Interviewer: CGPR Issue 1&2

Interviewee: Dr. Beyer

(5 minutes)

CGPR: Can you tell us a little bit about the patients you see and the clinical work you do?

Dr. Beyer: Surely. I am John Beyer. I’m a psychiatrist at Duke University specializing in geriatric psychiatry and mood disorders also. I see patients through our outpatient clinics and I can supervise residents, too, which is always a pleasure.

In my geriatric work I see primarily a lot of patients that come in with mood problems - whether or not they’ve been problems they’ve dealt with all their life or just new onset mood problems, and since I’m known as kind of focusing on mood disorders, especially bipolar disorder, I see a large number of geriatric bipolar patients.

But, unfortunately, when we talk about mood disorders unipolar depression remains ubiquitous and the most common mood problem, so much of my patient load also is just regular depression treatment as well.

CGPR: Wonderful, so today we’re gonna be talking about the medication treatment of bipolar disorder, and one of my first questions for you is bipolar depression is one of the most difficult to treat conditions in psychiatry, and in older adults very often they’ve had multiple medication trials; they may be treatment refractory; and sometimes they have comorbid cognitive impairment, where do you go first for bipolar depression in older adults?

Dr. Beyer: Yeah, I appreciate that, and the amazing thing that we have today is that if we were to have this discussion about 20 years ago, the options that we would have in treating bipolar depression in general was very limited. It was ECT or try and antidepressant plus lithium or just lithium by itself and that was it; that was the only thing that we had. And even if we were to have this discussion ten years ago, the number of medications that we actually had FDA approval for the treatment of depression were three, and we haven’t had a large number of options for treating bipolar depression, but now in 2022 we have now five medications that have the FDA approval for bipolar depression plus a lot of experience about using other medications for this indication as well.

The one problem that comes up is that all these medications have been approved for adults and primarily that research was done in younger adults.

And so if we’re kind of just select out our geriatric population and say what do we do for our older group, what we end up finding is that we’re using data that has been selected from the registration trials to say what has worked for the older group of this registration trial and is it the same as the younger group. The good news is that in the two or three trials that we’ve looked at data just taking out the older group, it looks like the older group responds about as well as the younger adult population. And so we have about five different medications that we can use.

The problem that we end up having with older adults with bipolar disorder is that they have often been tried of lots of medicines already, and they may have some reasons that we can’t use lots of medications already. If you were to ask me what is the number one treatment thing that I look at is have people responded to a certain medication in the past, and if they have then stay with what’s been there. Often patients come seeing us already on medications, and if they have the problem already on the medication of this recurrent depressive episode, but they’ve had some stability with the medication, I may continue that medication as a baseline medication and find a medication, augment the treatment just to support us through that time. Unfortunately, many times patients come not on any medications as well, and that gives us a lot more ideas about which medications we should start with.

If I were to look just at evidence-based medicine, the medications that probably have the best data in geriatric or older adults with bipolar depression are going to be quetiapine and lurasidone, and in fact a lot of that is present because we had taken those registration clinical trials of older adults and selected out those that are above the age of 60 and 65 to say how did they respond to treatment. In this case, we have 142 patients that we were able to look at that were over the age of 55 to kind of say how did they respond to lurasidone. And we had about 72 patients in the clinical trials with quetiapine that we could look at that were above the age of 55 to say how they responded. And what we found is that they responded equally as well as younger adults. So often we find that quetiapine or lurasidone may be the best evidence-based medicine for the initial treatment monotherapy with our geriatric depressed patients.

(10 minutes)

CGPR: How does that compare say to lithium?

Dr. Beyer: Lithium, which is the gold standard for treatment of bipolar disorder in general, is good. Unfortunately, we don’t have a lot of data about lithium in bipolar depression. We do have good data, especially for our geriatric bipolar group in mania. Lithium is a fantastic medication and probably the most effective treatment, even a little more effective than valproate, for treatment of mania, but its use in bipolar depression in the geriatric depression is really not much information that we can hang our hat on. What we do seem to find when we took a look at the lamotrigine registration trials, is that they compared the use of lamotrigine as a maintenance treatment for preventing relapse of either depression or mania, and they compared it with lithium and placebo. Both lithium and lamotrigine showed significant improvement in keeping patients well and not having recurrence of illness. It’s interesting that lamotrigine seemed to do better at keeping patients from getting a recurrence of depression while lithium seemed better at keeping patients from getting a recurrence of mania suggesting that even though we have often used lithium as augmentation strategies for unipolar depression and definitely use it as the main strategy for bipolar disorder in general, it may be more effective for the manic symptoms rather than the depressive symptoms – at least we have data that does show that it can be effective in both.

CGPR: Yes, that’s helpful. So you would start a treatment-naïve patient on quetiapine or lurasidone, can you go through the other three treatments and why they would move down a little bit on your algorithm?

Dr. Beyer: Probably the other data that we have was from the data that came out in the early 2000’s looking at the combination therapy of olanzapine and fluoxetine. Early on the pharmaceutical company actually suggested that maybe there was a role for second-generation antipsychotics in the treatment of bipolar disorder, and they did indeed find that almost all our second-generation antidepressants are effective treatments for mania.

But very few actually tried it in the treatment of bipolar depression, and there’s been some controversy about how well it might have responded. Of all those antipsychotics, as I mentioned before, the combination of olanzapine and fluoxetine, quetiapine, lurasidone, and now cariprazine and lumateperone have actually been FDA approved for bipolar depression. We have no reasonable data for quetiapine and lurasidone. We have more limited data for the combination of olanzapine and fluoxetine in part because that combination arm in the initial study was actually fairly small. But there was information that suggested that those that were over the age of 55 also responded well to this combination treatment, and in fact this combination of olanzapine and fluoxetine does appear to be a very effective treatment for significant depressive symptoms in our bipolar patients, and I think it’s also a jewel for treatment of our geriatric bipolar patients as well.

Where we go from here about some of the new medications is unknown. We’re still waiting to get information about use in older adults on the most recently FDA-approved medications which are cariprazine, and also just this last year now lumateperone, and I look forward to seeing how that fits into our own armamentarium in the future.

CGPR: When you dose quetiapine in an older adult as your first line, how slow do you go? Where do you start? How quickly do you increase the dose? What do you use to guide your dosing?

Dr. Beyer: Yeah, in the registration studies there was a fairly aggressive increase starting at about 100 mg and going up. That was for all adults. And it is true that when we took a look at the older adults, they were a little bit more likely to kind of have fallen out of the study because of the side effects compared with younger patients. So probably going up more slowly in our older population makes sense. Initially, we kind of start out with 100 mg, and then every few days we will increase. I think it’s important to realize that the dose that was found in the quetiapine studies in general was 300 and 600 mg; the average dose I believe was 550 mg, which is a lot of medication for those patients. I think in our adults when we do it within our clinic we often find that they respond at lower doses than what is and so I tend to aim toward 300 mg and see how they respond with quetiapine.

(15 minutes)

CGPR: And assuming that they don’t respond and you try a lurasidone trial and they don’t respond, where do you go next?

Dr. Beyer: So the question is do you continue switching medications to find a monotherapy that’s effective or do you think about augmenting treatments? For most of my patients in the clinic, we will already have an established medication, a baseline medication, and I find that in my clinical practice I end up augmenting treatments.

However, there is reason to think that if a patient is absolutely having no response to an identified medication treatment for their bipolar depression that another trial of switching to another medication makes sense. However, I think after two, three or four monotherapy trials that is probably the place at which you need to stop doing monotherapy trials and start looking at augmentation strategies.

There’s been a real push in the last decade to actually thinking about more augmentation strategies rather than monotherapy with kind of this need to kind of get efficacious treatment as quickly as possible. But elderly adults are probably more sensitive to side effects and a more conservative management technique - if they are not in acute distress - probably is the best way of going, so if we’ve kind of gone through quetiapine or maybe lurasidone I’m going to be thinking about augmentation strategies.

And where I think about is actually going back to those that we have a lot of clinical experience with which is augmentation with lithium or augmentation with valproate. And I think using a combination of what has traditionally been considered a mood stabilizer with a medication that may be considered a second-generation antipsychotic that has been targeted for bipolar depression makes sense.

CGPR: Okay, that’s helpful. And when you do combination therapy very often older adults have medical comorbidities, so which ones do you pay special attention to when thinking about mood stabilizers?

Dr. Beyer: I think in our older adults first it’s not uncommon for our patients to be on somewhere between five and ten medications, and so the idea about adding medications to this vulnerable population is something that we should take very seriously, which is why we talk about monotherapy, if possible. With the fact that they may have five to ten medications - most older adults that we treat already have about four or five significant medical comorbidities that they’re dealing with, the most of which are going to be like hypertension or coronary vascular disease or diabetes or one of those. Kidney disease in the elderly is very common as well, especially strain on kidneys.

And so if we think about these as being the most common medical comorbidities, there are some medications that may cause some difficulties with that. I think especially with our lithium patients that we want to be aware that kidney disease and thyroid disease, which also is higher in older adults, may be a limitation for its use and we need to be thoughtful about that.

We are a larger people as well, and we need to be thoughtful about the metabolic problems that many of our second-generation medications, antipsychotic medications especially can cause, so that if I have patients that are obese or who have cardiovascular disease or type II diabetes, I’ll be more concerned, especially with those second-generation antipsychotics that may have metabolic concerns such as quetiapine or olanzapine especially.

CGPR: Do you do anything different in terms of monitoring when you prescribe a mood stabilizer in older adults? Do you change the frequency or look for anything else?

Dr. Beyer: Yeah, that is actually determined less by age and more by presentation and medical frailty. So if I have a fairly healthy older adult, I probably do not make any significant change in monitoring practices with one caveat where if they do have a history of cardiovascular disease, especially if I’m thinking about lithium, I might want to check an EKG which I may not do with a younger more healthy adult. But for most of my adult patients, I don’t make a significant change in how I monitor them other than I just make sure that we do appropriate monitoring as recommended by either the American Diabetic Association or the APA as we look at monitoring psychiatric medications unless they do have some significant health concerns.

20 minutes)

And again, for those patients that have kidney strain and I might be using lithium, I will be monitoring their creatinine, their kidney function more often than I would for maybe say a younger adult because that can be very tenuous and change very quickly.

CGPR: I’ve had a few patients who take lithium for decades who are stable, but then there’s a reason that they have to come off of lithium and then, unfortunately, they have a relapse, and I always wonder is there a way where they actually could have remained on lithium with closer collaboration with a specialist. I’m curious if you could tell us a little bit about the contraindications to prescribing lithium and how to minimize some of the relative contraindications.

Dr. Beyer: Thank you, no lithium has been around since the ‘70s and so we have some experience with that, although our younger psychiatrists probably have less experience than older psychiatrists with lithium, and it really takes experience to kind of know how best to manage lithium across the board. Lithium causes problems when we think about kidneys or anyone that has volume problems with water or some type of salt problem, so sodium problems or difficulty with orthostatic hypotension or people that have kidney disease, and those are the ones that we really kind of want to keep a closer eye on. If a person definitely has significant kidney disease, that is probably a contraindication for using lithium. We have relative contraindications for using lithium as well such as psoriasis; it can worse psoriasis, but we just want to be careful if there’s just mild to moderate kidney disease or difficulty in keeping up one’s salts, especially in relationship to the use of other medications.

I have seen patients who have had to come off lithium, and they’ve had bad courses afterwards because lithium has been a very effective medicine for them, and they often wonder “Could we go back on the medication?” That is something actually that we have been able to do in collaboration with the patient’s nephrologist as we kind of work through what are the exact parameters. Just if a patient has some mild kidney disease, that does not necessarily mean that they have to come off the medication; what it does mean is that we have to monitor them more closely and as you say be more collaborative and care for that. And we do that working with nephrologists at monitoring the creatinine levels or the GRF’s that patients have.

CGPR: Have you had a patient where you’ve closely collaborated with a nephrologist, and how high was the creatinine; what did it look like?

Dr. Beyer: Yeah, I have actually. The patients that I’ve have had that have come off their lithium and they’ve had just a relapse of pretty severe disease despite our trials of other medications; we finally put them back on the lithium; they stabilized. And so the question is: how can we kind of keep them as stable and monitor the creatinine levels? In our studies you know we start getting anxious when the person’s creatinine gets 1.3, 1.4, and 1.5. In some of the research that we’ve done, we’ve actually kind of made a creatinine of 2.0 to be kind of the absolute place where we would not start a person on lithium, but we would need to definitely work in close collaboration with the patient’s nephrologist on that. Again, being aware that there are some things we can do to try to improve kidney functioning so that lithium is more effective, and making sure that the patient doesn’t put themselves in situations where lithium toxicity is at a higher risk, but that is something that should be done very, very carefully and with collaborative medicine.

CGPR: I’m curious about your use of antidepressants together with mood stabilizers or antipsychotics in refractory depression.

Dr. Beyer: It goes back…we do actually have some data about antidepressant use in bipolar depression and we actually have one antidepressant that is approved for bipolar depression, and that is fluoxetine, but only in conjunction with its use with olanzapine.

We have a mixed understanding about the role of antidepressants in general in bipolar depression and part of that is that there is not great evidence about their efficacy in treating bipolar depression. The number needed to treat for good outcomes is actually pretty high, and so the question is are the use of antidepressants actually helpful in bipolar depression? With that being said, the clinical realty is that antidepressants are the most frequently prescribed class of medications for patients with bipolar depression, and that’s just the actual work that’s being done in the clinics themselves.

(25 minutes)

So we have to understand kind of what our goals are for using antidepressants, know what the data is, and then also know the patient’s history with the antidepressant about whether or not there is a response or not.

There are a couple of reasons why we would not use antidepressants in bipolar depression besides the fact that efficacy data is relatively minimal. One is that is that we want to avoid doing harm, and what we found is that we may do more likelihood of harm if we’re treating a patient with mixed features or with rapid cycling bipolar disorder with an antidepressant.

The other time that we may be doing harm is that if we treat a patient with an antidepressant without a mood stabilizer also.

So antidepressants may have a role in bipolar depression, but it probably is not a first or secondary or even tertiary treatment; it’s something to be considered down the line, and based upon a person’s history of use, and with the understanding that actually antidepressants can cause harm and that the doctor needs to be also able to understand that the efficacy is limited.

CGPR: In older adults are the rates of affective switching and rapid cycling similar to younger adults?

Dr. Beyer: Yeah, honestly I don’t know. I wish I had data to kind of look at that, but I don’t know. What I do know is that as we look about bipolar disorder across the lifespan that bipolar disorder depressed episodes appear to increase in number as we get older compared with mania or hypomania, and so the most likely presentation that a patient with bipolar disorder will make to their physician is one of depression. And as far as switching back over, a lot of that probably depends upon their exposure to antidepressants in the past.

What we do know is that patients that have more exposure to antidepressants in the past, especially without a mood stabilizer, do have more sensitivity to rapid cycling and switching later in the picture.

CGPR: Knowing that, if you saw a patient in clinic who you inherited on lithium and an SSRI, say Zoloft, and they were at that moment stable, would you taper off the Zoloft (the sertraline) or would you continue?

Dr. Beyer: As with everything, there’s no one rule that takes care of all cases like this and it’s on a case-by-case basis. I probably, if they were stable and I was just seeing them, I would probably keep them on the medications that have been effective. In general what we find is that if we taper a patient off an antidepressant - bipolar disorder patients - off an antidepressant too quickly, we have a likelihood of actually causing the depressive episodes to return and they have an increased likelihood of having depression, and that’s not what we want.

But at the same time, we don’t want to keep them on unneeded medications long term either. And so the idea is that we would like to observe stability if they are on an antidepressant over at least a 9-month to a year period of time before considering do they need that as an ongoing medication. There are some people that by their history we will have discovered that they do better when they have an antidepressant medication, and there are some by history and by experience we will discover that they actually do worse long term with more cycling. So a lot of it is case by case, but I would not reactively take a medication off, but I would observe kind of their course of treatment and try to discover what their course in the past has been as well.

CGPR: You mentioned “switching” versus “augmenting” and I just want to throw in a third option of ECT, at what point do you think about ECT rather than another medication trial or augmentation?

Dr. Beyer: ECT still remains one of the most effective and powerful treatments towards depression - bipolar or unipolar depression. If the patient is so severely depressed that they are really not functioning and have not been able to tolerate medications or even participate in their treatment, ECT in that case may be a primary option. In general though in the course of bipolar depression, ECT tends to be about the fourth of fifth step after several other trials have been made. But a lot of it really depends upon how quickly an intervention needs to be done in that depression. Depression is a terrible illness, and it weighs not only on the patient but also the family and so taking that into account and the previous trials would help the decision be made about ECT.

(30 minutes)

CGPR: And what about TMS?

Dr. Beyer: TMS. There is really not as much information known about TMS in the elderly, especially elderly with bipolar depression. It has been shown to be effective. It is often a very time intensive treatment that we have to find patients that have the ability to get to the TMS treatment on a regular basis and have the time and ability to get that done, and it does appear to be effective if they have failed one antidepressant trial before that.

CGPR: So where would it fall in your algorithm?

Dr. Beyer: I tend to put it down below ECT. But the data actually suggest that it really is for patients that actually might have a reasonable approach to be thoughtful as an intervention earlier on too depending upon accessibility and the patient’s desire, and medical comorbidities as well.

CGPR: So what other treatments, sort of complementary or alternative treatments do you discuss with patients who suffer from bipolar depression?

Dr. Beyer: With almost all my depressed patients, one treatment that we always discuss is exercise. And that does not necessarily have to be a full aerobic exercise, but especially for my older adults even just walking. If we can get them to walk even one mile a day that is a good prognostic sign for actually improvement. And so engagement in physical activity is a good treatment to actually prescribe to our patients as well.

Other things we are finding are that diet probably does make a difference. It may not make a difference where we might be able to find it in a clinical trial, but it is supportive, and it is a commitment that patients often make saying, “I want to change something in my life” and doing that they change much of their lifestyle that may prevent ongoing depressive symptoms, and so diet is a good thing to discuss with patients as well.

CGPR: Do you ever discuss light therapy?

Dr. Beyer: Light therapy – yes we do and I appreciate you bringing that up, especially with patients…Light therapy use in patients with bipolar disorder may be different than in unipolar depression and so we just need to be aware that there are different protocols for the different indications, especially light therapy for patients that give any indication that they may have a history of seasonal affective concerns. They may be especially receptive to light therapy as well.

And the other part that is kind of associated with that is also just a more scheduled social rhythm changes to their day. You know having defined times that they get up out of bed; activities that they identify that they will participate during the day, and defined bedtimes as well can be very helpful for regulation and improvement of bipolar depression.

CGPR: Have you ever seen light therapies switch a patient into mania? I’ve never seen it.

Dr. Beyer: I’ve not seen it either. I’ve heard about it anecdotally, but it’s not been something I’ve actually experienced.

CGPR: We spoke a lot about bipolar depression, I’m wondering about any tidbits or any changes you make in treating mania in older adults?

Dr. Beyer: You know I’ve actually been so pleased to be part of a research study that was published in The American Journal of Psychiatry. Dr. Robert Young was the primary investigator for that looking at older adults does lithium actually work and does valproate actually work, and I’m just pleased to be able to say that we actually have good studies that show lithium and valproate do work in bipolar mania, lithium probably a little bit more effective than valproate, maybe a little less tolerated than valproate, but they both are very effective treatments for our older population.

With that being said, we have a whole panoply of other treatments that are now available for bipolar mania, and I think we are switching kind of to this understanding that we want to make sure that we’re protected from both sides.

One medication I haven’t mentioned much is lamotrigine and where it fits in this. I mentioned that antidepressants are the most commonly prescribed class of medications in bipolar depression. Lamotrigine is the most rapidly fast rising class of medicine that’s being prescribed in bipolar depression, especially as we look over the past 10-15 years. And I think that a lot of it as we discussed before that lamotrigine may be helpful in preventing relapses in depression and may have a role in underlying depression as well. But lamotrigine, which does not have the FDA approval for bipolar depression; it does have the approval for bipolar maintenance, may have a role for some of our bipolar patients, especially in combination treatments too.

(35 minutes)

CGPR: Is there anything in the research pipeline we should know about?

Dr. Beyer: As I mentioned before, we have gone in the period of three years, we’ve gone from just having two medications for FDA approval for bipolar depression to now having five medications. We’re anticipating that another medication, brexpiprazole, may be submitting data about its role in bipolar depression within this next year as well and look forward to that.

There are also actual studies being done now with ketamine and the use of bipolar depression. Ketamine actually is also being looked at for the treatment of bipolar depression. It has already the indication for treatment-resistant depression and treatment for severe depressive episodes associated with suicidal ideation, and will see how also ketamine may be an effective intervention for bipolar depression as well.

CGPR: With the newer medications, are there any advantages to them? Efficacy-wise, it doesn’t sound like they will beat out the others, but what would your thoughts be about why you would recommend one of the newer medications?

Dr. Beyer: We were disappointed when both ziprasidone and aripiprazole’s FDA trials did not show a differentiation from placebo because they were the promise of the newer class of second-generation medications that did not have a lot of the metabolic side effects that we experienced with olanzapine and quetiapine – effective medications, but often with significant problems that our vulnerable geriatric populations may be more susceptible to as well. But with the introduction of lurasidone and the data that supported its use with its limited metabolic concerns, and especially now with the anticipation of cariprazine and lumateperone that with limited evidence that they have a lot of metabolic side effects of weight gain or changes in cholesterol or problems with glucose, that these seem to be better medications that our patients can tolerate and, hopefully, be as efficacious of course. I think we will see increasing use of these medications just because of the difficulty it is bouncing the multiple medical comorbidities and problems associated with our medical treatments for bipolar disorder.

CGPR: Very helpful; that was incredible. Is there anything else that you feel that we did not discuss that you feel you want the readers to know about?

Dr. Beyer: Just a couple of things…Bipolar depression in geriatrics still remains a significant problem, and as I said increasingly we often see depression is the predominant episode that comes to patients, even more so than younger adults in which it is essentially three-to-one compared with hypomania and mania. So we have to deal with these patients. And also the difficulty; it is not an easy thing to treat bipolar depression; it’s not an easy thing at all. And I appreciate the researchers that are really kind of looking for this to help guide us in some of these decisions.

One good thing I think is that when we take a look at suicide rates, we find that our older adults that have bipolar depression through their lifetimes may actually have lower suicide rates which is significant because bipolar disorder is the psychiatric disease most closely associated with suicide behaviors and seems to be most closely associated, especially within the first (39 min\_\_\_\_\_\_\_\_\_\_ (? 7-10) years after the diagnosis, and with the acuity, especially if they have a lot of rapid cycling. Our older adults may be beyond some of that as well, and so that’s one hopeful sign about kind of our ability to learn to manage the disease.

The only thing that we probably should talk about at some point and maybe in the future are the cognitive effects that bipolar disorder has cumulatively over life, but also especially for our older population, and how that might interact with some of the medications that we have our patients on. Again, this goes to the point that the treatment of bipolar disorder, especially treatment of bipolar depression, is not an easy thing to do.