Atypical Antipsychotics: Patient Acceptance, Positive Outcomes
Henry A. Nasrallah, M.D.
and
S. Charles Schulz, M.D.

Schwartz: ...for many years. He's an outstanding teacher and is the Professor and Chairman of Psychiatry at the University of Minnesota, where they think if it's 28 below zero it's warm out. Chuck is going to be preceded by another good friend of mine, Dr. Henry Nasrallah. And Dr. Nasrallah is a man of wide-ranging interests and is so knowledgeable about so many different things that he is not only professor of psychiatry at Mississippi, but he is also the professor of neurology and internal medicine. And I have a very hard time getting my head around a small fraction of psychiatry, so I really have great admiration for his capacity to stay up to date in these three very large, complicated areas. But Dr. Nasrallah is going to speak in just a minute.

I would like to just begin with a few housekeeping announcements. First and foremost, we want to make all of the Congress very useful to you, and in line with that, in the front of your syllabus booklet are these question cards. After our speakers have given their talks we will have time for a Q&A period, and we ask if you would like to pose a question that you print it as legibly as you can on the question card. And then during the second talk that Dr. Schulz is going to be giving, if you could just hold it up at your place, members of our staff will be circulating, hopefully unobtrusively through the room, and they will grab the question card from you. And after Dr. Schulz finishes his talk, Dr. Nasrallah and Dr. Schulz will go over here, they will look through the question cards and they will answer a large number of them, hopefully all of them in the time we have. And that always proves to be interesting, useful for members of the audience who have asked the questions, and interesting and often challenging for the faculty members, because you ask good questions. And so please, don't hesitate to print your question as legibly as you can, and just hold it up patiently during the second talk and we will collect that from you And hopefully, one of the members of our faculty will be able to respond.

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Additionally, I'm going to start nagging you tonight—and, forgive me, but I'm going to be doing this for the next four days because I am a nag—we want to make our future meetings even better. And the way we've been doing that for 24 years is relying on your candid feedback. And so you have an evaluation form in here, and we ask that you fill it out properly so our computer scanner can read it. But by the same token, we are not just interested in the little boxes that you are supposed to fill in to answer these generic questions. If you have any constructive criticism or comments or suggestions you would like to make, please, simply turn over the evaluation form, print it as legibly as you can and turn it in, because we actually look at the back side and are interested in your feedback. We have made a lot of running changes over the last 24 years that have come from wonderfully helpful, constructive criticism from

our wonderful attendees. So please remember to fill out the evaluation form and turn it in so we can make even better programs in the future.

Well, I think it's time for us to begin. Let me just say again, thank you so much for coming to our 15th Annual Psychiatric Congress. And now will you help me welcome my friend Henry Nasrallah. [applause]

Nasrallah: Thank you very much, John. Good evening, everyone. I hope you are enjoying yourself in Las Vegas. Good to see all of you here again. We do this every year as a kickoff for the U.S. Congress, which is, as you know, becoming one of the best meetings that psychiatrists go to ever year. I also would like to thank AstraZeneca for their generous support of this CME event. And let's proceed. I want to use every minute of my time to give you my part of this symposium.

Now notice the title of the symposium—it's gone already, but—"Patient Acceptance and Good Outcomes." The patient is happy, the physician is happy. We want good outcome for our patients. How do we get there? How do we get there? Well I would like to spend the next 30 minutes with you describing how can we use the atypicals to get the best outcomes out of our patients, and how do they compare in effectiveness, not just in efficacy. Because, you know, effectiveness is much more than just efficacy. It's a very complex interaction of side effects and tolerability as well as efficacy. And also in the real world, will everybody be responding to the patients the same way that the controlled research trials come out with their results after very controlled conditions? The real world is messier than research settings, as you know.

So moving along, you know that the atypicals—great tools, new generation—has really become widely accepted for first-line members of that generation. Clozapine remains, in my opinion, the best for the refractory patients, not necessarily—in first-line patients, Clozapine really does not differentiate itself from the other drugs, although we don't use it for those patients anyway. But in countries where they do, it doesn't shine unless it's a refractory patient. But I'm going to concentrate on the first four, the ones that we use widely every day.

First question, let's get it out of the way: are there efficacy differences? Is there one atypical that is better than the others? If so, let's use it. People do like to have the maximum possible efficacy. The simple answer is no. And I'm going to show you a few slides to prove my point. When you look at the big picture, the meta-analysis, the entire sum of data, not just one study here, one study there, because every drug company will have a really good study to show you. And look how good we are, we are better than them. You know, but that's marketing. When you come down to facts and science, it's wonderful to know that no matter which one you use, you are going to get really the same efficacy in our patients. And let me show you why.

At the right dose, when you titrate your patient to the best dose of Risperdal, Zyprexa or—let me use the generic, chemical names, you know—risperidone, olanzapine, quetiapine and ziprasidone, you are going to get very similar results. Here is the sum total of controlled studies for risperidone. And when you take the big picture view and calculate the effect size, which is—how many points in the Positive and Negative Symptom Scale does risperidone decrease, on the average, in thousands of patients studied? It's about 18.5 points; between 10 and 25, generally.

Here's the studies on olanzapine. There are four controlled trials. Guess what? Exactly the same range; 10 to 25 points from the lowest to the highest study. The average is 18.3 or 18.4, practically identical.

Same thing with quetiapine. You look at the controlled trials there, exactly the same range. Isn't it amazing? You know, different companies do different studies with different patients and different investigators; get exactly the same results. It shows you that, probably, the class of serotonin dopamine antagonists really do the same amount of good in the brain.

And finally, we don't have several studies with ziprasidone, but we have a representative study from the couple that Pfizer did for ziprasidone for approval. And you can see that at the optimal dose (in this case 160 for chronic schizophrenia)—you need the higher dose of ziprasidone, usually—it gets exactly the same thing; about 18-point drop. So don't, you know, let anybody mislead you. When you look at the big picture, they are very much alike. And if you look at the negative symptoms only—what I just showed you is the positive and negative symptoms together. Look at the negative symptoms and look at the spread in this slide. I don't have ziprasidone there, but believe me, it's very much in the same ballpark. You can see that the number of points drop in the Negative Symptom Scales are also the same. So it's good to know that we have a class that is very equivalent.

Now just for the sake of comparing the drugs, there are a few, literally a handful or less of studies where the pharmaceutical companies sponsor their own trials and compare their drug with another drug that they consider a leading competitor. In this case, you remember this slide probably from the Lily sponsored study where they compared olanzapine vs. risperidone. And when you look at the study, a detailed one, there really are hardly any differences. The only thing, among 35 variables, the two drugs were very, very similar. The only thing that they could show was better was, what percentage of patients achieved 40% or more drop in the score. That's what they found as the only significant thing, one out of 35 variables.

Well Janssen responded by doing their own study, same design. And what did they find? The same thing for their drug. So it's almost like a chance finding. When you look statistically at too many variables, you are bound to find one that is different or statistically significant. We don't consider that a solid finding. The good news is that both these drugs are equally good.

What about quetiapine and it's comparison—I think it was Zeneca at the time, before they became AstraZeneca—did a study, a large 700-patient study comparing quetiapine and risperidone. And they didn't find any difference either. Quetiapine and risperidone were very much alike in their efficacy. And as you can see in the slide, there are no significant differences Actually, this happened despite the fact that back then when this study was first presented in '99, the average dose of quetiapine was 317, which is, in my opinion and the opinion of many clinicians and researchers, you know, quite lower than the going dose for schizophrenics at this point in time, which is more like 600—500 to 600, as an average. Despite that, we still got equivalence, again indicating that in real life, in the real world with clinicians where this study actually happened, you really don't get much differences in outcomes.

What about ziprasidone? Well we had one study that Pfizer sponsored comparing ziprasidone with olanzapine, which they considered, you know, at that point a competitor worth comparing to. And guess what; exactly the same. At six weeks no difference between the two drugs. So again, further consolidating the impression that these drugs are very similar.

Now let's take a longer view. Most of the studies that I just presented to you—in fact, all of them—are the classic six-week research controlled trials. What about long-term, because that is what our patients need; long-term stability, good outcome, relapse prevention. How do these drugs compare? Frankly, they are very similar too.

Janssen did this study published, actually, earlier this year in the *New England Journal*. It's a good paper. Risperidone vs. Haldol, a one-year study (or slightly more, actually) where they followed patients on Risperdal and Haldol for a year and looked at the outcome and relapse prevention for all types of reasons. At the end of the year, clearly risperidone was better than haloperidol. And I think that study set the tone for all the atypicals. Atypicals do prevent relapse more and better than the conventionals, which is represented by haloperidol. And this actually is why these drugs are considered superior. Maybe in the acute setting they are very much like haloperidol; they reduce the pathology psychopathology the same amount. But in the long run they really do work in terms of effectiveness. Relapse prevention is an effectiveness measure; staying well, being stable, being able to go back to work or avoiding suicide, suicidal attempts, and being able to stay away from the hospital, reduced hospitalization. It's a very important factor. So this is the kind of study that we consider an effectiveness study. Risperidone was superior to haloperidol.

How about olanzapine? Well Lily did it's own study comparing its drug olanzapine with haloperidol, and they too found a significant difference. It doesn't look too impressive, but statistically it is significant at the end of the year. Olanzapine is better than haloperidol in terms of the percentage of patients who don't relapse.

What about aripiprazole? It's a new drug. Hasn't even hit the market yet? Here we are talking about it. Well the company, to their credit, did a study also because now they have to compete. They are coming into a crowded market. All of those four drugs are widely used and they have to show the data earlier than the other companies did. So they did a study about discontinuation for any reason. That includes patient acceptance. It may include lack of efficacy. Maybe there is a side effect problem. Maybe drug-drug interaction. Whatever, whatever the reason, medical condition. And they, too, found that aripiprazole has fewer relapses at the end of the year than haloperidol, again confirming that all of these drugs do equally good things.

So if all of these drugs are equal in efficacy, why are we talking about that? Why should we not stop at this point and go home? Because there is a lot more than efficacy. When we treat our patients for any condition in medicine, we look at efficacy and safety; safety tolerability, actually. What the doctor sees as the safety problems and what the patient experiences as complications; from their point of view, tolerability. That's where the drugs do differ. These compounds may be very similar in efficacy, but boy are they different in their side effect profiles. Sometimes they have similar side effect profiles, sometimes they really diverge. And the side effects that we consider are serious, medically serious, worth discussing, are listed on

this slide. And I'm going to leave the neurological to Dr. Schulz. He is going to follow me and give you a nice talk about the EPS comparison of the drugs. So let me talk about the rest: endocrine, metabolic, cardiovascular, etc.

And first, the prolactin. Everybody knows that conventionals increase prolactin because of the strong inhibition of dopamine receptors, which of course, as you know, dopamine is an inhibitor of prolactin. So we disinhibit a hormone that is not supposed to be in the body at high levels except in a woman who is breastfeeding her newborn baby. So any man or woman who has high prolactin is going to suffer some sexual dysfunction, loss of sex drive, menstrual irregularities, erectile dysfunction, depending on the gender. Well how do these drugs compare?

There are differences. The typicals, of course, have increased prolactin, and the higher the dose of haloperidol or similar drugs, the higher the prolactin. With the atypicals, risperidone seems to be similar in that regard. It also increases prolactin, even at lower doses. But as you go higher with the risperidone, the prolactin levels also go higher.

The only two that don't seem to have any sustained prolactin increase of any kind, any degree, extent, are clozapine and quetiapine. And I think when Chuck gives you a review of the kapoor-pet [??] occupancy, the D_2 occupancy literature, you will realize why. You know, they don't, they never exceed 72% occupancy, which seems to be the threshold. So those two are very safe for people who are sensitive to sexual dysfunction.

Olanzapine and ziprasidone are not bad at all either. At lower doses you hardly see any increases. If you go to the upper limits—and sometimes we use olanzapine at 20, 25, 30, 40—when you get there you do get a doubling, sometimes a tripling of the prolactin. Still not as high as the conventionals or risperidone at higher doses, but it is noticeable. And ziprasidone is very good at lower doses too. You really have to push the dose higher, really higher than 160 to see it.

Aripiprazole, interestingly, because of it's a partial agonist that it kind of simulates dopamine in its action, it does exactly what dopamine does, which is suppress and inhibit prolactin secretion. So if you see anything with aripiprazole, it's going to be a slight decrease. So again, it doesn't increase prolactin either.

All right, let's go to metabolic problems. I think personally (and a lot of colleagues share that with me in psychiatry and in medicine) that the next big challenge to our patients that now appears to be emerging in a very prevalent way is weight gain, obesity. It's becoming, you know, as worrisome as tardive dyskinesia used to be for the conventionals, and I think we've conquered tardive dyskinesia for all practical purposes. But now we are starting to pay attention to the weight gain issue, which occurred with some of the conventionals like Thorazine and Mellaril, but now appears to be really increasing markedly in some patients with some atypicals more than others. Weight gain is a serious disease. Our country is suffering from a lot of obesity and overweight. In fact, it's been in the media lately a lot because of the *JAMA* article that just came out about two weeks ago indicating how serious weight gain is in the United States. So our patients suffer even more because their eating habits, the lack of exercise and then you add a drug-induced factor. It puts them clearly at risk.

The weight gain creeps up on people. They are not aware of it initially; you know, some fatigue, some back pain, some joint pain, and some stress incontinence, shortness of breath, etc., and maybe buying new clothes, you know, to fit. But then it gets more serious. Then you get the hypertension, the diabetes, the cardiovascular events, the strokes, major cancer. Not many people realize the link between cancer and weight gain, obesity. A National Cancer Institute colleague told me a few months ago that if the United States population, all of us Americans, would go back to our normal optimal body weight, loose the excess weight we have, small or large, we would reduce cancer in the United States by 42%. That's a huge number; 42% of cancer in this country is due to weight gain and obesity.

Now you are probably familiar with the J-curve. These are the metabolic studies done at NIH are the guidelines, basically, to what is optimal. What is the body mass index that will give you or put you at the lowest risk for cardiovascular disease? Twenty to 25 is the best place to be. Don't be too thin now, don't go under 20, and don't be too overweight; 25 to 30 is overweight, 30 to 35 is obese, over 35 is highly obese, over 40 is morbidly obese. And the risk of death and cardiovascular disease skyrockets with increased weight. Unfortunately, most of our patients are in the 30s. Chronic schizophrenic patients and many of the bipolars that we treat also with atypicals are gaining far more weight than they can afford.

What are the data? Let's go back now to the evidenced-based approach to this. We have the first meta-analysis appeared in American journal by Allison and colleagues. And they looked at the short-term studies. This is a short-term, 10-week weight gain chart of the leading antipsychotics in terms of weight gain. The worst of the conventionals was Mellaril (7 pounds in 10 weeks). The worst of the newer antipsychotics are clozapine and olanzapine (about 9-1/2 pounds in 10 weeks; a pound a week, roughly). And risperidone, half as bad (about 4-1/2 pounds in the first 10 weeks). But what really matters is long term. Do patients continue to gain weight? Do they stabilize? Do they level off? What do we know?

Well here is a summary of the literature as we know it from various sources, again indicating that clozapine and olanzapine tend to cause the highest degree of weight gain after one year. Remember, our patients are going to take these drugs for years. So at the end of the year, clozapine 29 pounds average weight gain; olanzapine 26.5 pounds average weight gain. Now you are going to see other literature that, you know, maybe is less, especially from the manufacturer. They try to convince you that it's less than that. But that is actually published by the manufacturer of olanzapine back in '97, shortly after it came out.

Then you have risperidone and quetiapine, about 4.7, 4.8 pounds at the end of a year; not bad at all. It's no more than the first few weeks; it stabilizes and may even decline a little bit at the end of a year. Ziprasidone practically weight-neutral; there is hardly any weight gain at the end of a year. So we have four first-line atypicals, of which one of them is clearly an outlier compared to the other three. And if your patient gains weight you have options. You can switch to one of the other three, and you are going to be able to correct the weight gain. In most instances they do lose the weight.

Now olanzapine also tends to increase body fat. Hyperlipidemia is an automatic complication of obesity. If we gain weight our lipids are going to go up, cholesterol and triglyceride.

Cholesterol goes up maybe 20%, 30%. It's not that high. It's still not good to have an increase 20% to 30% in cholesterol, but the triglycerides appear to be more sensitive. In the case of olanzapine, we did a quick study in our VA and found that both blacks and whites—I mean, I though the African-American patients would increase more, just for theoretical reasons, because of more metabolic disorders prevalent in the African-American community. But it turned out both of them doubled their triglycerides after about six months on olanzapine. And it does go down when you switch them to one of the other three, by the way.

Now in addition to triglycerides there is, of course, hyperglycemia and diabetes, a very big worry because diabetes is one of the nastiest diseases you can get in terms of morbidity and mortality. It just damages the body vasculature. By the time you are diagnosed with diabetes, the damage has already been more than half way through. So we take it seriously. Unfortunately, being psychotic is already a risk factor for diabetes. We can't blame all the diabetes we see in psychotic patients on drugs, although some people think, you know, it's that. Well yes, the drugs do contribute. But just being psychotic, schizophrenic or bipolar, has been shown to be a risk factor. They have two to three times more diabetes, probably because of the coinheritance of the genes for both diseases on the same chromosome. We think it's a linkage problem.

But when you give certain antipsychotics (atypical), unfortunately, you may push the patient over. You do challenge them and make them either worse if they are already diabetic, or you can uncover and bring out fresh diabetes, new cases. And it can get serious. Diabetes is a very serious illness. There is about 16 million people in the United States. Not all of them are diagnosed; only about two-thirds. And there about 800,000 new cases every year, and the vast majority will die from cardiovascular disease. It's very nasty for the heart and the brain, vasculature.

Now here is a simple kind of cartoon to show you the three ways that diabetes can develop in a psychotic patient. One, before you even treat them, they are at higher risk. So that is one way that some of our patients get diabetic. The other two ways are related to predominately those two drugs. There is a smattering of cases with risperidone, with quetiapine and maybe even ziprasidone; no reports yet, but I've heard of one case, you know, here and there, very rare event, relatively. But olanzapine and clozapine have been shown in numerous studies (there are about 29 published papers on olanzapine alone) showing that, with weight gain, you are going to get diabetes. It is well-known that Type 2 diabetes (the late-onset it's also sometimes called) is directly related to weight gain. So that is one way that our patients are going to get diabetic.

But then there is the third way, which is that direct arrow straight to noninsulin-dependent diabetes, which is not related to weight gain. You can have sudden severe, you know, coma, semicoma in patients with blood levels of 1,000, 12,000, 1,500—this is a deadly amount of glucose in the blood—without or with hardly any weight gain (maybe 2 or 3 pounds) within a few weeks of treatment. There are people who are vulnerable to these medications. And those are patients who are dying, by the way. There is a recent report—here it is—Koller and Doraiswamy published this just two months ago. Elizabeth Koller is a physician at the FDA. She is not even a psychiatrist; she is just a physician who works at the FDA. And they did a review of the reported cases that the FDA knows of (because not all cases are reported). They found 230 cases. In fact,

the deaths are 22 now, the deaths. At the time of writing the paper, it had gone up to 22. It was 15 at the time of submitting the paper.

The other citation I put there, the Koro, is just one of six studies, epidemiological studies, using health care, health plan databases. There are Blue Cross/Blue Shield studies, there's Medicaid studies. This one is from England, the United Kingdom, where they have 3.5 million people in a health care system, national health insurance. And they looked at the relationship between atypicals and diabetes and found, again, highly significant difference with olanzapine associated with diabetes but not risperidone. And we just finished a study—actually we published a study, myself and a few other colleagues in the *Journal of Clinical Psychiatry*. It just appeared a couple of weeks ago. If you have that journal you can read it; very similar findings.

Here is one example of a setting. This is the VA in Portland, Ore. Dr. Dan Casey, gave olanzapine—. Looked like a great drug when it came out. It is a good drug. He gave it to 120 veterans at that VA. The baseline diabetes at the VA there is higher than the general population because they are overweight middle-aged men. And it was 14.5. But it jumped to 28% at the end of a year; leveled off, and the second year went up further to 35%. That's a huge increase in diabetes. Patients cannot afford that.

Now remember, diabetes and weight gain and lipid increases are what we consider a cluster of the metabolic syndrome. It's a very serious problem in medicine, and it's established whenever you have three of those risk factors that I list on the slide. You now, weight gain, sometimes, or obesity is measured with waist size, but the triglycerides would be exceeding 150. The high-density cholesterol, like a protein again, should be higher rather than lower, and sometimes the atypicals may decrease the HDLs. Then there is the blood pressure and fasting glucose. And what I've described to you is that some of the atypicals may give you three of those right away; hyperlipidemia, hyperglycemia and weight gain. So be careful, protect your patients. Switch them whenever they gain more than 7% body weight. That is the risk factor, the risk threshold, rather, with weight gain. That's about 10 pounds for a female, average female; 15 pounds for an average male. Don't let your patients gain more than that, because that is when trouble starts, according to the NIH studies; 7% or higher.

Now let me switch gears for the last part of my talk, and just address the issue of an additional dimension of effectiveness. In addition to finding that these drugs work so well in psychotic patients, which they do, we have now found over the last few years that so many others psychiatric disorders benefit from the atypicals, not necessarily at the higher doses that we use in schizophrenia, but at lower doses. And they certainly seem to work, usually, most of the time, as adjuncts, add-ons. And those psychiatric disorders sometimes have no indication whatsoever. We simply don't have a drug indicated for them. Or sometimes they are treatment-resistant and we have no choice but to try something new. These are off-label uses, by the way. I'm not advocating that we use them routinely, but we are. Then you as physicians, psychiatrists and primary care physicians are using them for a variety of child and adolescent conditions. As you know there are very few drugs indicated for children and adolescents because the FDA trials are just not done. And pharmaceutical companies are now doing more of them, and the FDA is incentivizing them to do that. But then there is the Axis I, II and III for adults, in general, and also as augmentation for treatment-resistant conditions.

Now here is a slide I put together based on a lit of literature that my residents and I kind of reviewed together, showing you that there is, of course, indications in mania. Every atypical works in mania, we know that. One of them that is officially indicated, Zyprexa or olanzapine, is the only one that has the official indication, but all of them work equally well. So do the conventionals, frankly, as antimanic drugs. So all of them have been used. But I doubt that we can treat bipolar disorder with monotherapy. At this point the standard of care remains combination therapy. So all of them are used with a mood stabilizer of your choice.

Depression. Again, you can add these atypicals to the existing antidepressant that is not doing the job fully, adequately, treatment-resistant. And you get another degree of response. OCD, same thing. Augmentation, not monotherapy in this case. Some of them may actually induce OCD if you use it monotherapy. Anxiety, treatment-resistant anxiety; you add it to the antidepressant you are giving them. PTSD, a very complex multidimensional disorder with anxiety and depression and mania and psychosis and impulsivity and anger and aggression and sleeplessness and—you name it—flashbacks, etc. Very difficult disorder. We find that adding those atypicals is really a very valuable tool. And the associative disorders and other disorders as well.

Axis II, I don't have to tell you that, very difficult disorders to treat. We find that psychotherapy with those patients can become much easier and much more productive when you give them small doses of one of the atypicals. And it just settles them down, it reduces the lability, the anger, the aggressivity, whatever the personality you are dealing with. Borderline is a very good example. And all of them seem to help with that disorder.

Axis III disorders; Parkinson's disease with L-DOPA psychosis. As you know, about 25% of patients receiving L-DOPA develop psychotic symptoms. Atypicals help a lot without worsening the Parkinsonism, which the older drugs did a lot; they made the patient stiff, actually. And of the atypicals, the one with the lowest EPS, which Chuck will talk about, which happens to be quetiapine or clozapine, tend to be the treatment of choice with neurologists there. Similarly, Tourette's, stuttering, Huntington's disease, a variety of organic conditions see to respond to atypicals, all the atypicals much better than the conventionals.

So when we look at the effectiveness of these drugs, the reason they are becoming so popular and useful is because we, as clinicians, we got to treat our patients, they are suffering, we got to treat them and sometimes we have to go beyond the obvious. We should not care what their diagnosis is. We should look at the target symptoms. If the patient is suffering and being disabled from a symptom or two (like severe impulsivity, severe hostility, aggressivity, hyperactivity; child and adolescent patients tend to have a cluster of them all at the same time), then we should attack those symptoms, regardless of the diagnosis, with whatever works. And in this case it happens to be the atypicals, even though they are off-label. A lot of studies are going on, though, to try and make them officially indicated.

Children under 12; a lot of difficult conditions there. I'm sure there are child psychiatrists in the audience who find that augmenting these patients with some of the, any one of the atypicals at lower doses, usually, tend to help a good proportion of the patients; maybe not cure them, by

any means, but reduce the symptoms and make them manageable. Same thing with adolescents and the various symptoms that occur in adolescence, which sometimes overlap with adults, sometimes overlap with preadolescents.

So coming back then to the heart of the matter, if we are using those atypicals in a variety of psychiatric disorders, it behooves us to use the atypical that produces the least amount of side effects or medical complications, because those nonschizophrenic, nonpsychotic patients tend to be more sensitive, usually, to many of those side effects we mentioned. So EPS, weight gain and sexual dysfunction, particularly, turn off a lot of those patients. And if we want our treatment-resistant depressive or OCD or anxiety or PTSD patient, or child and adolescent kid with any condition, to stick with the medication if it helps them, we better avoid the side effects.

So here is a summary of the literature, really, based on the data published about the profile of the four atypicals that we have on the market and which one tends to produce more of one side effect vs. the other and customize it. There are patients who tolerate one more than the other, depending what their susceptibility is. The highest dose-related EPS—risperidone is good at lower doses, but if you start titrating up, you are more likely to get EPS with it than you would with the others, even though some of the other do too, eventually. And it also tends to have more prolactin compared to the other atypicals, so you have sexual dysfunction. The weight gain, though, is pretty moderate with risperidone. With olanzapine it's biggest problem is the metabolic problems with weight gain and the consequences (hyperlipidemia, hyperglycemia). It's not bad with the other conditions (sexual dysfunction, EPS, not bad). And quetiapine tends to have the lowest profile with EPS and also the lowest complications with sexual dysfunction. So it's pretty good for patients who are sensitive to those things. As you know there are many, many populations who are sensitive to EPS (like geriatric, child and adolescent, African-Americans, bipolar disorders, etc.) and also sexual dysfunction (which is very common among adolescents and women and men in childbearing years). Ziprasidone has also a very good profile with EPS and sexual dysfunction on the low side, and it actually has an excellent profile with weight gain. So you can use any one of those, depending on the patient that you are treating and their background, their medical history and susceptibility.

So in conclusion, the atypicals appear to be comparable in efficacy. They also are quite different in their side effect profile. And we, as physicians—this is why physicians should be psychopharmacologists, because you know, giving drugs is not just something that a nonphysician can do without a physical exam, a neurological exam, medical history, review of systems and understanding even family history. You integrate all of this as a physician and then select the drug that's best for your patient, based on their profiles.

Thank you for your attention. I'd better give the rest of my time to Chuck. [applause]

Schulz: Well, Henry, thank you very much for an outstanding talk, and I appreciate your setting the stage for the comments that I will have, as you have clearly demonstrated the efficacy and effectiveness of the medications and demonstrated for us the similarities for outcome for these medicines. Before I begin my lecture this evening, there are a few comments I would like to make. First, I really appreciate CME asking me to participate in this extremely constructive and fun meeting. I hope all of you have a terrific time while you are here and I know you are going to learn a terrific amount. I would also like to thank AstraZeneca for their unrestricted grant in support of this evening's symposium. And I was quite happy to see a number of my friends and residents, etc., here in the audience. My mom brought along a few of her friends as well to fill out the audience. Thanks, mom.

On a more serious note, though, as you heard, I am from Minnesota, and so this evening I do have some very sad feelings because of the loss of our senator, Paul Wellstone. Paul is one of the most tireless workers on behalf of the mentally ill I have ever met. His push for parity for our patients, both from private insurance and from Medicare, is just untiring, as is his support in suicide prevention. So therefore I would like to dedicate my comments this evening to his efforts on behalf of the seriously mentally ill. [applause]

I've had the opportunity to work with a variety of atypical antipsychotic medications for about 16 or 17 years now, and what I would like to do this evening is share some of the thoughts that I have. When you look in your booklet, I've hidden some of the slides just so I can be finished with the talk nearer on time, but we might go back and discuss some of those issues during the discussion. So I'm going to take off from Henry's point about that the medications work, and what I would like to do this evening is talk about optimizing the outcomes of antipsychotic pharmacotherapy.

Even though there is five bullets here, I've always been told you really have to just focus on three things. So what I'm going to do is, I'm going to talk to you this evening about PET scanning and how it can inform us about how medications work in the brain. I'm going to talk a little bit about efficacy, I'm going to talk a little bit about EPS, and maybe a little bit about how the medications interact with the receptor. I'm going to talk about some special populations. Henry has already alluded to the special issues of our adolescent patients who suffer from psychosis, schizophrenia, schizoaffective disorder. And then I'd like to conclude with some ideas about our psychosocial interventions.

You know that the goals that we have now are substantially higher than they were some years ago. I thought this would be a relatively brief and succinct slide, and I just couldn't help myself because we now really want to do so much more for our patients. Not only do we want our patients to be safe, we want to help them with their positive symptoms. Maybe a few years ago the slide would have stopped there, because we were pretty hopeless about negative symptoms and thinking disturbance. Now instead of arguing with our patients about using antipsychotic medications, our goal is to optimize a balance of efficacy and our patients' acceptability. Certainly in my work with people suffering from schizophrenia, I feel our conversations about the use of antipsychotic medications has improved dramatically. We want to be able to integrate

our treatments with psychosocial treatments, our pharmacologic treatments. We talk a lot about how we are pleased with the new medications, but I try to talk with our residents and say, "You know, if these medicines were that great, we would just mail them to the patient's house." Obviously, we don't do that. We have a better chance of helping patients with mood (both ends of the spectrum), depression (a big problem), elevated mood also substantially can incapacitate our patients. We want our patients to do things other than be in the hospital or resident treatment. We want to improve their quality of life. This is all a tall order, but now all within our reach with the appropriate use of antipsychotic medications.

Well let me tell you a little be about PET imaging. I know that many of you are well aware of the technology that goes into this, but maybe not everybody does. And I do understand that I might be able to use the pointer here, so I'm going to give this a try.

When we do a PET scan, first we have to make a radioactive compound or to label, generally, carbon. Then we send this over to the radiochemistry laboratory, and this slide taken from Shateesh [??] Kapur work is where the carbon is labeled on a compound named raclopride that goes to dopamine receptors in the brain. We then inject the compound, whether it's raclopride or n-methylstiporone [??] in our work, and then we do a PET image. We then construct that image anatomically. And this is an axial slide through the brain this way. And when we inject a radioactive compound that goes to receptors, we can see where those receptors are, in this case in the basil ganglia of the brain in this subject. We can then even do more fancy things, like put the PET scan on top of an MRI scan. And then you can see exactly where those dopamine receptors are.

I'm going to skip the dynamic activity curves in some of these modeling, and just point out that by doing this sort of work we can find out where the dopamine receptors are and we can...

[End of Side A]

...Our group at Case Western Reserve University in the early 1990s wanted to understand what some of the differences between typical and atypical agents were, and we used a compound, carbon-11 n-methylstiporone [??], that binds actually to both serotonin and dopamine. A normal subject underwent PET scanning and then received this compound, and without being on any medications, this medication found its way to the serotonin receptors in the cortex, as well as to the dopamine receptors in the basil ganglia. When patients stabilized on typical antipsychotic agents were then PET scanned with n-methylstiporone, the n-methylstiporone couldn't find a place to go on the dopamine receptor because, really, almost all were blocked (80% to 85% as you will see in a second), but could find lots of space on the serotonin receptors in the cortex.

Now this study was done in the early '90s, and the atypical agent that we were testing at that time was clozapine. We see that the n-methylstiporone, even though the patient stabilized on clozapine, still finds lots of room on the basil ganglia but can't find any room on the serotonin receptors. So you see really a remarkable difference between the atypical agents and the typical agents when we use dopamine- and serotonin-binding agents. Now we did do quantification of

this study. But I wanted to qualitatively demonstrate for you the differences when we do this type of PET scanning between the typical and atypical compounds.

Now the group at University of Toronto (Bob Zipursky, Shateesh Kapur, Gary Remington and others) have done a series of studies I'm going to talk about now in which we are going to take a look at a traditional agent (haloperidol), we are going to take a look at risperidone, olanzapine, clozapine and quetiapine. The group was very interested in the dosing of first-episode patients and trying to find a dose of a traditional agent (studies that started before risperidone had come out) that might be useful. And what I've done here on this slide is describe what they did. And in the interest of time, what I'd just like to say is they start at relatively low doses of haloperidol. You can see how long the patients were treated and when they got the PET scan, and that some of the patients went up to 5 mg a day if they had not shown improvement. Well let's see what happened to their PET scans.

Taking a look at the percent occupancy here, we see that those patients who haloperidol didn't block very many of their receptors (and remember when you were looking at that last slide, some of the doses were somewhat in the low areas, trying to find a lowest effective dose)—. We see that those low doses are those actually kind of below the 65% to 68%, really are not responders. Whereas many of those above 68 [%] are responders, although some of these patients are not. It led the group to say that somewhere around 68% or 70% dopamine receptor occupancy with haloperidol is the amount of blockade that is sufficient and necessary for the patients to get better.

Well then they took a look at the extrapyramidal side effects, and as Henry mentioned, I'm going to talk about EPS and weave this into the PET scan story during my talk. For those patients whose D_2 occupancy was lower (remember some of those dots from the previous slide; there were some people 40%, 50%, 60%), they are not having any EPS. Once we get up to the area of around 78, you can see that four out of five of those patients or four out of six if this person is right at that 78 point, they are beginning to have EPS. So we do have a little gap right between 68% and 78% in which we might be able to dose haloperidol. However, unfortunately, that may be using tenths of a milligram, something that is probably too fine for us to do in clinical practice.

And then lastly, Henry commented substantially on prolactin, and we can see also that the PET scan studies inform us a little bit about prolactin. We see here dopamine receptor occupancy; two of 15 patients had prolactin elevation when D_2 blockade was below 72 [%], and five out of six of the patients above 72 [%] had increases in prolactin. So in taking a look at the traditional agents, early PET scan work, we can see that we are able to identify the percentages that are generally associated with efficacy, side effects (including EPS) and prolactin increases.

This is a slide that I think everybody has seen pretty many times. What I'd like to use it for this evening is to say we obviously now are mainly using atypical antipsychotic medications to help our patients. I apologize for not having ziprasidone on this slide. And I think we all know that there are two major groups of these medications; the multiple receptor-blocking compounds, and then ziprasidone and risperidone mostly act on serotonin and dopamine.

Now what happens when we start doing PET scans with the first of the atypical front-line agents to come out (risperidone)? Well what we see is probably consistent with what you are seeing in your practice. When we give 2 mg of risperidone we have a receptor occupancy that's just above 60 [%], so we are getting right in the range of being helpful for schizophrenia, and the 5-HT_2 serotonin occupancy exceeds dopamine. So we have demonstrated, not just in test tube but also in the human brain, that these compounds lead to more serotonin than dopamine blockade.

At the average dose that people in the United States use for schizophrenia (about 4 mg), we see that the D_2 receptors are right around that 78 point. Serotonin is way up here. At 4 mg we are not seeing EPS (those are the orange dots). When we get to the 6 mg, 8 and higher, get above 80%, then we are beginning to see EPS. And that led the group, and I would have to agree with this, that risperidone actually works at typical levels of D_2 receptor occupancy. These curves are pretty similar to what we would see if we were using haloperidol.

The high serotonin occupancy may explain its superiority in negative symptoms (that Henry has already talked about), and at EPS in the doses we are generally currently using. However, when D_2 occupancy is greater than 80%, generally around a dose of 6 mg to 8 mg, then risperidone begins to lose some of the atypical character (and by this I mean atypical meaning an efficacious dose for a person with schizophrenia without movement disorder side effects). And the group concludes (and I agree) that appropriate dosing is crucial with risperidone.

Well let's move on to olanzapine. Now olanzapine is a very interesting compound as we address its efficacious use as well as its EPS side effects or that definition of atypicality. Not only does it bind to the D_2 receptor in ways that are not dissimilar from the traditional antipsychotics, but of course it also has binding characteristics to cholinergic and histaminic receptors. Taking a look at D_2 binding, this is a control person, the D_2 ligand goes to the basil ganglia. With haloperidol it can't find it so well. And with olanzapine (although these look pretty much alike), olanzapine does, can find the D_2 receptor. As far as the serotonin binding, here is the control subject, here is the cortex again. Haloperidol is not blocking those and olanzapine is blocking about 95% or 100% of those receptors in the cortex.

Now what happens when we take a look at the receptor occupancy of dopamine and serotonin? And let me talk over here for a little bit. We have the receptor occupancy here. Then we have increasing doses here. The D_2 date, D_2 receptor occupancy is going up with dose. You can see that serotonin is blocked almost maximally, even at very low doses, and that in this range here (the dose we use for patients with schizophrenia, mostly 10, probably 15 to 20) is more likely that there is no EPS, no increase in prolactin, and this is associated with efficacy. Once we get out here, 25 mg and 30 mg, at least in these studies, patients are beginning to have EPS and/or prolactin increases. So olanzapine is beginning to lose a little bit of its atypicality, at least as we look at it in PET scanning.

So we see that olanzapine saturates the serotonin receptors. And I already mentioned, it binds to some of the others as well. Olanzapine works at typical levels of D_2 occupancy, meaning it is efficacious in that range of about 70% to 80%. At its recommended dose, the group says that it is safe. I would say it's safe and efficacious. Beyond 20 [mg], D_2 occupancy can go higher and some of its atypicality may be lost.

Well even though I frequently like to take a historical view of presenting the medications, I'm going to cycle back here for a minute and take a look at clozapine. Interestingly enough, the dose place here along the bottom and D_2 occupancy here shows something quite interesting. There is not a dose, by either Bob Zipursky's group or Nordstrom's group at the Carolinska [??] that can get above about 64 mg. This reminds us that when clozapine was first synthesized and folks were using it in the lab and screening it as a possible psychotherapeutic agent, there was no dose of clozapine they could give the experimental animals that made them stiff. And that's why the drug sat for so long, because nobody thought it could be an antipsychotic drug if it didn't make the rat as stiff as a board. So we see something different going on with clozapine than with haloperidol, risperidone or olanzapine. Keep giving these doses, they keep getting higher, 400 is a dose that works for most patients and yet we are up here at 900 mg.

Now Shateesh [??] then moved on to take a look at quetiapine, the third front-line agent to come out. What he did here, this is the clinical portion of his experiment; baseline at endpoint on CGI, a nice reduction in symptoms, so it was working. Five patients had akathisia at baseline. They all got better and prolactin went down. But let's take a look at what's going on in the PET scans.

So Shateesh started off with the same protocol that he had been using, giving the medicine at night and then PET scanning in the morning. And whatever dose he gave, the medicine looked pretty much like clozapine; serotonin blockade high, dopamine down in the 20s or 30s. He then moved on to take a look at the medicine over time and found that within three hours at doses that are effective, actually, D_2 occupancy was pretty close to what you would see with clozapine. But three hours plus nine hours later, prolactin is normal and D_2 occupancy is only 20%. Twenty-four hours later in this subject, no D_2 receptors were blocked. So it appears that clozapine and quetiapine may be distinguishing themselves to some degree from haloperidol, and risperidone maybe a little bit from olanzapine. Not only for kinetic reasons, but in addition to that, these are compounds that are not tightly binding to the dopamine receptor, and thus they allow some more physiologic dopamine function. And as I think you all know, dopamine comes out in a pulsatile fashion from the presynaptic neuron, and with these compounds that are not tightly bound to the dopamine receptor, there is a little bit more of a physiologic reaction in the brain.

I'd like to show you two more slides about PET scanning, but they don't have much to do with what I've just been talking about, but do talk about the topic that I'm assigned, which is to talk about patient acceptability. Now I've found this study to be very interesting. We are talking about prolactin and EPS, etc. But the group published in the *American Journal* in 2000 that the subjective experience of being on an antipsychotic medication is related to D_2 blockade. They looked at 20 patients treated with either risperidone or olanzapine, and then studied them with SPECT scanning (not PET scanning), and found that both negative symptoms and depression were related to D_2 receptor occupancy, even though positive symptoms were not. And interestingly, none of these patients had Parkinsonism. So when we are thinking about helping our patients we have to try, I think, to try to get even to the lowest effective dose with our atypical compounds.

Strategies for the traditional antipsychotic medication; you know, each new medicine that has come out has evolved—I mean the atypical antipsychotics—each new medicine has had a dosing strategy that has evolved after its approval and introduction. Some of the medicines now have a start low and go slow strategy whereas others propose a more rapid titration. Let's just quickly take a look at some of these different strategies.

Well when I was in training we had an idea that we just were looking at, if you will, a seesaw between efficacy and EPS. So I've draws this little cartoon to point out that low symptoms, that's a good thing; high EPS, that's a bad thing and our little friend is unhappy. However, as Henry has very nicely pointed out, we are now taking a look at many more things when we make the decision about dosing and choosing a medication. Along this axis (if we have an x, y and z axis) we are looking at the reduction of symptoms. We want to find a dose that leads to the best outcome in symptom reduction. We also want to take a look at EPS and other neurologic side effects. We want to not overdose our patients and block too many of the D_2 receptors that we have already talked about. But in addition to that, not just the seesaw anymore, we want to take a look at our nonneurological effects (sedation, QTc; Henry has already talked about weight and endocrine). We are now dealing with much more sophisticated and complicated decisions when we are using the atypical agents for our patients.

Now this, I was talking with some friends of mine who said you know, we have so much neuroscience available to us now that pretty soon all you have to do to be a psychiatrist is just do this formula and you won't have to use clinical judgment anymore, you just fill in brain imaging, negative symptoms, mood, EPS , etc. And then you just divide that by these other variables here on the bottom and you will end up with the medicine of choice. I don't think we are going to go there.

I know that I have fallen a little bit behind. What I would like to do at this point, looking at my watch, is, the next three slides are in—the next four slides are in your book and I'm just going to move through those without commenting. I want to save time for some discussion. And get to here.

As I think all of you are aware, when pivotal trials are done with any medication, but certainly for all of the atypical antipsychotic medications that are approved now, the exclusion criteria are anybody below age 18. As soon as the medication is approved, then any of us general or child and adolescent psychiatrists can use these medicines in young people. Yet there is no formal data on how to use the medicines or whether or not they are even effective in this age group, although we do assume that they are. Our group has had the opportunity to do some of the case series that Henry alluded to on atypical agents, and I'd like to talk with you a little bit about those now.

We are very concerned about the use of the new antipsychotics in our adolescent patients, first because of the sexual side effects and appetite control are often difficult for teenagers to discuss, and can lead to poor compliance or outcome. These side effects are less common with the atypicals but have not been part of the monitoring program so far. So specific discussions about galactorrhea, breast tenderness (both sexes, in our experience) and weight are appropriate when using these new antipsychotics in teens. Let me tell you a little about the data in young

people. Our group did a case series with risperidone when it first came out. We looked at 16 teenagers, mostly with schizophrenia. They were assessed by two raters looking at their BPRS. And what we found was that risperidone was very effective in these youngsters, and really most of the youngsters finished the entire trial and found the compound to work well for them Interestingly enough, we found that they needed a dose that was quite similar to that used in adults. Negative symptoms were also reduced.

We move on to olanzapine. Bob Findling [??] at Case Western Reserve University and I conducted a 15-patient study of olanzapine that was eight weeks long. I'll show you the results of that study here. So patients took the compound for eight weeks. They had a reduction in their Clinical Global Impression Scale. The total of their PANSS went down about 20% and their positive symptoms went down about 25%. The average dose for teenagers with schizophrenia turned out to be about 13 mg. So just in our study with risperidone, we also found that teenagers required the same amount of medication to get better. Not surprisingly, the teenagers in this study gained a substantial amount of weight in the eight weeks, thus underscoring the point I mentioned earlier about teenagers perhaps being especially susceptible to weight problems.

Quetiapine has been tested with teens in a couple of different studies. This is by Dr. McConville at University of Cincinnati. He is looking at psychotic adolescents, some with bipolar illness, some with schizophrenia. And you can see in this slide the BPRS total by trial day and how within three weeks there was a substantial reduction, also in the CGI. When I was reading this paper and I was aware of, in other studies, the dose being the same for teenagers as for adults, I was quite stricken that it was an 800 mg dose that each youngster was tested on as part of the pharmacokinetics part of this study.

I'm going to say a few words about QTc. Henry so nicely discussed endocrine and metabolic issues, and with ziprasidone coming on the market, I think we probably all know more about the heart than we ever did, because we have been barraged by safety information about our antipsychotic medications. Many of you have seen slides from a Pfizer study 54 taking a look at QTc. I thought I'd use Sandy Glassman's review article from the *American Journal* to focus my comments on. They reviewed the risk of Torsade de Pointes and sudden death associated with antipsychotic medications. The dose dependency and the percent of people with QTc over 500 milliseconds. They conclude in their article (in which they are neither trying to sell you a medicine or make you not use a medicine) that: some of the older medicines had the biggest problems; that ziprasidone (the medicine that refocused our attention on QTc) is that there is no association with Torsade de Pointes in their review to date (and I'll show you a slide about that in a second); and absolutely none for olanzapine, risperidone or quetiapine.

Here we see a slide taking a look at the amount of QTc increase that an individual goes over 450 milliseconds. Here we see there are some patients on ziprasidone here (this is their steady state and this is with a metabolic inhibitor) who go over 450. Interestingly enough, in the first 3,000 patients studied, only one or two patients exceeded 500. Here we see risperidone. olanzapine, quetiapine essentially at zero; and then thioridazine (which earned a black box for its performance in this study) and haloperidol. Go on to the next slide now.

I'm going to skip this because you can take a peek at this. I'm going to close with a couple of comments about psychosocial in my conclusions.

The principles of psychosocial treatment of schizophrenia have changed dramatically in the last 25 years, from individual psychotherapy and/or being in an asylum to more active family psychoeducation, often combined with social skills training. Both individually, but especially those two together, dramatically reduce relapse rates in our patient. Structured case management and social supports also help patients feel better, reduce symptoms and decrease relapse. And lastly, cognitive behavior therapy has been now shown in a substantial number of studies to improve function. But those are some of the, if you will, older things, and all of those psychosocial treatments were done frequently with patients on Prolixin decanoate, so that the medication compliance could be held constant while the psychosocial intervention was applied.

This slide, which describes a study by Don Velkin [??] from San Antonio, describes a new psychosocial treatment that takes off on the ability of the atypical antipsychotic medications to help with cognition, a point that Henry has already talked about. And in this group 45 patients were randomly assigned to a compensatory strategy as compared to two other controlled interventions. Training in cognitive strategies (not ones that the patient can't do, but focusing on the strengths, cognitively, that the patient can perform) led to increased global function and a lower relapse rate.

So finally I've made it all the way to the end. I appreciate your attention. I would like to just say the new medicines offer a lot of advantages to our patients with schizophrenia. They have a broader range of efficacy and decreased EPS. And I hope after this talk that you now understand some of the underlying principles of EPS with the new medicine. Dosing strategies generally have not paralleled the results of the Pittle [?] trials, as I think we all know. And in addition, I think our adolescent patients are going to emerge as having some special needs. EPS appears to be dose depending for some of the new medicines (not all), and I think we are going to be seeing newer agents that don't act only on a serotonin dopamine blockade theory. In making treatment choices, the clinician will continue, I hope, to take into account multiple factors with each compound and deliver that compound in the context of a psychosocial program.

Thank you all very much. [applause]

Nasrallah: While Dr. Schulz is getting his questions ready here, I'm going to start answering some of mine. And we appreciate your questions. Several questions came to me about monitoring lab tests and especially metabolic parameters with the use of atypicals. I think this is a very important topic. I urge you to do several tests at baseline and regularly thereafter, either monthly or quarterly at least. But do something because you really need, for the sake of the patient, monitor their health; and also for medical/legal reasons, as some of these side effects become pretty contentious, with lawyers always on our back. In fact, there is a very important conference that just took place a week ago at Mount Sinai, led by Steve Marder and several investigators who are putting together a set of recommendations of measuring body mass index at baseline (not just weight; you've got to measure body mass index, the weight in kilos divided by the height squared, because that's what all medicine experts use), and then baseline fasting blood sugar, baseline blood lipid profile and also—you don't need to measure prolactin, but you can ask a couple of questions about sexual function if you want. And then follow up these parameters over time and detect them early, because some of the patients may develop hyperglycemia much faster than others. This paper by Koller and Doraiswamy I mentioned to you; 80, you know 75%, three-quarters of the patients develop hyperglycemia within six months So the ones who are destined to become diabetic are going to show it early, and I would urge you to measure it regularly in the first few months. Most of the patients who develop diabetic ketoacidosis develop it early also. In Japan and now in the European Union they have changed the label of olanzapine to put a warning, a bold warning about using it in patients who either have diabetes themselves or have a family history of diabetes. And this is related to one of the questions I have about ethnicity; why don't some of those studies mention ethnicity?

That's a very good point. I have a lot of African-Americans in my population down in Mississippi, and there is higher diabetes in the African-American community. I don't prescribe olanzapine first line to them for that reason. They tend to have a higher degree of diabetes already and I don't want to exacerbate it or push them over the edge. Even if they had a family history and they don't have diabetes themselves, maybe there is a diathesis and you don't need to challenge them to bring it up. Same thing with Caucasians. I mean, I do it for everybody, but especially with African-Americans. So the label change hasn't happened yet in the United States, but I anticipate it might soon. And when that will happen waits to be seen.

One last question here about weight gain and Topamax, and let Chuck answer some of his questions. Should Topamax be used, etc.? Will it be useful on weight and lipids and diabetes onset? The answer I have—and my residents ask me this question a lot—I do not like to add a drug to counter the side effects of another drug, because all you do is get polypharmacy and the side effects of the second drug complicate the picture. Topamax is not a safe drug to use, especially off label. You are liable if something happens. It is only indicated for epilepsy. It does reduce weight. We know that. But I would not use it. I would rather switch the patient to another atypical. The only time I would use heroic measure like adding Topamax is if the patient responded

to nothing else but this drug. In that case, yeah, I would stick my neck out and I would document in the chart, that's why I'm using Topamax and that's why my patient has to put up with some cognitive deficits so that I will reduce their weight.

And the last thing I will say about this, yes, the lipids go down when the weight decreases. There is no, to my knowledge, nothing has been found about whether it would reduce the diabetic risk. The diabetes risk, of course, is related to weight gain, so Type 2 would be lessened, the risk would be lessened. But the Type 1 type diabetes, the diabetic ketoacidosis is really more like Type 1. You need insulin for that. That, I think, is not preventable by any drug. And to finish another question related to the mechanism, we don't know, but it is probably due to insulin resistance that develops at the receptor level. Chuck?

Schulz: Whew! What a tour de force, Henry. I'm going to address as many of the questions as I can, but I'm delighted to stay around if anybody wants to come up and discuss theirs. I would like to come in on a question that came up about the use of atypical antipsychotic medications for borderline personality disorder. The question is, what is the dosing strategy being used?

Our group has had the opportunity to test risperidone, olanzapine and quetiapine in borderline personality disorders. Our studies indicated that risperidone at about 2.2 mg was the mean dose in a double-blind study. When we tested olanzapine, 7.7 was the average dose. In Mary Santarini's [??] double-blind study at McLane, 5 mg was the average dose for her ambulatory female patients. And somewhat surprisingly to us, the average dose of quetiapine for borderline patients is around 200 mg. But that may not be so surprising these days as many people are aiming toward, perhaps, a 400 mg or 600 mg dose of quetiapine.

Someone asks, and perhaps stimulated by the PET scan study, how come one daily dose of quetiapine works at the D_2 occupancy, it's gone within an hour? That is a very interesting question and one in which many of us are trying to understand whether just solid blockade of the D_2 receptor is what makes the drug an antipsychotic, or whether blockade for some period of time is sufficient to change things inside the cell, perhaps at secondary messengers. We don't know why. We've—I think many of us have observed that once-daily-in-the-evening quetiapine is an efficacious strategy, and it's something that we are going to keep looking at in the research. Henry, you want to try again? I may have some metabolic ones for you here too.

Nasrallah: Sure. Okay. There is a question about the dose ranges for bipolar disorders. Even thought we didn't talk about bipolar, I'll be happy to answer that. If you look at the studies done with olanzapine and more recent ones with quetiapine (and quetiapine is probably the second, the next drug to get the FDA indication because the trials went well), the does used for bipolar that seem to work best are really higher doses, like in the schizophrenia range for acute mania. So the trials with olanzapine didn't do as well with the 10 mg initially, the first study. So the second study then they used 15

mg and got a better response. So it took 15 mg for acute mania. The average dose with quetiapine in the studies that just got finished and were presented just a month ago was actually 580 mg, which is very similar to a schizophrenia dose (about 600 mg a day). Acute mania needs higher doses. Remember that. Maintenance may be is less than that, but in the first month I would use a higher dose.

Schulz: So there is a question here that I think relates to both Henry's and my talk saying that this doctor has not seen too much sexual dysfunction and was wondering if I was commenting mostly on people in the adolescent age range. This person has seen a few cases of lactation on Zyprexa and also on Seroquel. Just a couple of comments.

First of all, the relationship between increased prolactin and the complaint of side effects is interestingly not that highly correlated. So we as clinicians are going to need to be asking our patients about these problems. Yes, you are right that in my experience youngsters, both male and female, are complaining of breast enlargement, breast tenderness; the females, galactorrhea. But there is also in some men decreased sexual desire or erectile dysfunction. And yes, I would agree this can occur with any of the front-line agents. Henry, do you have any comments or additions to that?

Nasrallah: I think that there is a vulnerability in about 20% to 30% of the patients I treat to sexual dysfunction, regardless of the prolactin level. Some of them get sexual dysfunction idiosyncratically at lower levels. A small increase is enough for some people to throw them over the edge. Others need higher doses. And there are some who tolerate it, you know, with no problems at all. I have a patient with very high level of prolactin who doesn't have sexual dysfunction. So you cannot generalize, and that is why we need to ask our patients. You can start any drug you want, just monitor the patient. Sometimes they are too shy to tell you. But if you ask them, "Are you having decrease in sex drive? Are you having an erectile dysfunction?" And for the woman, ask her if she has irregular periods. "Are you having breast tenderness? Are you having any liquid coming out of your nipples?" If you don't ask those questions, some of the patients may not volunteer that.

Schulz: You know, Henry, that will dovetail with this comment. Should risperidone be changed to another atypical if a young female is reaching puberty? And I'm not sure I would say that because of some people will have an increase in prolactin without any symptoms; others will. So it is not a reason to change a medicine. And as we know, there are liabilities to changing medications. Changing from one to the other can sometimes lead to a person having a brief period of time with increased symptoms. So I'd keep going, but Henry made a nice point of making sure to ask about symptoms.

Nasrallah: Right. And that's why quetiapine is helpful. If patients are doing well on risperidone, keep them on risperidone. But if they develop sexual dysfunction, they complain, you have now the opportunity to give them a drug that does not increase prolactin.

There is a couple of questions here about mechanism of weight gain and the relationship between weight gain and cancer. There is a large literature in the medical literature, not in the psychiatric literature, about the relationship of weight gain with breast cancer in females, like gynecological cancer, breast cancer, ovarian cancer, endometrial cancer and cervical cancer in females. And in males prostate cancer and colon cancer, a very strong relationship exists. So you can reduce your risk in yourself and in your patients dramatically by avoiding weight gain.

The exact mechanism of weight gain is believed to be multifactorial. Histaminic affinity, H_1 affinity, seems to be a key factor for some. We know olanzapine has a high histaminic affinity. But also the serotonin 5-HT_{2c} affinity seems to play a role. We know that subtype of receptors of serotonin does have a lot to do with weight gain. There is also another mechanism that seems to play a role in olanzapine, which is like knocking out the satiety center. So patients don't get the sense of fullness that we usually have; feedback, "Stop eating, I'm full." They don't have that, so they just eat and gorge their food. And the patients tell you, "I'm living next to the refrigerator."

Another potential factor is the lack of activity, you know; sitting down, being lethargic, sleepy, etc. Olanzapine is sedating. Quetiapine is sedating too, but does not cause the weight gain like olanzapine does. So it may be an additive factor when there is a primary factor at play. And finally, even prolactin was found to be, to contribute to some weight gain in some studies.

And one last complicating factor, just to confuse the picture; patients who are starting diabetes, without you knowing it, they already have insulin resistance starting to build up. That can lead to weight gain. Interestingly, it's not chicken-egg, it could be egg-chicken. The patient can start having higher insulin levels due to the development of diabetes and that is known to trigger weight gain and increase in appetite. And then you thin the patient developed diabetes because of the weight gain. Actually they were becoming diabetic before they gained weight.

Schulz: Henry, thanks very much. I have a question here that I wanted to talk about a minute. The doctor says that all of the atypicals seem to act about the same. And I think Henry and I have talked about that, although on occasion a person who is not doing well on one, when switched to the other, can improve. Goes on to describe the patient who remains symptomatic despite adequate doses of a combination of medication, has been considering switching to Geodon.

What I have observed over the last few years, maybe five to eight years, is a decrease in the use of clozapine. And as Henry commented, it's still the only medication for which there is evidence, as a treatment of last resort. And so although I realize we have many more tools in our armamentarium than we did in 1990, if a person has been tried on front-line atypical agents and is still persistently ill and then especially after nonneuroleptic augmenting agents, my recommendation would be to start thinking about clozapine. Henry, I don't know what you think.

Nasrallah: I think you've said it enough. Let me answer this colleague. I'm glad he's challenging me because I was provocative on purpose, and I said that you should treat the symptoms, not the diagnosis. And here is my colleague being very traditional, saying, "Wait a minute. I thought diagnosis was very important and the treatment needs to follow the research findings from treatment, biological, psychological, social skills training, etc. I think I heard you say that pay attention to the symptoms. Don't pay attention to diagnosis, treat the symptom. Please explain. What do you mean? Is this a new standard of care?

Yeah. I'm telling you what I'm saying is that *DSM-IV* can be very constraining when you manage patients. It's very easy to have nice, you know, arbitrary criteria to define. I mean all of it's arbitrary. Let's face it. Five out of nine symptoms define depression. Heck, I treat patients sometimes with three symptoms who really improve dramatically, rather than wait to five. And what I'm telling you is that many of the pharmacological tools we have don't treat a diagnosis. They treat symptoms. The signs and symptoms of the disease is what responds to the illness. I'm very surprised that the FDA, for instance, cut down, limited the indication of atypicals from psychosis in general (which it used to be in the old days) to schizophrenia only. Then you have to do another set of studies for mania, and another set of studies for another type of psychosis. That doesn't make sense to me. The symptoms of psychosis (delusions, hallucinations, thought disorder, disorganization, agitation) respond to the medications. It's the symptoms that respond, not the diagnosis. So I'm proposing to you that maybe in *DSM-V* we may have a different paradigm for diagnosis. But the psychopharmacology may not necessarily conform very closely with how we diagnose.

Schulz: Well I think, Henry, you certainly are provocative. You've taken on *DSM* and the FDA, etc.

Nasrallah: Like I need more battles.

Schulz: Yeah, that's right. There is a question here: in a woman who is 67 and is on Zyprexa, is being treated for severe anxiety, developed Parkinsonism. Question is, could this be due to the Zyprexa? It goes on to say that when the person has been off the Zyprexa, the symptoms are still there. So I think it's awfully unlikely that the Zyprexa itself caused Parkinson's disease. But this patient's anxiety remains and it is severe, and the person feels that an atypical antipsychotic medication might be indicated. I would not go back, personally, to Zyprexa. I would pick quetiapine, which in a number of different studies now has been found to be very useful in Parkinsonism or Lewy body dementia.

Nasrallah: And anxiety.

Schulz: Pardon me. And anxiety. And it's not so long ago, only 10 years ago that the treatment for psychosis in...

[End of Tape]