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Roundtable

New versus Old Neuroleptics: Efficacy versus Marketing

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Participants: Yesne Alici, MD,[2] Tom B. Strouse, MD[3] and Rosene Pirrello, BPharm, Rph[4]

Charles F. von Gunten, MD, PhD (Moderator): To start, I think one of the clinical challenges that people in the field face now, more than pain, is managing behavior disorders and delirium. Often, clinicians are flummoxed by whether they should use haloperidol or whether they should use one of the atypicals. And I am hoping you can help us understand this.

For example, I received a call recently about an elderly man with advanced cancer who is now pulling at the bedsheets. His family says he is petting the dogs that are not there. He is up all night agitated, and the nurses are saying, "Would you please give him something?"

Tom B. Strouse, MD: I would make a couple of comments in overview, and I believe that embedded in the agreed-upon topic area was the question of whether the so-called newer drugs are any better than the so-called older drugs.

Charles F. von Gunten, MD, PhD: Absolutely.

Tom B. Strouse, MD: What is worth saying up front is: most of our decision making about using drugs we put in this class of "antipsychotics" in the setting of palliative care is seat-of-the-pants empiric treatment. I think everyone recognizes it, but it is probably worth noting. These are drugs whose primary or exclusive FDA indications are for the treatment of psychotic illnesses such as schizophrenia or the manic phase of bipolar disorder. There is actually very little data, and even less good data, that might inform our decision making.

There has been a lot said in the last five years, and a lot of money spent on metaanalyses, to try to answer the question, Are the atypicals or second-generation agents in fact any better than the first-generation agents for the treatment of schizophrenia?

There is some evidence that, compared to the Thorazines and the haloperidols, the second-generation agents have, in most patients, a more benign side effect profile when it comes to extrapyramidal symptoms; for example, patients may have an easier time adhering to treatment with them and they may have more efficacy in the treatment of depressed mood in the context of schizophrenia. They are also much better at causing people to gain weight and get metabolic syndrome. This is in the psychotic patient population for which they are approved.

Some people believe that the atypicals or second-generation agents—I keep using provisional titles because no one can agree on what the new drugs should be classified as—are the result of a marketing effort and that there is no evidence that they are better. I think that is probably a wrong statement.

Charles F. von Gunten, MD, PhD: When I was a medical student and heard about first-generation, second-generation, and third-generation cephalosporins, I thought, "Every ten years they come up with something new." And then I found out: No, they were all produced at the same time, and this was a way to market them so we could figure out whether it was Gram-positive or Gram-negative or both.

With the atypical second-generation agent, it was meant to make us think, "It is better and different," whereas the truth is, the comparison is only made with haloperidol and haloperidol is a unique drug. Of all the 30 antipsychotics that have been in the formulary for the last 30 years, haloperidol is the outlier. And yet everything is always compared to haloperidol, so already it is not only uninformative, it is actually a lie.

Tom B. Strouse, MD: It is stacked. The critics say, "Well, all of those trials were framed to choose a drug that has high risk for extrapyramidal symptoms so the so-called new drugs would look good compared to it."

Yesne Alici, MD: This is a discussion about delirium and treatment with antipsychotics in patients with delirium. However, even for patients with schizophrenia, I would be careful in stating that atypicals are better or better tolerated. As with any other patient population or illness, we have to be thinking about each patient individually, so the risk-benefit of whether the metabolic complications are more of a concern in this particular patient as opposed to extrapyramidal symptoms—those kinds of discussions and deliberations should take place when giving an antipsychotic to any patient of any diagnosis.

All that is to say, one could not make the assumption that risperidone or quetiapine would be much better for a 60-year-

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old patient with schizophrenia, much better than, let us say, haloperidol or perphenazine.

As for delirium, I agree that the haloperidol has the most evidence, and it is still considered to be the safest medication in patients with delirium in the sense that if we were to use it intelligently and thoughtfully, if it was dosed less than 2 mg to 3 mg/day, we know that the extrapyramidal symptoms, like you mentioned, are not as much of an issue when compared to the atypicals.

And the question also comes up, when the patient needs parenteral routes of medication in the treatment of delirium—which is usually the case—then the atypicals are clearly not that useful despite some people using olanzapine and aripiprazole.

Charles F. von Gunten, MD, PhD: Interesting. I was at a team meeting recently talking about managing a patient at home for delirium and getting haloperidol up to 2 mg/day. The problem was, particularly, day-night reversal and then crazy behavior all night. I said chlorpromazine would make more sense as a nighttime drug because it is sedating. And then what my pharmacy colleagues said is, actually, it has a pharmacological profile more similar to the atypicals. It is a lot more like olanzapine. It is just a 40-year-old drug, and off-patent and cheap.

Tom B. Strouse, MD: And arguably, in an older patient, also more likely to cause orthostatic hypotension or to provoke anticholinergic worsening of the delirium.

Charles F. von Gunten, MD, PhD: Is this the case at 25 mg or 50 mg or 100 mg?

Yesne Alici, MD: That is a very good question, Charles, because if you were to use 12.5 mg of the chlorpromazine as opposed to using 10 mg of olanzapine, you might actually have a safer medication, because once you go above around 10 mg of olanzapine, then your anticholinergic effects are not much different than giving chlorpromazine.

Charles F. von Gunten, MD, PhD: If you look at the effects of dopamine, serotonin, and cholinergic receptors, and look at the various subtypes and the various profiles from risperidone, quetiapine, or olanzapine, they are all very similar to chlorpromazine. And then you come down to: chlorpromazine is cheap, olanzapine is expensive, and quetiapine is even more expensive.

Tom B. Strouse, MD: Right. As the saying goes: the most expensive antihistamine being prescribed in North America is quetiapine.

Charles F. von Gunten, MD, PhD: I have heard the pharmacists say that if you are using 25 mg of quetiapine, you might as well be just giving diphenhydramine.

Tom B. Strouse, MD: Yes, right.

Yesne Alici, MD: Except that diphenhydramine would be very anticholinergic. But you could be giving anything else that is equally sedating. It depends on what you are using the quetiapine for: if you are using it for treatment of delirium, you are probably giving your 25 mg dose only to fix the sleep-wake cycle, but not necessarily doing anything to the dopamine levels.

Charles F. von Gunten, MD, PhD: Geriatricians are prescribing 25 mg of quetiapine. The nursing homes are full of it.

Yesne Alici, MD: That is probably because there is not a good sleep alternative outside of using that lower dose of quetiapine. Think about some of the other sedative hypnotics—benzodiazepines or zolpidem, or some of the diphenhydramines, the hydroxyzines. All of those are dangerous in their own ways.

Charles F. von Gunten, MD, PhD: In the palliative care world, trazodone is a sleeper of choice in the elderly and the ill, or 10 mg of chlorpromazine. Do you agree that that makes more sense than all the things you just listed?

Yesne Alici, MD: Not for sleep. I would not necessarily use chlorpromazine for sleep, and that is partly because of the orthostatic hypotension that Tom mentioned, which is also a problem with the trazodone.

Charles F. von Gunten, MD, PhD: So you are saying quetiapine as a sleeper at low dose is not a great choice, but it is because there are no good choices?

Yesne Alici, MD: That is true; exactly.

Tom B. Strouse, MD: I think a lot of us approach it in that our goal, in addition to getting people sleeping, is to not make their cognition worse. It is a sort of negative way of framing the goal. But when I talk with patients and families about the choice between benzos or other conventional sedative hypnotics and an antipsychotic of one sort or another, that is usually how I frame it.

I think William Breitbart and others have taken this as far as we have been able to go, which is not as far as we should be able to go, to test that. For example, some of Breitbart's trials compare antipsychotics and benzodiazepines in delirium.[1] But I feel fairly confident articulating the dilemma that way. We do not want to make your thinking worse, and we do not want to make you fall down and break your hip, because both of those things would be worse rather than better.

Charles F. von Gunten, MD, PhD: And in the palliative care setting, by and large, there is a serious medical illness getting worse.

Tom B. Strouse, MD: Yes.

Charles F. von Gunten, MD, PhD: One of the things I took away as an internist coming into this field is, when I hear about someone who was doing fine and now is sleeping all day and is up all night and is beginning to say crazy things, but not too crazy, I should think, "Oh, incipient delirium. Quick, let us get on top of this," as opposed to, "Oh, no, he just needs a sleeper."

Tom B. Strouse, MD: Absolutely.

Yesne Alici, MD: Correct, yes.

Charles F. von Gunten, MD, PhD: So even though the chief complaint may be, "He is not sleeping," or, "I am not sleeping," the real issue is not just a matter of no stimulation. This is really day-night reversal. It is really a hypoactive delirium and a hyperactive delirium, right? It is not just, "He sleeps all day because he was awake all night."

Yesne Alici, MD: That is right. And we do not know a lot in terms of the pathophysiology of delirium in the sense that we do not know how those antipsychotics, including haloperidol, actually help with delirium. The answer is still out there. Is it the antidopaminergic effect, which has been the case for years? We thought that it was the antidopaminergic that was helping with the treatment of delirium.

And it likely is, but then the question is, does the antidopaminergic effect kick in with the first dose of haloperidol, or even the second dose? So other things might be in play in the treatment of delirium with antipsychotics. But there is strong enough evidence to suggest that antipsychotics, especially the strong B2 blocker ones, help with the treatment of delirium.

Your question about the sleep-wake cycle disturbance, though, Charles: I think that delirium should be the first to rule out. That is for sure. But then the second question to the person with the complaint or the caregiver should be, does the patient have underlying dementia? Because that on its own can also present with sleep-wake cycle disturbances, especially with change of setting.

Charles F. von Gunten, MD, PhD: So you make a distinction, then? Dementia with a changed cognition, with change of settings, I have always thought of that as delirium. And of course, the best treatment is: get them back to their previous setting. But you are saying I should not think of it that way?

Tom B. Strouse, MD: Yes, and perhaps also that dementia or other impairments in cognition or perception, like having a hearing aid that is out or not wearing your glasses, are just risk factors for people getting rip-roaring confused, agitated, etc.

Charles F. von Gunten, MD, PhD: Well, certainly, in the unit I work, the patients come in and it is a mixed bag. There are some who have dementia of Alzheimer's type, have been wandering and saying crazy things for years, getting gradually worse, and the recent evidence is the neuroleptics should not be used for those patients. And yet it looks an awful lot like the person with advanced cancer who now is wandering around saying crazy things, and we decide, "Oh, that is delirium, and the neuroleptics are good for them."

Tom B. Strouse, MD: Well, I might reframe your summary statement slightly differently. I think what you were referring to in your comments was the increasing recognition that folks with dementia and psychosis who are treated with antipsychotics may have excess sudden death risk, which is thought to be of a cardiac arrhythmic mechanism. Is that what you were referring to, Charles?

Charles F. von Gunten, MD, PhD: Well, you are helping to clarify my thinking. Part of it is that in all nursing homes, if you say haloperidol or chlorpromazine, it is like saying, "The IRS is here to audit you."

Tom B. Strouse, MD: Yes, yes. I run a psychiatric hospital and because we have a geriatric psychiatry unit in that hospital, we have looked long and hard at this issue. And I think about a couple of things. Undoubtedly, it is the case that antipsychotics have been historically, and perhaps are still, used excessively in the nursing home setting. So it is very important to ask the question, Does the patient have psychotic symptoms, whether it is from dementia or something else, which require a pharmacologic intervention? We have developed a whole nonpharmacologic behavioral management algorithm—good nursing homes are doing the same thing—that sort of put off the question.

The reality is, there are still a lot of people who require antipsychotics, because their psychiatric agitation in the context of their dementia is sufficiently dangerous to them or others, or causing sufficient suffering for them that something needs to be done. And again, we know with a high degree of certainty that benzodiazepines and other sedative hypnotics are going to make them worse, not better. So with those folks, we may be between a rock and a hard place clinically, and then we start low, go slow, and choose carefully.

Yesne Alici, MD: In terms of the use of antipsychotics in the nursing home patient population or in the palliative care setting, the dosing is really important. One of the reasons why there are so many regulations in terms of at least trying to reduce the dose or stop the medication and stop the antipsychotic in the nursing home population stems from the fact that people use those medications at too high doses for an 80-year-old. In other words, if you are going to use haloperidol for the treatment of delirium in an 80-year-old, you should really be targeting doses of 0.25 mg to 0.5 mg, as opposed to starting them out at 2 mg/day. Or if you are using something like quetiapine, you should think about using 25 mg rather than starting them at 50 mg/day.

And at some point, someone should ask the question, Does this patient still have to be on the antipsychotic? In other words, we should not be starting those patients on antipsychotics and then continue them for two months, three months until they fall and break a hip.

Rosene Pirello, BPharm, Rph: I agree, and even in our hospice patients we always have to remind ourselves at the end of their episode to stop the antipsychotics. I would have to say we were not always successful. I think the history of the nursing home culture goes way back, many years, to when those drugs were considered chemical restraints when physical restraints were discouraged.

Charles F. von Gunten, MD, PhD: I remember a nursing home doc, when I was a third-year medical student, saying when he has a crazy nursing home patient—this was 30 years ago—"I shoot them down with 200 mg of chlorpromazine IM." So I think that captures what you are describing.

But to Dr. Alici's point, all doctors have heard "start low, go slow" associated with older people. And so they do the 0.25 mg of haloperidol and will not do anything more, and the patient's behavior makes him a danger to self and others, and he is likely to die within days to weeks. But if the patient had a pain crisis, they would be quite willing to appropriately dose-escalate the opioids. The question is, Can we have a delirium emergency like we have pain emergencies?

Rosene Pirello, BPharm, Rph: We have been more successful with scheduling the haloperidol as opposed to just making it a PRN, because they really do not like their licensed vocational nurse having to make that judgment. If the physician prescribes something like 0.25 mg or 0.5 mg we have scheduled it Q12 hours; a longer interval because the half life is long. And sometimes just that is enough, and then maybe adding a really explicit PRN order with the symptoms described, such as "for agitation as exhibited by striking staff, throwing food." And then we add the total amount of drug from those PRN doses and divide by 2 and add it back into the Q12 dosing, and, as Dr. Alici said, we are always looking for the opportunity to withdraw it quickly if the behavior improves.

Charles F. von Gunten, MD, PhD: Well, you are adding another variable, which is location of care. You are saying knowing that it is LVNs or an RN in a nursing home as opposed to in, say, Tom's psych hospital or a dedicated palliative care unit or hospice unit, where you have highly skilled staff and access, and the staffing ratios are such that you could dose-escalate. Because I am thinking of the patient who is wildly delirious, pulling at lines, crawling out of bed, the family is distraught, and haloperidol can be given via IV push every 15 to 30 minutes until you get the symptom controlled. Then you can figure out what your maintenance dose is going to be. But it is as much an emergency as somebody who is 10 out of 10 pain.

Rosene Pirello, BPharm, Rph: Do you mean having that trouble in acute care hospitals? In an inpatient palliative care unit, you could do that if needed.

Charles F. von Gunten, MD, PhD: The question is, Do palliative care teams in hospitals know about it, and are they willing to do it? And then the second level is, Is the nursing staff or the pharmacy staff on a general med-surg unit willing to do it?

Tom B. Strouse, MD: And do they have the sophistication to assess the impact of their interventions? Because the other challenge, particularly with haloperidol and, in the old days, when we used to use it, IV droperidol, and now with risperidone is, in an agitated patient, you give these high-potency butyrophenone agents that can cause akathisia, then you have to try to distinguish between not having given enough and the delirium persisting, or in fact making them acutely akathetic as an emergence phenomenon which might dictate that you change agents. And that is a tough call.

Charles F. von Gunten, MD, PhD: Help me with that, because I have always been bad at being able to diagnose akathisia.

Tom B. Strouse, MD: Well, it is particularly hard in the nonverbal delirious patient because the hallmark of akathisia is the subjective sensation of restlessness or needing to jump out of one's skin and run down the hall. I think when patients say that—and they really do say it when they are sentient and able to—it is clear. But when they cannot speak, it is a challenge. During a physical exam, certainly if you can find cogwheeling or other physical symptoms, that would help you diagnose.

Yesne Alici, MD: Between akathisia and Parkinsonism, it is not that difficult to pick up Parkinsonism as opposed to akathisia. You can still, through a cogwheeling examination, and getting the patient to walk if you can—you can capture some of that. And I do not think that is a good enough reason to switch someone to an atypical.

And a lot of the times, patients who are delirious, partly because of the hypocholinergic state they are in—they do not tend to get extrapyramidal symptoms as much as, let us say, a patient with schizophrenia who was given antipsychotics. So that is one of the things.

In terms of akathisia, phenomenologically, it does not look much different from increased agitation. So you are left to think about, in your differential diagnosis—if you keep giving the patient haloperidol and they are not getting any better, then you have to wonder, Could this be akathisia?

Then at that point, when you give your haloperidol, maybe you introduce a little bit of a benzo, like as small as a 0.5 mg or 0.25 mg of lorazepam along with your haloperidol, just to see if they will be any calmer with that.

The other thing: we talked about chlorpromazine earlier—that is a little safer in terms of its effect on akathisia because of the intrinsic anticholinergic activity, kind of like olanzapine, which also has the intrinsic anticholinergic activity. But if you have to choose one of the typicals for someone who is prone to akathisia, then why not use chlorpromazine as opposed to haloperidol at very low dose?

Rosene Pirello, BPharm, Rph: I agree with that. I was going to say, Charles, I have seen some physicians give benztropine as an anticholinergic to those haloperidol patients with akathisia, and the ones who can talk almost have an immediate response of relaxing and feeling better. So Dr. Alici's comment about being cholinergic overloaded is right on point. And sometimes I have seen people distinguish it by actually giving an anticholinergic like benztropine.

Charles F. von Gunten, MD, PhD: So in rapid titration of opioids for a pain crisis, one of my rules of thumb is if you are appropriately doubling the dose, give it every 15 minutes, trying to get on top of it. But if, despite doing that, the pain gets worse, that is when I think, "This is hyperalgesia. Change the drug or switch to a different drug class." So you are saying: If I am treating a delirium crisis and I am appropriately dosing the neuroleptic—let us say haloperidol—and everything is getting worse, I should say, "I may be causing akathisia. Change the drug."

Tom B. Strouse, MD: I agree emphatically. And I would add that sometimes we need to add benzodiazepines in, even though that violates the cardinal rule that we think benzos make cognition worse. Sometimes it is simply a requirement in these circumstances.

Charles F. von Gunten, MD, PhD: What I thought I heard Dr. Alici saying is, in the setting of where the patient is a danger to self and others, and the immediate therapeutic goal is sedation, adding the benzo to haloperidol, particularly if that is all you have at hand, is a good thing to do.

Yesne Alici, MD: Correct.

Charles F. von Gunten, MD, PhD: And then we can correct it later: after the patient is out of the emergency state, then we can get our drugs right.

Yesne Alici, MD: Again, you are using very small doses. It is not like you are using 2 mg or 3 mg of lorazepam. You are only using 0.5 mg or maybe 1 mg.

Rosene Pirello, BPharm, Rph: Psychiatrists that I have worked with have used a small haloperidol, small lorazepam, small diphenhydramine dose to start with as a one-time dose in a really dangerously agitated patient, and then they have a higher-level dose if that did not work—just in the initial dosing to maintain safety.

Yesne Alici, MD: I would be a little hesitant to use the diphenhydramine along with the haloperidol and the lorazepam in a delirious patient. If it was a 30-year-old male patient with schizophrenia, then I would certainly do the combination you mentioned. But if I am treating a 70-year-old with delirium, then I would not do anything but haloperidol and lorazepam if I needed to calm that patient.

Charles F. von Gunten, MD, PhD: The other thing I notice about our conversation: We are not talking about old versus atypical agents anymore. We are talking about specific drugs with specific patterns of neurotransmitter action and whether or not it makes sense in the patient we are seeing. Am I hearing that right?

Tom B. Strouse, MD: I think you are, and actually that is a much more meaningful and correct way of classifying the agents, since if you look at the pharmacology of the atypicals versus the first-generations, there is a great deal of overlap, and they are not—as you said earlier, Charles—they are not really distinguished by those false categories.

Charles F. von Gunten, MD, PhD: So it is all marketing?

Rosene Pirello, BPharm, Rph: Yes, it turns out that haloperidol really is the most atypical of the entire set.

Charles F. von Gunten, MD, PhD: So we should turn it around, and we should think of haloperidol as the atypical unusual drug and the rest of them are just all neuroleptics with varying degrees of antidopaminergic and serotonin ratios. Dr. Alici, what do you think?

Yesne Alici, MD: I agree, because of the high-potency characteristics of the medication—kind of like fluphenazine, which is essentially similar to haloperidol, but is not as available as haloperidol. So all the high-potency medications are actually atypicals, in that they stand alone. You are right.

Charles F. von Gunten, MD, PhD: There is a sloganism that I have heard around the term atypical, or now second-generation: For the non-expert, it sounds better, and first-generation is older and bad. Are you saying that, no, we need to think about potency—haloperidol and fluphenazine are high-potency antidopaminergic drugs, and that puts them in a place apart from the ones that are relatively lower-potency across a whole range of neurotransmitters?

Yesne Alici, MD: Well, I do not think it is that black-and-white, but let us say risperidone, which is another atypical medication: it also has strong anti-B2 antagonism. So in that sense it is not much different from haloperidol. However, it also has all the other side effects, like the atypicals, the metabolic side effects, and the other shared side effects of the increased cardiac events or the CNS-related, stroke-related events. So I think in the atypical group, even, each medication is very different from each other.

In terms of atypicals versus typicals, if we were to just think about using oral antipsychotics, then we can talk about comparing those two medications in the treatment of delirium. Very frequently our fellows would ask me, "If we are using an oral antipsychotic for a delirious patient, should I be giving this patient olanzapine, risperidone, or haloperidol?" And the answer is, it is really based on a couple of factors. If you are going to use less than 2 mg per day, yes, go with haloperidol.

But if you are going to have to escalate the dose, and if there are concerns for extrapyramidal symptoms, and if you also wanted to help with patients' gastrointestinal symptoms and their sleep and some of the other things, maybe then use olanzapine. Although most of our palliative care patients do use haloperidol for the nausea and for other kinds of palliation purposes.

Tom B. Strouse, MD: Did you mean olanzapine for nausea and assistance with weight gain?

Yesne Alici, MD: No, actually. Haloperidol is used for nausea by the palliative care physicians quite frequently. But we almost have this understanding now, at least the younger generation of physicians, that it would only be the olanzapine that will help with the nausea.

Tom B. Strouse, MD: Maybe there is a distinction between antiemetic effects, where there is no question that haloperidol is effective, and frank appetite stimulation/assistance with weight gain in the less acutely delirious, more chronic palliative care outpatient. And there are some small trials in support of this. Olanzapine, and to a lesser extent in depressed patients, mirtazapine and Remeron, have really caught on as sort of tertiary or quaternary drugs to consider when people have cachexia.

Obviously, they do not change the biology of the underlying cachexia, but they seem to help sometimes.

Charles F. von Gunten, MD, PhD: Well, you are saying we are using the drugs for their adverse effects?

Tom B. Strouse, MD: Yes, that is exactly right.

Charles F. von Gunten, MD, PhD: So the weight gain of mirtazapine or olanzapine in a 35-year-old schizophrenic patient is bad, but in a 65-year-old person with advanced cancer and anorexia, weight gain would be good?

Tom B. Strouse, MD: Yes.

Charles F. von Gunten, MD, PhD: Do you have any closing thoughts about this issue of new versus old agents or marketing versus the real?

Yesne Alici, MD: Haloperidol is still the safest and the best tolerated if used properly at doses that do not exceed 2 mg to 3 mg a day, and given its availability in the parenteral forms of use, as well.

However, it is also important to note that atypicals are also available, and if a patient is not able to tolerate haloperidol, then we have options, which is good. And recent studies have shown that in the treatment of delirium all antipsychotics are equally efficacious. Compared to placebo, for which there are only two studies, both of them with quetiapine, it looks like, at least with the quetiapine, the effects are not as pronounced in terms of the efficacy in delirium.

Rosene Pirello, BPharm, Rph: I would like to lose the term atypical. I think of chlorpromazine, born in the 1950s, as the grandparent for what we currently call atypicals. I think of haloperidol as a cousin who lives around the corner. And in fact, since the the term 'atypicals' was coined, they were atypical only to haloperidol. Haloperidol had a reign from 1960 to 1990. That was the comparator drug which made the 'atypicals' atypical. There has been a metaanalysis that compares the so-called atypicals to chlorpromazine and finds very little difference because they are in the same family.

Tom B. Strouse, MD: I am thinking about this less in a pure psychiatric context and more in a palliative care physician context, because that is mostly what I do. And with that bias plainly stated, I am a relatively infrequent user of haloperidol or chlorpromazine. I am a more frequent user of the newer agents, I think probably because I find myself targeting multiple things at once, like cognitive difficulties in intermittent delirium, and some degree of anxiety and some degree of nausea and cachexia, etc. That is probably not a very scientific statement, but it is my truth.

Charles F. von Gunten, MD, PhD: But it is very practical, and that is what this whole exercise is about—being practical for all those clinicians who are trying to make sense of this. So with that, I will bring us to a close. I am so grateful that each of you would take your time to have this discussion.

Reference

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