Mini-CAT: Spring 2019
Rotation 4, Weeks 3-4

Clinical Question:
29 year-old male with past psychiatric history of paranoid schizophrenia x several years. He has been taking Abilify for it but does not adhere to his medications since he believes that taking medications daily is a "nuisance." Patient wants to know whether taking Invega Sustenna or similar injections (long acting injection taken once a month) will increase adherence and his quality of life.

Search Question:
In adults diagnosed with schizophrenia, does Invega Sustenna (paliperidone palmitate), a long acting atypical antipsychotic injection, promote patient adherence and increase quality of life as compared to conventional oral antipsychotics?

PICO Question:

P	**I**	**C**	**O**
Schizophrenia	Invega Sustenna injection	Conventional oral antipsychotics	Increased patient adherence
Male	Paliperidone palmitate injection	Oral Abilify	Increased quality of life
		Oral aripiprazole	Increased patient compliance
			Medication adherence

**I chose not to include specific types of schizophrenia in this version of the mini-CAT because we no longer differentiate between the different types of schizophrenias in practice.

Search Strategy:

PubMed
- Invega Sustenna patient adherence→77
- Invega Sustenna patient adherence/Limits: humans→54 (best match)

Cochrane Library
- Invega Sustenna patient adherence→1

Science Direct

- Invega Sustenna patient adherence→18
- Invega Sustenna patient adherence/Limits: 5 years→13 (best match)

Google Scholar

- Invega Sustenna patient adherence→495
- Invega Sustenna patient adherence/Limits: 5 years→337 (best match)

In PubMed, there were only 54 articles left after sorting by best match and limiting to humans. The first article is an RCT that compared long-acting injections like paliperidone palmitate to seven other oral anti-psychotics, which is exactly what my patient was asking. We were interested in whether injectables medications would increase patient adherence and quality of life as compared to having to take oral medication every day as long as the patient needs for the rest of his life. This RCT also looked into adverse effects, which was a plus. Even though the medications may be the same, the vector in which the medication is delivered could give rise to other side effects previously not noted. As for the second article, even though it was a retrospective cohort and not the highest level of evidence, it still remains valuable due to following 763 patients (large sample size is another plus) over a course of 15 months. As we know, conducting these studies are expensive, especially over a 15-month period. Moreover, long-acting injectables are given once a month, thus you cannot terminate this type of study over the span of several months. Rather, it is better if we follow the patients over a longer period of time. The study also highlighted some factors that contributed to stopping treatment, which is helpful in practice so we could educate patients and prevent non-adherence before it occurs. The third article takes patient adherence and quality of life one step further and relates them to treatment patterns and healthcare spending and resources. This is valuable since it looks at the bigger picture at how individual patients with schizophrenia are affecting spending and resources on a larger, hospital scale setting. As for the fourth article, even though it dates back to 2015, which was 4 years ago, this RCT looked into the effectiveness of paliperidone injection in terms of the clinical features in addition to real-world design elements. I think that they set up a really realistic environment for the study since the authors included flexible dosing and use of concomitant medications. We could say that this allows for more bias or more confounding factors but the reality is that patients are normally not on the same dosages of anti-psychotics and most of them take more than one medication at a time. Additionally, this study included patients with comorbid substance abuse since substance abuse is found at a higher incidence in patients with psychiatric disorders, history of incarceration (true for this as well), and with unstable living conditions (also true), providing us with information that relates more to real life patients.

Results found:

1. Once-monthly **paliperidone palmitate** compared with conventional and atypical daily oral antipsychotic treatment in patients with schizophrenia.
Kim E, Correll CU, Mao L, Starr HL, Alphs L.
CNS Spectr. 2016 Dec;21(6):466-477. Epub 2016 Sep 15.
PMID: 27629292

Abstract

OBJECTIVE:

This analysis of the Paliperidone Palmitate Research in Demonstrating Effectiveness (PRIDE) study (NCT01157351) compared outcomes after administration of once-monthly paliperidone palmitate (PP) vs conventional oral antipsychotics (COAs) or atypical oral antipsychotics (AOAs).

METHODS:
PRIDE was a 15-month study of 444 individuals with schizophrenia and a history of incarceration. They were randomly assigned to PP or to 1 of 7 commonly prescribed OAs. Primary endpoint was time to first treatment failure (TF). Event-free probabilities were estimated using the Kaplan-Meier method; treatment group differences (PP vs COAs, PP vs AOAs, and PP vs oral paliperidone/risperidone) were assessed using a log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox proportional hazards regression models. No adjustment was made for multiplicity.

RESULTS:
Compared with PP, risk for first TF was 34% higher with COAs (HR: 1.34; 95% CI: 0.80-2.25), 41% higher with AOAs (HR: 1.41; 95% CI: 1.06-1.88), and 39% higher with paliperidone/risperidone (HR: 1.39; 95% CI: 0.97-1.99). Incidences of extrapyramidal symptom-related adverse events (AEs) were 45.7%, 13.7%, and 10.6% in the COA, AOA, and oral paliperidone/risperidone groups vs 23.9% in the PP group. Incidences of prolactin-related AEs were 5.7%, 3.8%, and 3.5% vs 23.5%, and incidences of ≥7% weight increase were 11.4%, 14.9%, and 16.0% vs 32.4%.

CONCLUSIONS:
Results suggest a lower risk of TF but a higher rate of some AEs after treatment with PP vs COAs, AOAs, and paliperidone/risperidone. Deselection of specific OAs and low patient-compliance rates with OAs likely biased the safety results.

Link: Article 1

2. Comparison and predictors of treatment adherence and remission among patients with schizophrenia treated with paliperidone palmitate or atypical oral antipsychotics in community behavioral health organizations.
Anderson JP, Icten Z, Alas V, Benson C, Joshi K.
BMC Psychiatry. 2017 Oct 18;17(1):346. doi: 10.1186/s12888-017-1507-8.
PMID: 29047368

Abstract
BACKGROUND:
Nonadherence to antipsychotic treatment increases the likelihood of relapse and progressive symptomatology in patients with schizophrenia. Atypical long-acting injectables, including paliperidone palmitate (PP), may increase adherence and improve symptoms. This study compared and assessed predictors of treatment patterns and symptom remission among schizophrenia patients treated with PP versus atypical oral antipsychotic therapy (OAT) in community behavioral health organizations (CBHOs).

METHODS:
This retrospective cohort analysis evaluated 763 patients with schizophrenia and new (PP-N; N = 174) or continuing (PP-C; N = 308) users of PP, or new users of OAT (N = 281) at enrollment in the REACH-OUT study (2010-2013). Treatment outcomes assessed at 1 year were discontinuation, and

adherence, measured by proportion of days covered (PDC) or medication possession ratio (MPR). Remission status was assessed using the Structured Clinical Interview for Symptoms of Remission (SCI-SR). A machine learning platform, Reverse Engineering and Forward Simulation (REFS™), was used to identify predictors of study outcomes. Multivariate Cox and generalized linear regressions estimated the adjusted hazard ratios (HRs) or odds ratios (ORs) with 95% confidence intervals.

RESULTS:

Among PP-N users, 27% discontinued their initial treatment regimen versus 51% ($p < 0.001$) of OAT users. PP-N (vs OAT; HR = 0.49 [0.31-0.76]) users and males (HR = 0.65 [0.46-0.92]) had significantly lower rates of discontinuation. Relative to OAT, PP-N had a 36% [31%-42%] higher MPR and a 10-fold increased achievement of PDC ≥80% (OR = 10.46 [5.72-19.76]). PP users were significantly more likely to achieve remission in follow-up (PP-N vs OAT: OR = 2.65 [1.39-5.05]; PP-C vs OAT: OR = 1.83 [1.03-3.25]).

CONCLUSIONS:

Relative to OAT, PP was associated with improved adherence, less frequent treatment discontinuation, and improved symptom remission in this CBHO study population.

Link: Article 2

3. Treatment Patterns, Health Care Resource Utilization, and Spending in Medicaid Beneficiaries Initiating Second-generation Long-acting Injectable Agents Versus Oral Atypical Antipsychotics.
Pilon D, Tandon N, Lafeuille MH, Kamstra R, Emond B, Lefebvre P, Joshi K.
Clin Ther. 2017 Oct;39(10):1972-1985.e2. doi: 10.1016/j.clinthera.2017.08.008. Epub 2017 Sep 15.
PMID: 28919292

Abstract

PURPOSE:

Second-generation long-acting injectable therapies (SGA-LAIs) may reduce health care resource utilization (HRU) and health care costs compared with daily oral atypical antipsychotics (OAAs) in patients with schizophrenia due to reduced dosing frequency, delivery/monitoring by a health care provider, and improved adherence. The aim of the present study was to compare treatment patterns, HRU, and Medicaid spending in patients with schizophrenia initiated on SGA-LAIs (overall and according to agent) versus OAAs.

METHODS:

Medicaid claims data (2010-2015) from 6 states were used to identify adult schizophrenia patients initiated on SGA-LAIs or OAAs. Treatment patterns (proportion of days covered [PDC] ≥80% and persistence [no gap ≥30, 60, or 90 days] to index treatment), HRU, and costs were evaluated over 12 months and compared by using multivariable logistic, Poisson, and ordinary least squares regression models, respectively. P values for HRU and cost outcomes were obtained from a nonparametric bootstrap procedure. Costs (2015 US dollars) reflect the Medicaid payer's perspective before any rebate.

FINDINGS:

Overall, 3307 and 21,355 patients initiated SGA-LAIs and OAAs, respectively (paliperidone palmitate LAI [PP-LAI; n = 2182], risperidone LAI [n = 968], aripiprazole LAI [n = 108], and olanzapine LAI [n =

49]). During follow-up and compared with OAA patients, SGA-LAI patients were more likely to reach PDC ≥80% (odds ratio [OR], 1.28; P < 0.001) and be persistent (eg, no gap ≥60 days; OR, 1.45; P < 0.001) to the index treatment. Relative to OAA patients, SGA-LAI patients had fewer long-term care days (incidence rate ratio [IRR], 0.75; P < 0.001) and home care visits (IRR, 0.75; P < 0.001) but more mental health institute (IRR, 1.16; P < 0.001) and 1-day mental health institute (IRR, 1.16; P < 0.001) admissions. Moreover, PP-LAI patients had fewer inpatient days (IRR, 0.78; P = 0.004) versus OAA patients. SGA-LAI patients had lower medical costs (mean monthly cost difference [MMCD], -$168; P < 0.001) than OAA patients, offsetting more than one half of the higher pharmacy costs (MMCD, $271; P < 0.001). Compared with OAAs, only PP-LAI was associated with significant medical cost savings (MMCD, -$225; P < 0.001).

IMPLICATIONS:
Medicaid beneficiaries with schizophrenia initiated on SGA-LAIs had better adherence and persistence to therapy over 12 months than patients initiated on OAAs. SGA-LAIs, particularly PP-LAI, were associated with lower medical costs that successfully offset more than one half of the higher pharmacy costs relative to OAA.

Link: Article 3

4. **Real-world outcomes** of **paliperidone palmitate** compared to daily oral antipsychotic therapy in schizophrenia: a randomized, open-label, review board-blinded 15-month study.
Alphs L, Benson C, Cheshire-Kinney K, Lindenmayer JP, Mao L, Rodriguez SC, Starr HL.
J Clin Psychiatry. 2015 May;76(5):554-61. doi: 10.4088/JCP.14m09584.
PMID: 25938474

Abstract

OBJECTIVE:
The Paliperidone Palmitate Research in Demonstrating Effectiveness (PRIDE) study compared the effects of once-monthly paliperidone palmitate with daily oral antipsychotics on treatment failure in adults with schizophrenia.

METHOD:
The PRIDE study is a 15-month, randomized, multicenter study (May 5, 2010, to December 9, 2013) of adult subjects with a DSM-IV diagnosis of schizophrenia and a history of incarceration. Subjects were randomly assigned to once-monthly paliperidone palmitateinjections or daily oral antipsychotics (randomly assigned from 7 acceptable, prespecified oral antipsychotics) for 15 months. The primary end point was time to first treatment failure, defined as arrest/incarceration; psychiatric hospitalization; suicide; treatment discontinuation or supplementation due to inadequate efficacy, safety, or tolerability; or increased psychiatric services to prevent hospitalization. Time to first treatment failure was determined by a blinded event-monitoring board and analyzed with the Kaplan-Meier method.

RESULTS:
In this study, 450 patients were randomly assigned, and 444 were included in the intent-to-treat population. Paliperidone palmitatewas associated with significant delay in time to first treatment failure versus oral antipsychotics (hazard ratio, 1.43; 95% CI, 1.09-1.88; log rank P = .011). Observed treatment failure rates over 15 months were 39.8% and 53.7%, respectively. Arrest/incarceration

and psychiatric hospitalization were the most common reasons for treatment failure in the paliperidone palmitate and oral antipsychotic groups (21.2% vs 29.4% and 8.0% vs 11.9%, respectively). The 5 most common treatment-emergent adverse events for the paliperidone palmitate treatment group were injection site pain (18.6% of subjects), insomnia (16.8%), weight increased (11.9%), akathisia (11.1%), and anxiety (10.6%).

CONCLUSIONS:
In a trial designed to reflect real-world management of schizophrenia, once-monthly paliperidone palmitate demonstrated superiority compared to oral antipsychotics in delaying time to treatment failure.

Link: Article 4

Summary of the Evidence:

Author (Date)	Level of Evidence	Sample/Setting (# of subjects/ studies, cohort definition etc.)	Outcome(s) studied	Key Findings	Limitations and Biases
Kim, et. al., 2016	Randomized, prospective, open-label, event-monitoring, board-blinded, parallel-group study	-15-month study of 444 patients (aged 18-65) with schizophrenia and history of incarceration, randomly assigned to once-monthly paliperidone palmitate (PP) or 1 of 7 conventional oral antipsychotics (haloperidol, perphenazine, olanzapine, aripiprazole, quetiapine, risperidone, and paliperidone)	-Primary endpoint was time to first treatment failure (TF), which included arrest or incarceration, psychiatric hospitalization, suicide, d/c of treatment due to inadequate efficacy as determined by the investigators, treatment supplementation with another antipsychotic due to inadequate efficacy, d/c of treatment due to safety issues or tolerability, or increase in psychiatric services to prevent imminent psychiatric	-Risk of treatment failure was 34-41% higher with oral antipsychotics than with long-acting injections -Haloperidol (59.9%) and perphenazine (39.4%) were the most commonly deselected oral antipsychotics prior to randomization due to EPS and other adverse effects -Paliperidone was the least deselected -Compared with PP, the risk for treatment failure was 39% higher with ORAL delivery of similar/identical medication (paliperidone/risperidone), suggesting a difference between the route given -PP has a longer half-life than its oral counterpart, contributing to longer duration of continuous	-Although these findings were more reflective or real-world outcomes (partially due to inclusion of incarcerated patients), the data cannot be generalized to all patients with schizophrenia -Certain subgroup analyses had lower N values than others

			hospitalization	effective exposure over its oral formulation	
Anderson, et. al., 2017	Retrospective cohort analysis of prospective observational REACH-OUT study	-763 patients with schizophrenia, if initiated treatment with risperidone or PP 8 weeks prior to enrollment or at least 24 weeks prior to enrollment without gaps in between injections >30 days	-Treatment outcomes assessed at 1 year were discontinuation and adherence, measured by proportion of days covered (PDC) or medication possession ratio (MPR) -Discontinuation in the enrollment regimen consists of any changes in treatment, medication substitutions, or stoppage -MPR = days covered by injection or Rx from initiation to d/c, n / days from initiation to d/c, n -PDC = days covered by injection or Rx from enrollment to 12 mos, n / 365 days	-27% of patients discontinued their PP regimen as compared to oral antipsychotics (51%) with a p-value of less than 0.001, thus PP use had significantly lower rates of discontinuation -PP also had a higher medication possession ratio in addition to 10x increased achievement of proportion of days covered -PP users were more likely than oral antipsychotic users (OAT) to be male, single, on Medicare/Medicaid, smokers with underlying lung conditions, and living with chronic schizophrenia for a longer duration -PP users were less likely to be of Hispanic origin or live in private residences -PP users were significantly more adherent than OAT users, as evident by for the MPR and the 1-year PDC metrics -Predictors for d/c include nonadherence, # of hospitalizations, substance abuse, and comorbid dx -The strongest predictor of tx adherence was PP use and was highly associated with remission -Other predictors of remission are female gender, education status,	-PP users were a combination of both new users and continuing users, which may have skewed the data more favorably for PP over OAT -PDC was calculated for all participants upon enrollment, regardless of actual f/u status

				satisfaction with social relations, favorable attitude towards medications, and lack of lung conditions	
Pilon, et. al, 2017	Retrospective study	-Participants were chosen from claims data for Medicaid in Florida, Iowa, Kansas, Mississippi, Missouri, and New Jersey to identify adult patients with schizophrenia, resulting in 3307 patients on second-generation long-acting injectable therapies (SGA-LAIs) and 21, 355 patients on oral atypical antipsychotics (OAAs)	-Study outcomes included treatment adherence and persistence, health care resource utilization (HRU), and Medicaid spending -Adherence was also measured in PDC like Anderson, et. al. -Persistence to index tx was defined as having continuous supply of medications with no gaps at 30, 60, 90 days, and at 12 months -HRU was measured by frequency of healthcare visits (inpatient, outpatient, 1-day mental institute vists, long-term care admissions, mental health institute visits), and length of stay -Medicaid expenditure was measured by total healthcare costs (both medical and pharmaceutical)	-SGA-LAI patients were generally younger with fewer comorbidities -SGA-LAI patients were more likely to be adherence than OAA patients, especially at 12 months -SGA-LAI patients were associated with fewer long-term care visits and home care services (statistically significant $P < 0.001$) but with more health institute and 1-day mental health institute visits as compared to those on OAA -SGA-LAI patients had lower medical costs than compared to OAA patients, averaging $168 less -Increased adherence was driven mainly by PP-LAIs whereas adherence among aripripazole-LAI and risperidone-LAI were similar to that of OAA patients	-Only 6 states were included in this study, which may not be inclusive of the patient demographics in other states -Data stemmed from Medicaid databases, which are subjective to possible inaccurate billing and/or missing information -Medicaid spending did not account for rebates or discounts, which may have driven the pharmaceutical costs higher than estimated (as compared to the real world)
Alphs, et. al, 2015	RCT – randomized, open-label, review-	-Participants were diagnosed with schizophrenia	-Primary end point was time to 1st treatment failure (from arrest or	-PP was superior to oral antipsychotics in delaying time to 1st treatment failure with $P = 0.011$	-Although the number of study visits was similar for PP

	board, blinded, multicenter, 15 month study	and history of incarceration, randomly assigned to once per month PP injections or daily oral antipsychotics -Participants were enrolled in 50 sites across 25 states in the US and Puerto Rico with strong efforts to recruit subjects from homeless shelters, soup kitchens, and jail-release or diversion programs	incarceration, psychiatric hospitalization, suicide, tx d/c, or supplementation due to inadequate efficacy, safety, or tolerability -Throughout the 15 months, study visits occurred on day 8, day 15, day 38, and monthly thereafter -Secondary outcomes measured included time to 1st psychiatric hospitalization or arrest/incarceration, change in Personal and Social Performance Scale (PSP) scores, and change in Clinical Global Impressions-Severity of Illness scale (CGI-S) score	(median time of 416 in PP and 226 in oral antipsychotics) -The most common reasons for 1st treatment failure were arrest/incarceration and psychiatric hospitalization -There was no significant difference in PSP scores between the two groups -The most common adverse reactions for PP include injection site pain, insomnia, weight gain, akathisia, and anxiety as compared to headache, dry mouth, anxiety, and sedation in the oral antipsychotic group -Overall, in the US, the criminal justice system has overtake psychiatric hospitals as a site for institutionalization, thus the outcomes for this vulnerable population may be improved by PP medication choice	and OAA patients, it is uncertain how many Rx were filled for the oral group and whether the patients took their medications as directed upon prescribing -There may be some selection bias since subjects who were not willing to receive LAI therapy would not have enrolled

Conclusion(s):

Kim et. al., demonstrated that risk of failure was 34-41% higher with oral antipsychotics than with long-acting injections (PP). The most commonly deselected oral antipsychotics were haloperidol and perphenazine due to their side effect profile. Compared with PP, the risk of treatment failure was 39% higher with oral delivery of paliperidone or similar medication, which suggests that delivery of medication (injection vs. oral) plays a role in treatment adherence. PP also has a longer half-life than its oral counterpart, contributing to longer duration of continuous effective exposure over its oral formulation.

Anderson et. al., demonstrated that compared to oral antipsychotics (OAT), PP was associated with higher rates and improved adherence, less frequent discontinuation of treatment, treatment stability, and improved symptom remission. PP therapy would be especially helpful in patients who fail other OAT regimens. Additionally, PP users were more likely than OAT users to be male, single, on Medicare/Medicaid, smokers with underlying lung conditions, and living with chronic

schizophrenia for a longer duration. PP users were less likely to be of Hispanic origin or live in private residences.

Pilon et. al., demonstrated that patients with Medicaid on second-generation long-acting injectable therapies were observed to have improved adherence, longer persistence, and lower medical costs, which is consistent with previous studies. Additionally, these patients had fewer long-term care visits and home care visits as compared to OAA patients. Paliperidone-palmitate LAI patients were associated with significantly lower medical costs that offset almost half of the increase in pharmaceutical related costs relative to those on OAAs.

Alphs et. al., demonstrated that PP was superior to oral antipsychotics in delaying time to first treatment failure in which the most common reasons included arrest, incarceration, and psychiatric hospitalization. In addition, this study looked into the adverse effects of PPs and OAAs, which consist of injection site pain, insomnia, weight gain, akathisia, and anxiety for the PP group and headache, dry mouth, anxiety, and sedation in the OAA group.

In conclusion, patients on long-acting paliperidone palmitate have decreased risk of treatment failure, delayed time to first treatment failure, improved adherence, longer persistence, and lower medical costs, which has been consistent in all of the aforementioned studies and in previous studies. Additionally, PP users were more likely than OAT users to be male, single, on Medicare/Medicaid, smokers with underlying lung conditions, and living with chronic schizophrenia for a longer duration and less likely to be of Hispanic origin or live in private residences. The most common adverse effects reported in PP use include injection site pain, insomnia, weight gain, akathisia, and anxiety.

Clinical Bottom Line:

The first article (an RCT) compared long-acting PP injections to seven other conventional oral antipsychotics, as well as looking into the side effect profiles of these medications. There was an N of 444, the study was conducted over a length period of time (15 months) and the authors made a strong effort to include participants otherwise excluded in other studies, such as those who were incarcerated, which contribute to its strengths. Compared with PP-LAI, the risk of treatment failure was significantly higher with oral delivery of paliperidone, which suggests that delivery of medication (injection vs. oral) plays a role in treatment adherence, possibly due to increased half-life that requires less management.

Even though the second article (a retrospective cohort analysis) was not of highest evidence, it still provided us with valuable information because the authors identified that PP therapy would be especially helpful in patients who fail other OAT regimens. Additionally, they discovered the patient population that were more likely to use PP, which were identified as male, single, on Medicare/Medicaid, smokers, and living with chronic schizophrenia for a longer period of time. The study also highlighted some factors that contributed to stopping treatment, which is helpful in practice so we could educate patients and prevent non-adherence before it occurs.

The third article (another retrospective study) takes patient adherence and quality of life one step further and relates them to treatment patterns and healthcare spending and resources. This information is important since it looks at the bigger picture at how individual patients with

schizophrenia are affecting spending and resources on a larger, hospital scale setting. Additionally, there were many participants (3307!) but they were recruited from only 6 states. In future studies, we should aim to include patients from as many states as possible.

As for the fourth article, even though it dates back to 2015, this RCT looked into the effectiveness of paliperidone injection in terms of the clinical features in addition to real-world design elements. The authors set up a realistic environment for the study since they included flexible dosing and use of concomitant medications. Although this may allow for more sources of bias or more confounding factors, in reality, patients are normally not on the same dosages of anti-psychotics and most of them take more than one medication at a time. Additionally, this study included patients with comorbid substance abuse since substance abuse is found at a higher incidence in patients with psychiatric disorders, history of incarceration (true for this as well), and with unstable living conditions (also true), providing us with information that relates more to actual, real life patients.

In conclusion, patients with past psychiatric history of schizophrenia or newly diagnosed patients should be given the option to either take oral antipsychotics daily or be given long-acting injections such as Invega Sustenna. Utilizing such injections in schizophrenic patients are associated with increased treatment adherence, better management of symptoms, decreased risk of discontinuation, and reduced hospitalization rates for relapses, which ultimately reduce healthcare and hospitalization costs and resources. In turn, this may also increase patient quality of life since long-acting injections may be more convenient and prevent patients from becoming hospitalized due to medication non-adherence. As always, it is important to monitor the side or adverse effects of using long-acting injections and select the best option for each patient.

Going forth, we now have enough evidence to conduct a meta-analysis or systematic review, which I have not seen as of yet. This should provide the higher level of evidence needed to further support the use of long acting injectables in practice to increase treatment adherence, better manage symptoms, decrease risk of discontinuation, and reduce hospitalization rates for relapses.