commonly that produces the -- the QTc increase greater

than 450, sometimes as much as 500. Ziprasidone is second. And then we really drop down. And the others there's no real significant issue.

Again, that's even when you use an inhibitor and you raise up the blood levels of the drugs.

MR. NARALLAN: Yeah, judging from this slide, Mike, it looks only like -- only Thioridazine experienced a significant increase in the -- in the QTc when the metabolic inhibitor was added compared to steady state. But for the rest it looks like they are very similar.

MR. REINSTEIN: Yeah. I think as long as

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clinicians are careful, I don't think they'll run into problems.

MR. NARALLAN: Right.

MR. REINSTEIN: Right. We use Ziprasidone to help people with refractory-negative symptoms. It seems to have a stimulating effect.

In any case, the approved Ziprasidone label is that the prescribers should be aware of the prolongation of the QTc interval. And this is what leads to the bold warning on the product insert and in the PDR.

MR. NARALLAN: But to my knowledge, Mike, no one has died from Ziprasidone yet.

MR. REINSTEIN: No. We're not aware of it.

MR. NARALLAN: 4,000 patients tested, only two patients exceeded 500 millisecond, which was equal to placebo. So if one exercises commonsense and avoids patients with heart disease and use in patients who are taking other drugs that prolong the QTc, you're okay.

MR. REINSTEIN: Yeah. Yeah.

We have started some people on Ziprasidone. We've been doing serial EKGs. And there is a slight increase in the QTc interval, but not enough to cause us any concern that we've had to stop anybody's Ziprasidone dose.

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MR. NARALLAN: But eating one heavy meal increases your QTc by 20 millisecond. That's slightly more than Ziprasidone. So one has to take the context into consideration.

MR. REINSTEIN: That's true.

Anyway, Ziprasidone does have the bold warning and clinicians need to use care, but it's not a major concern to us.

MR. NARALLAN: So only atypicals look like they are fine in this regard.

MR. REINSTEIN: Yeah. And we don't -- we don't think clinicians should not use the drug because of any cardiac safety concerns, except against Ziprasidone one should use a little discretion. But there's no reason not to use Risperidone, Ziprexia or Quetiapine because of concerns about it.

MR. NARALLAN: Right. Anything else? Do you want to wrap up?

MR. REINSTEIN: No. I think we've covered all of the important parts of this. Certainly one thing I like about doing this is hearing other people's questions and comments.

MR. NARALLAN: I'm sure we've got some

questions.
I appreciate you covering the -- the nonEPS side effects, which are emerging now as -- as a -- not only tolerability issue, but also a health hazard issue. We have to protect our patient's physical health.
MR. REINSTEIN: Right.
MR. NARALLAN: And we have to mind what we're giving them.
MR. REINSTEIN: Yeah.
MR. NARALLAN: Well, I think this is a good way to -- to wrap it up.
And -- and now we'd like to turn to the audience and -- and ask you to open up. We're going to open up the phone lines so that you can participate in the discussion and start sending in your questions.
If you do have any questions for Dr. Reinstein or myself, please give us a call now. The toll free number is 1 (800) 494-0655 or you can fax us your question at 1 (651) 308-0533.
But right now we're going to take a short break and when you come back we're going to take the calls.
Thank you.
(Break.)
MR. NARALLAN: Jennifer from New York. Welcome to DLN, Dr. Magender. What is your question?
DR. MAGENDER: Do you think that -- do you think that Ziprasidone with other antipsychotic medications like Seroquel, does it have any cumulative effect on QTc interval?
MR. REINSTEIN: Actually, Dr. Magender, we've tried every drug combination. We actually have some patients on Ziprasidone and Seroquel -- Quetiapine. We've been monitoring the QTc interval. And we've not found any significant problems with the combination of Ziprasidone and Quetiapine.
It's sort of an interesting combination. Ziprasidone seems to be a more stimulating kind of drug for the negative symptoms. And Seroquel seems to work better for some of the positive symptoms and the anxiety. So it's an interesting combination. We actually have some patients on it and we're not seeing any problems with it with the QTc interval.
MR. NARALLAN: Very good.
Next caller. Dr. Ferber from New York. Welcome to DLN. What is your question, Dr. Ferber?
DR. FERBER: Hi. How do you switch people from Haldol and Risperidone to Quetiapine?
MR. NARALLAN: That's a good question. Switching is always an issue. How do you do it? You do a lot of that here.
MR. REINSTEIN: Yeah. We do a lot of switching. And we also sometimes do partial switches with combinations with the EPS.
With Risperidone if you have a patient that's not doing as well as you'd like or they're starting to get into problems with extrapyramidal symptoms or the prolactin level issue, it's essentially the 1 for 100 switch. So for every milligram you take away, you add 100 milligrams of Seroquel. And that's --

that's pretty much what -- what we do with Haldol, as well.

So I -- we start usually lower by about 25 percent of either the Haldol or Risperdal, the 1 for 100 ratio, at the same time that we start them on Quetiapine. A lot of the patients actually end up on the combination. The Quetiapine actually buffers the EPS and the prolactin level problems that they had with either the Haldol or the Risperidone.

And if we don't get maximum benefits from the Quetiapine, we'll of course leave them on a little extra dopamine blocking which they'll get from the Haldol or the Risperidone. And it is a very good combination.

MR. NARALLAN: Yeah, I want to add something to that. You focused on the -- on the dose equivalents, but I'd like to focus on the pace.

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I take my time when I'm switching from a strong dopamine blocker, like Haldol or Risperidone, and do it over several weeks. The longer the patient has been on Haldol or Risperidone the more -- the longer I take. So I might take anywhere from six weeks to 12 or 14 weeks slowly cutting down over -- I add the Quetiapine and start slowly tapering off the previous drug. That's what I do to avoid relapse.

MR. REINSTEIN: Yeah, it's good for several reasons. But one is you get to view the patient first of all on monotherapy with Haldol Risperidone and then you get a view of them with the combination and if you -- if you taper them off, you might get a third view with the Quetiapine. And then you can decide which view you like.

Actually, for us about half the patients end up on monotherapy with Quetiapine and half of them seem to do better with the combination.

MR. NARALLAN: Okay. We have another call from -- from Veronica Devitos from New Jersey. Welcome to DLN. What is your question?

MS. DEVITOS: I have -- I have a question from the nurse's point of view because we have a patient apparently on the medication and the doctor ordered an EKG. And what are the signs and symptoms that the nurse

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should watch in regards to this mediation sensitivity-wise or, you know... (Pause.)

MR. NARALLAN: Good question.

MR. REINSTEIN: Okay. Well, we will get a routine baseline EKG with anybody admitted to the hospital. Should the patient develop significant dizziness, drowsiness, cardiac palpitations, weakness, we would get a follow-up EKG just to make sure there's no arrythmia.

So I think if your patient has any of those symptoms you should review it with the attending doctor and you may want to get a follow-up EKG.

MR. NARALLAN: Yes. Syncope is a bad sign. When the patient has syncope it means you may be getting close to serious QTc prolongation.

I have a question from Kathleen Banstrom from New Jersey. Welcome to DLN. The question?

DR. BANSTROM: Hi, Mr. Reinstein. You mentioned that some of your patients are on 2,000

milligrams of Seroquel. Can you describe the demographics of these patients and does the increase in Seroquel cause sedation?

MR. NARALLAN: That's a good question.

MR. REINSTEIN: Yeah, that's a very good question.

We find when we initially use Clozapine it was sort of interesting. We'd have some people who got 25 milligrams or 50 milligrams of Clozapine. And they were doing fine. And of course, our temptation was to say, Well, if they're doing so well with the low dose let's push it up a little more. So then we'd push it up to maybe 100 and then all of a sudden the patient is saying they're dizzy or drowsy.

Well, Quetiapine is somewhat like Clozapine. There is a small percentage of patients that seem to be either superabsorbers and/or slow metabolizers of both Clozapine or Quetiapine and they are kind of sensitive and they tend to get dizzy or drowsy very easily.

On the other hand, we have a lot of patients who go up to Clozapine 900. And, again, that's a 1 for 2 titration that gets you close to 2,000 of Quetiapine. And they were still having symptoms and we do their blood level and it was only like 100. So we'd have to add something, which would kind of artificially raise up the Clozapine level of a drug like Luvox.

Again, every patient is different. Most patients, particularly the very sick ones, seem to tolerate the very high dose Quetiapine. And those are the ones that we gave the high dose Quetiapine therapy.

Now, we also use Quetiapine a lot off label for anxious patients, panic disorder patients, borderline personality patients, elderly patients. But these patients get much lower dosages of Quetiapine than we do for the more severe psychotic patients. And we may even have them carrying around -- some of the borderline anxious phobic patients with panic disorders, they may carry around low dose Quetiapine. And I direct them to take it when they feel anxious or panicky. But they're not on as high a baseline dose as the very refractory, psychotic, maniac patients.

MR. NARALLAN: Yeah. I agree with you. And I've used Seroquel for PRN, anxiety, panic attacks. And I -- and all of the atypicals, by the way, work off label for many of those conditions. But I think Quetiapine has a unique antianxiety effect more so than the others. And I think it's worth studying.

MR. REINSTEIN: Yeah, I fully agree with you. We're using it a lot off label for -- for PRN for those patients with anxiety and symptoms like that.

MR. NARALLAN: Okay. Next go to Dr. Lansis from Vermont. Welcome to DLN. What is your question Dr. Lansis?

DR. LANSIS: Seroquel -- I'm getting feedback here.

Seroquel causes sedation when it's given in a split dose. Do you -- do you ever use something like Provigil to counteract the daytime sedation?

MR. NARALLAN: Do you use that?

MR. REINSTEIN: Well, that's a very good question, Dr. Lansis.

We try to give our Quetiapine mainly at night. And believe it or not we have people that are taking 2,000 milligrams at night. We try and avoid it during the day to -- to avoid the problems you're talking about.

Now, if the patient complains of -- of -- of a bit of drowsiness during the day, I -- I generally just tell them to take a caffeine-oriented beverage, coffee, diet soda, whatever they like.

I personally haven't used Provigil but other people have. And I think Provigil obviously would have a stimulating effect. I'm not sure if it weren't worse than the symptoms of psychosis and that's why I haven't personally used it.

MR. NARALLAN: Can I say something about this? I personally do not like to add a drug to counter the side effects of another drug. To me, that's polypharmacy. The only time I use polypharmacy is when it's constructive, rational polypharmacy and that is to

0043

enhance efficacy, but not to counteract side effects.

I totally disagree with the individual who says, let's use Topamax with Olanzapine to reduce the weight gain. That's bad polypharmacy. You don't add a potentially neurotoxic drug just to counter the side effects of another drug that's causing a side effect.

So Seroquel I do what you do, Dr. Reinstein. I give it all at bedtime, about 40 to 50 percent of the patients get sedation in the early stages of the treatment. Most of it is in the hospital. The good news, this is one side effect that really goes away. Tolerance develops to sedation much more than the other side effects. You don't get tolerance to EPS or diabetes or weight gain.

So my suggestion is you give the medication VID or TID or however you want to do in the hospital. It's up to you. They're there. But on discharge I give the medication at that time. It really greatly enhances compliance and it lets them sleep it off.

MR. REINSTEIN: Yeah. I fully agree with you. And Topamax, we've had people complain a lot about cognitive effects of that.

MR. NARALLAN: I think it's really unethical to give -- it's not even indicated. The physician could be liable if they used a medication like

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Topamax before it's even indicated.

We have a question from Dr. Lee.

DR. LEE: Yes, Dr. Lee calling from the (inaudible) center in New York.

MR. NARALLAN: Yes.

DR. LEE: I have a question about your opinion. I have several patients who used to take other medication and then gained the weight. And then I switched their medication to Seroquel. Then they -- yeah, technically I see they're, you know, losing, much losing. And then they say they don't seem hungry. Then my question is: Does Seroquel, maybe, influence sense for appetite?

MR. NARALLAN: Your question is whether Quetiapine suppresses appetite?

DR. LEE: Right.
MR. NARALLAN: Okay. Have you seen that Dr. Reinstein?
MR. REINSTEIN: Yeah. There's actually some nurses in some of our facilities who have actually requested Quetiapine because they noticed it really did suppress the -- the appetite and they wanted to lose weight themselves.
But we've noticed this particularly when patients come down on their Olanzapine or their

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Clozapine dosages and you switch them to Quetiapine that they don't crave the carbohydrates anymore and they tend to lose weight. And we've jokingly kind of suggested to AstraZeneca that maybe they should look at Quetiapine as another indication of taking away excessive appetite.
MR. NARALLAN: Well, my -- Dr. Lee, based on this study that we described in this show, Dr. Breaker's study from Europe, there was a group -- a subgroup with a BMI higher than 28 that appeared to lose weight with Quetiapine. So in that sense it suppressed their appetite or did something. But I don't know if -- that it actually suppresses appetite or just prevents the increase of appetite.
I think that's all the time we have today. Thank you very much, Mr. Reinstein. It's been a pleasure to have you here.
And thank you to -- to the Somerset Halfway House staff for hosting us here today here at this unique facility.
And thanks to all the participants in the audience.
As a reminder, though, please take a minute to sign the sign-in sheet and fill out the program evaluation. Your input is of great value to us as we try to bring you the best in educational program.

0046

I'm Dr. Henry Narallan for the Distance Learning Network and University of South Dakota School of Medicine saying thank you for joining us and good-bye until next time.
(End of tape.)

0047

REPORTER'S CERTIFICATION

I, SHAUNA L. BEACH, RDR, CRR, Certified Shorthand Reporter in and for the State of Texas, hereby certify to the following:

I certify that I am neither counsel for, relate to, nor employed by any of the parties or attorneys in the action in which this proceeding was taken, and further that I am not financially or otherwise interested in the outcome of the action.

Certified to by me this 14th day of October, 2008.

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