TRENDS-in-MEDICINE

June 2014

by Lynne Peterson

SUMMARY

The ASCP meeting offered a peek at both the good and the bad news in psychopharmacology drug development.

Researchers are struggling with trial design issues, especially assay sensitivity and the increasing rate of placebo response, and a slowdown in big pharma interest in pain, schizophrenia, and depression.

Promising drugs include:

- **Alcobra**'s metadoxine ER for ADHD.
- **Alkermes**' ALKS-5461 for depression and aripiprazole lauroxil for schizophrenia.
- **Cerecor**'s CERC-301 for depression.
- **Intra-Cellular Therapies**' ITI-007 for schizophrenia and more.
- **Johnson & Johnson**'s Ketanest, a nasal ketamine for depression.
- **Pherin Pharmaceuticals**' aloradine for anxiety.

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AMERICAN SOCIETY OF CLINICAL PSYCHOPHARMACOLOGY (ASCP)
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The annual meeting of the American Society of Clinical Pharmacology (ASCP) is a forum for issues in clinical research in psychiatry. It used to be known as the NCDEU (New Clinical Drug Evaluation Unit) meeting and was sponsored by the National Institute of Mental Health (NIMH). Now, it is run by ASCP but with the partnership of NIMH, the National Institute on Drug Abuse (NIDA), the National Institute on Alcohol Abuse and Alcoholism (NIAAA), and the FDA.

A lot of big pharmas have pretty much exited the psychopharmacology development area. There is still a lot of work being done in multiple sclerosis and Alzheimer's disease, but pain, schizophrenia, and depression have quieted down.

Daniel Burch, MD, vice president and therapeutic area head for neuroscience at Pharmaceutical Product Development (PPD), a contract research organization (CRO), said, "Neurology is busier than it ever has been…but psychiatry is in a little bit of a lull…Big pharma will jump back into depression and schizophrenia if cognition targets work out."

A key issue in the field right now is the lack of assay sensitivity, which he said was a big topic of discussion at the ASCP meeting – and which is good for his business, "If you have a dramatically impactful drug, then you can show an effect on a small sample size, but these diseases are complex and pretty intractable…The challenge now is finding the right targets and making sure you have the right assay…A lot of this meeting is about trial methodology."

Dr. Burch said another hot topic right now is the placebo response in clinical trials, "There is some natural force going on that we don't understand…Placebo response in depression trials has been going up, up, and up. Why? There are lots of reasons it might be going up, but no one knows for sure…And as placebo goes up from 20% to 30% to 40%, it is much more difficult to show separation from the active drug…What can be done about it? Are we getting the patients in the trials? At the end of the day, a lot of this is very sub-jective. There are even websites where people can learn to be depressed subjects to get in trials. That is particularly a problem in southern California, New York, and Florida."

Among the other points about specific disorders that Dr. Burch made were:

- "For **Alzheimer's** I don't think we will come up with something dramatic; probably it will be a cocktail that slows the disease or improves symptoms or a combination of both…We will see what happens with the BACE inhibitors and beta-amyloid, but there are other things being investigated for symptoms."

- "**Autism** drugs have been disappointing [so far]."
- "**Degenerative diseases** are tough. We don't understand all we need to know about the biology. We need a lot of basic research and translational stuff to say will it turn into something meaningful in the lab."
- "In **depression**, the jury is not quite out on NMDA antagonists and ketamine drugs…Depression is still an area of high unmet need. The problem there is assay sensitivity… The only drugs approved for depression work through the monoamine pathway (serotonin, dopamine)…If the Alkermes drug [ALKS-5461] is successful, this will be the first approval not in that pathway, so it is pioneering in that perspective…The trial design is unusual but it may be a good way to help with assay sensitivity…And I would watch the Intra-Cellular Therapies drug [ITI-007]…The NMDAs work in people who failed other therapies and will be rapid acting."
- "In **multiple sclerosis**, neuroprotection is the next frontier. Anti-CD20s will be really good advances, and they have to top that. They have to find ways to get nerves remyelinated."
- "In **pain**, we still have the opiates, the COX-1 and -2 inhibitors, and Neurontin [Pfizer, gabapentin], but not much else. It is kind of like Alzheimer's disease – a pretty tough nut to crack. The key may be to go after syndromes…The 5-HTP inhibitors – on top of acetylcholinesterase inhibitors – for symptomatic Alzheimer's are interesting." Companies to watch in this space: Lundbeck, Otsuka, and GlaxoSmith-Kline.
- "**Schizophrenia** is in a little lull right now. There is a lot of cognition work being done. The nicotinic receptor antagonists are very important there…Will they be dramatic? Probably not. You will probably need 200-500 patients to show a difference."

THE PSYCHOPHARMACOLOGY PIPELINE: POTENTIAL WINNERS

A session on drugs in the psychopharmacology pipeline highlighted some possible winners – and a few failures.

ALCOBRA PHARMA's metadoxine extended-release – a synthetic antioxidant for ADHD and cognitive disorders

Jonathan Rubin, MD, MBA, chief medical officer of Alcobra, an Israeli specialty pharma, said that the immediate-release formulation of this drug has been approved in some countries since the 1980s to treat alcohol intoxication and alcoholic liver disease. Alcobra's proprietary dual-release formulation was granted orphan drug status by the FDA in December 2013 as a potential pro-cognitive agent in Fragile X syndrome, a genetic disorder that causes intellectual disability, behavioral and learning challenges, and various physical characteristics, but it also is being investigated in ADHD and other cognitive disorders.

Dr. Rubin described it as rapidly effective with no potential for abuse or addiction in animal models. The mechanism of action is not yet fully understood, but he said it is monoamine-independent, a GABA/glutamate modulator, and a serotonin 5-HT_{2B} receptor antagonist.

Completed Phase II trials include:

- A 120-patient, 6-week Phase IIb study in Israeli adults with ADHD. The primary endpoint was CAARS-INV, which Dr. Rubin said is an accepted endpoint by the FDA for registration studies, and the drug showed a "moderate" effect (0.4 point effect size), which started at Week 2 and continued out to Week 6. In a subgroup of predominantly inattentive ADHD patients, there was a bigger effect (0.9). He said, "That is considered a strong effect size…We see a preferential effect on the predominantly inattentive subtype, and we believe that merits further exploration." In terms of safety, there were no serious adverse events, some nausea and initial insomnia, but no effect on appetite or mood.
- A 36-patient, crossover, single-dose Phase IIb study in ADHD. The high dose (1400 mg) significantly improved the TOVA ADHD score ($p=0.009$), but the low dose was not significant.

A 300-patient Phase III trial in ADHD is underway in the U.S. and Israel with the 1400 mg dose, and a pediatric ADHD study is expected to start soon. A Phase IIb study in Fragile X adolescents and adults is about to start, with a pivotal Fragile X study planned for 2015.

INTRA-CELLULAR THERAPIES' ITI-007 – a serotonin 5-HT_{2A} receptor antagonist for schizophrenia, bipolar disorder, and other neuropsychiatric indications

Kimberly Vanover, PhD, vice president of clinical development at Intra-Cellular, said that a 335-patient, placebo-controlled Phase II trial in acute schizophrenia met the primary endpoint (PANSS score change) with the low dose (60 mg QD) but not with a higher dose (120 mg QD), adding, "We can't fully explain that." But she said the company is taking the 60 mg dose forward into Phase III.

Dr. Vanover said, "Unlike risperidone, it improved negative symptoms, especially in patients with negative symptoms at

baseline…There was significant improvement in certain PANSS subscales consistent with improved social function, and significant improvement in other prosocial measures, such as reduced depression…There were also anecdotal reports of more social interaction – patients coming out of their rooms… We did a post hoc analysis, and the 60 mg dose had a statistically significant improvement in the prosocial PANSS factor score, with an effect size of 0.6, which is encouraging."

In terms of safety, she said the drug was safe and well tolerated, with no cardiovascular issues, adding, "Unlike risperidone it does not cause sustained tachycardia…Numerically, there is less weight gain than risperidone. And there was no increase in suicidal ideation or behavior."

A Phase III trial in acute schizophrenia is in the planning stage.

JOHNSON & JOHNSON's Ketanest (esketamine) – an NMDA receptor antagonist in treatment-resistant depression

Several companies have tried to develop a ketamine for treatment-resistant depression (TRD), including BioLineRx, Cypress Bioscience, and Johnson & Johnson. So far, nothing has been really successful, though experts continue to believe the drug has utility, with quick onset. The drug is generally safe but has CNS symptoms in ~50% of patients.

J&J's version is an intranasal spray formulation that is still in clinical trials.

The key issue is whether the FDA and/or the Drug Enforcement Administration (DEA) would ever approve any formulation of a drug known to illegal drug users as "Special K" because of the abuse potential.

NEUROVANCE's centanafadine (EB-1020) – non-stimulant for adult attention-deficit/hyperactivity disorder (ADHD)

Timothy Wilens, MD, a pediatric psychopharmacologist from Massachusetts General Hospital, said this drug has "strong biological plausability," and in preclinical studies it looked "almost identical to placebo and very different from amphetamine" in terms of abuse liability. Human abuse liability studies are underway. Dr. Wilens said studies show the standard-release formulation has no food effect and no insomnia but a small, dose-related increase in heart rate consistent with what is seen with norepinephrine.

Top-line results from a 4-week pilot study in 40 adult males with ADHD showed a statistically significant change in ADHD-RS-IV, which Dr. Wilens described as "a very positive, very dramatic response – from 40 to ~17…The efficacy is reminiscent of lisdexamfetamine [Shire's Vyvanse], a very significant reduction. They also showed improvement across the board on scales of executive function at Week 4, a signal that executive function improves as well as ADHD symptoms." There was no immediate relapse with discontinuation. A Phase IIb trial is planned.

PHERIN PHARMACEUTICALS' aloradine (PH-94B) – a synthetic neuroactive intranasal steroid for acute symptoms of anxiety

Michael Liebowitz, MD, founder and former director of the Anxiety Disorders Clinic at the New York State Psychiatric Institute and a member of Pherin's scientific advisory board, said an early study showed decreased heart and respiratory rates, increased alpha EEG and body temperature, with some subjects spontaneously reporting feeling distinctly calmer and more relaxed.

A randomized, double-blind, 91-patient, longitudinal Phase II trial in social anxiety disorder found that symptoms were reduced in 75.6% of aloradine patients vs. 37% of placebo patients. Both performance anxiety symptoms and social interaction anxiety were reduced during a public speaking challenge, and the effect was quick (within 15 minutes). After an end-of-Phase II meeting with the FDA, the company is revising its Phase III protocol and expects to start Phase III trials this year.

Dr. Liebowitz also said a study is just getting going where patients rate themselves in real-life situations.

THE PSYCHOPHARMACOLOGY PIPELINE: THE LOSERS

The pipeline session also included a few failures.

ASTRAZENECA

- **AZD-8529 – an mGluR2 modulator for schizophrenia.** Alan Cross, PhD, senior director of neuroscience at AstraZeneca, said a Phase IIa trial found no significant improvement in cognitive performance or reduction in clinical symptoms vs. either placebo or Johnson & Johnson's Risperdal (risperidone). Dr. Cross said, "Whether a different treatment regimen and adjunct treatment would provide a benefit remains to be determined…We have done a lot of ad hoc analyses, and nothing stands out…Ad hoc analyses have failed to identify a subgroup of responders."

- **Lanicemine (AZD-6765) – an NMDA channel blocker for depression.** Two posters reported on the results of the Phase IIb PURSUIT study, in which two doses (50 mg and 100 mg IV) failed to beat placebo in major depressive disorder (MDD). In fact, the Kaplan-Meier curves were nearly identical on the MADRS score. Post hoc analyses suggested the explanation could be high placebo response, less stringent criteria for treatment resistance, lower baseline severity of depression, the level of study center experience, and more. It is not clear whether AstraZeneca is abandoning this drug, but the company reportedly has a "family" of compounds in the cupboard.

JOHNSON & JOHNSON/JANSSEN and ADDEX PHARMACEUTICALS' JNJ-40411813/ADX-71149 – an mGluR2 PAM modulator for major depressive disorder

Justine Kent, MD, a psychiatrist with Janssen, said a 121-patient, multicenter, placebo-controlled Phase II trial in MDD with anxiety symptoms missed the primary endpoint ($HDRS_{17}$ score), but it did show efficacy in some other measures, including $HDRS_{17}$, HAM-D6, and IDS-30.

In the second part of the study, where patients who did not respond to placebo were re-randomized to drug or placebo, there was a clear separation between drug and placebo, suggesting that a sequential parallel comparison design (SPCD) trial design might show positive response. To confuse things even more, the high dose performed worse in the first phase of the study but better in the second phase. In terms of adverse events, there was significant dizziness (34%) and vertigo (23%) – as has been seen with other mGluRs. Dr. Kent said the dizziness is probably a class effect.

Dr. Kent concluded, "While an efficacy signal is evident, the totality of the data suggest a lack of a strong drug effect."

TARGACEPT's TC-5619 – an alpha7 neuronal nicotinic receptor (NNR) agonist in schizophrenia

David Hosford, MD, PhD, vice president of clinical development and regulatory affairs at Targacept, described a "registration-quality," 185-patient, 24-week Phase IIb trial conducted in the U.S. and India – that failed to show a benefit on the primary endpoint – a composite SANS score at both doses tested (5 mg and 50 mg) – or any of the secondary endpoints.

Dr. Hosford said the one small good news was a positive effect in smokers, but he said that was probably a false positive.

VOYAGER PHARMACEUTICALS' leuprolide acetate – an anti-androgen for Alzheimer's disease

Richard Bowen, MD, a primary care physician with OTB Research in Charleston SC and a co-founder of Voyager, reported on the 48-week, double-blind, 109-patient ALADDIN study of women given leuprolide (AbbVie's Lupron) for Alzheimer's disease (AD), and this anti-androgen therapy failed on both primary and all secondary endpoints.

However, Dr. Bowen said there is anecdotal evidence suggesting a synergistic effect with acetylcholinesterase inhibitors, and an a priori analysis of the trial data did show a statistically significant effect on ADAS-COG and CGIC, particularly a slowing in decline in both. The study was sponsored by Voyager Pharmaceuticals, not AbbVie.

MORE INVESTIGATIONAL DRUGS IN DEPRESSION

ALKERMES' ALKS-5461 [buprenorphine + samidorphan (ALKS-33)] – a partial mu agonist (buprenorphine) + a mu antagonist (samidorphan)

Alkermes believes this combination will provide efficacy with less or no euphoria or abuse potential. In a Phase II study the combination was superior to placebo in improving depressive symptoms. There were several posters on this combination drug at ASCP.

- A rat study looked at the method of action.
- A dose-finding, multicenter, double-blind, placebo-controlled Phase II trial study, using an SPCD design, found that a 1:1 ratio (2 mg of each drug) was the best combination. An Alkermes official said the company plans to explore doses lower than 2 mg/2 mg.

SPCD is a new trial design developed by Maurizio Fava, MD, and David Schoenfeld, MD, of Massachusetts General Hospital. It utilizes two stages of treatment – first stage where the investigative drug is compared to placebo, and a second phase that only studies placebo non-responders, who are re-randomized to either drug or placebo. Alkermes reportedly has said the FDA has agreed to accept an SPCD structured trial for registration, and Alkermes officials at ASCP said that SPCD will be used in the Phase III trial of ALKS-5461, but they would not say whether the FDA is requiring other analyses as well, but one official said, "It is a complex design."

This design is aimed at eliminating placebo response, so the true drug effect can be seen. The problem will be that in clinical practice there is no way to identify the placebo responders. In an oncology trial, it is likely the FDA would

require a companion diagnostic, but there is no equivalent diagnostic in psychopharmacology.

What do experts think about the SPCD design, the FDA approvability of a drug using the design, and the implications for clinical use of a drug approved using the design?

- "It lowers the expectation of the clinician and the patient. It is probably a passing thing."
- *William Potter, MD, PhD, a senior advisor at the National Institute of Mental Health:* "Because the treatment is so safe, any way we can enrich the patient population and show an effect is okay, but it doesn't tell you how to select patients in the real world. The FDA will accept SPCD [for registration]."
- "SPCD could be a negative by getting you to continue development of a drug that will fail."
- "It's far from real life…The Achilles heel with SPCD is the same as with crossover studies – the person in the second arm is not the same person."
- "It's a good design. It solves the problem of the increasing placebo response."

A researcher for another company said he had heard that ALKS-5461 will have to be a DEA-scheduled drug.

Week 4 Results in Phase II Trial of ALKS-5461

Measurement	Placebo	ALKS-5461	
		2 mg/2 mg	8 mg/8 mg
HAM-D17 change in all patients	– 7.1	– 9.3 (p=0.006)	– 6.6
HAM-D17 change in placebo non-responders	– 1.2	– 5.3 (p=0.013)	– 3.6
MADRS change in all patients	– 9.6	– 13.3	– 11.4
MADRS change in placebo non-responders	– 1.8	– 8.7 (p=0.004)	– 5.0

CERECOR's CERC-301 – an NMDA inhibitor

A poster was presented on the Phase II trial design for this oral agent (which is specific to NR2B), using a variation of SPCD. The focus with this agent is on the rapidity of the effect. It was "repurposed" from Merck (MK-0657) which had tested it unsuccessfully in Parkinson's disease. Data are expected by the end of 2014. The company has not yet found a partner to take CERC-301 into Phase III.

There is a chance this might not be a DEA-scheduled drug. An investigator said, "It has a half-life of 14 hours, so lacks the classic signal of abuse drugs." But he admitted addiction studies will need to be done.

LONG-ACTING INJECTABLE (LAI) ANTIPSYCHOTICS

First-generation vs. second-generation LAIs. At a session on LAIs, Taishiro Kishimoto, MD, PhD, a psychiatrist from Keio University School of Medicine, reported on a meta-analysis of 21 randomized clinical trials with a total of 5,130 patients, comparing LAIs to oral antipsychotics. Surprisingly, the LAIs were no better than the oral drugs. When just double-blind, double-dummy studies were examined, there was still no difference between LAIs and orals. And when trials of the same active ingredient were compared, again there was no difference between LAIs and orals.

However, when first-generation LAIs were compared to second-generation LAIs, there was a difference. First-generation LAIs were significantly superior to oral agents, but second-generation LAIs were not. When older studies were compared to newer studies, LAIs beat orals only in the older studies, not in the newer studies.

So, how did Dr. Kishimoto explain these counter-intuitive findings? He said it could be due to differences in relapse definitions, selection bias, or even publication bias (negative studies may not have been published in the past).

Second-generation oral antipsychotics vs. LAIs. Nina Schooler, PhD, a psychiatrist from Zucker Hillside Hospital, described the 305-patient, 30-month PROACTIVE study comparing second-generation oral antipsychotics with LAIs, which found orals numerically superior but not statistically different from LAIs on the primary endpoint of time to relapse. Time to first hospitalization also favored orals, but not significantly. On psychosis symptoms, the LAIs did a little better than the orals.

Asked how there can be a difference in psychosis symptoms that doesn't translate into a difference in relapses, Dr. Schooler said, "At the beginning ~20% of patients are psychosis symptom-free when they enter the trial…That bounces around for orals…but with patients on LAIs it increases to almost 40% of patients…This is an interesting finding. I would have expected patients who were psychosis-free to do better on a scale of functioning, and we didn't see an improvement in that."

Paliperidone vs. haloperidol. Joseph McEvoy, MD, a psychiatrist from Duke University, reported on the result of the ACLAIMS trial comparing monthly paliperidone (Johnson & Johnson's Invega Sustenna) and haloperidol. There was no difference between the two drugs on the primary endpoint of

rate of failure (relapse) within 8 weeks (33.8% vs. 32.4%). In fact, the Kaplan-Meier curves were virtually identical.

And there was weight gain with paliperidone vs. weight loss with haloperidol (+2.17 kg vs. -0.96 kg). There was no difference between the two drugs in tardive dyskinesia or Parkinson measures, but there was more Barnes akathisia with haloperidol.

Paliperidone vs. risperidone. A J&J poster reported on a retrospective claims database analysis which found that patients switching from Johnson & Johnson's Risperdal Consta (risperidone monthly) to Invega Sustenna had a lower risk of schizophrenia-related relapse and a longer duration of therapy than patients switching from Risperdal Consta to an oral antipsychotic.

Other Investigational Agents in Schizophrenia

AbbVie's ABT-126 – a selective alpha7 nicotinic acetylcholine receptor agonist that failed

A Phase II study presented in a poster at ASCP tested 2 doses vs. placebo. Neither dose showed a significant improvement in MCCB composite score, but there was a definite trend. In the pre-specified subgroup of non-smokers, there was a significant 38% improvement in MCCB score with both doses, but no improvement in smokers. The researchers concluded that it is worth studying ABT-126 further.

Two Phase IIb studies are ongoing and nearly completed with higher doses – a 430-patient study in smokers and a 150-patient study in non-smokers. It should be kept in mind that ~60% of schizophrenics are smokers.

Alkermes' samidorphan (ALKS-33) + olanzapine – a promising mu antagonist + an atypical antipsychotic

A Phase II study has started combining samidorphan + olanzapine in schizophrenia. A company researcher said they think the samidorphan will attenuate the weight gain with olanzapine without reducing its antipsychotic efficacy.

Another Phase II trial is expected to start this summer of this combination in schizophrenic patients with an alcohol problem.

Alkermes' aripiprazole lauroxil – a promising atypical antipsychotic

Alkermes developed the long-acting technology for J&J's Risperdal Consta and Invega Sustenna. Now, the company is developing its own long-acting antipsychotic, aripiprazole lauroxil, a prodrug of Otsuka and Lundbeck's Abilify Maintena (monthly aripiprazole).

The results of a multicenter, double-blind, 12-week, 623-patient Phase III trial of aripiprazole lauroxil vs. placebo in acute schizophrenia were presented in a poster at ASCP. Two doses were tested – 441 mg (comparable to 300 mg Abilify Maintena) and 882 mg (equivalent to 600 mg Abilify Maintena) – and both met the primary endpoint, significantly reducing the PANSS score (a measure of positive and negative symptoms) vs. placebo (-21, -22, and -10 points, respectively).

The results for the two doses were nearly superimposable. As with Abilify Maintena, the efficacy was apparent early (by Day 8) and continued to improve throughout the entire 12 weeks.

The adverse events also were similar to what has been seen with Abilify Maintena and oral daily Abilify (aripiprazole). In particular, the akathisia rate was ~11.3%, which Otsuka researchers said is comparable to their drug. An Alkermes researcher said, "We don't expect a different adverse event label from aripiprazole since we had ~600 patients in our study, and ~25,000 patients have been studied with aripiprazole."

The poster was presented by Srdjan (Serge) Stankovic, MD, MSPH, senior vice president of clinical development and medical affairs at Alkermes. He said, "We are very happy with the effect size with both doses. Another exciting thing is there is such consistency in the effect; the primary endpoint and all the secondary endpoints were met, with the effect starting early and continuing throughout the study…We believe the onset of action is quite impressive…On tolerability, we didn't see anything not expected with oral aripiprazole…What I like is the consistency. This is about flexibility."

Dr. Stankovic said Alkermes plans to file aripiprazole lauroxil with the FDA in 3Q14 for the treatment of acute schizophrenia.

Asked how their drug differs from Abilify Maintena, Alkermes researchers cited several things that differentiate aripiprazole lauroxil:

- **Flexibility in dosing.** Dr. Stankovic said, "Once it is injected, the dissolution is slow…It is a smooth dissolution." Approval will be sought for at least two doses, which will

allow doctors to use either dose – or anything in between off-label. Abilify Maintena only comes in one approved dose. Another Alkermes official said, "In our filing, we will provide dosing recommendations, not necessarily starting all patients at 441 mg."

- **Convenience.** It will come in a pre-filled syringe for easier administration. This is a real advantage since Abilify Maintena requires mixing.
- **Administration.** The low dose (but not the high dose) can be injected into the deltoid (arm); Abilify Maintena must be injected in the buttocks. However, Otsuka also is working on a deltoid version of Abilify Maintena and expects to submit that to the FDA in September 2014.
- **Onset.** The onset of action is quick. As with other long-acting antipsychotics, this drug is expected to have a requirement for an oral antipsychotic for three weeks after the first injection. Dr. Stankovic said the acute data have never been published on Abilify Maintena, but an Otsuka researcher said that Abilify Maintena separates from placebo during the first week, and Otsuka has filed for an expanded label for treatment of acute schizophrenia, and that is currently under review by the FDA.

Alkermes is studying whether the duration of aripiprazole lauroxil can be extended beyond 30 days (e.g., 45 days). There is a hint that the drug lasts longer than 30 days, and that might give doctors and patients a little wiggle room with when the next dose has to be administered.

Alkermes officials said the company also is working on other durations of action (possibly a Q3M dose), but Lundbeck is working on a Q3M formulation of Abilify Maintena, and Johnson & Johnson has a Q3M formulation of Invega Sustenna under review by the FDA now.

Is there a need for another long-acting injectable (LAI) antipsychotic? Dr. Stankovic said, "This is not about competing with other LAIs but about getting practices to get more comfortable with LAIs and increase their use. Right now, fewer than 10% of schizophrenics are on an LAI."

Psychiatrists who viewed the data on aripiprazole lauroxil generally described it as a me-too but were receptive to another option, depending on price and insurance coverage. There was little excitement about it, but doctors were receptive to the idea, and they did like some of the features. Many said use will depend on marketing. Among the comments were:

- "Patients did very well on it."
- "The side effect profile looks impressive. I see more akathisia with oral aripiprazole. There is no real advantage over the existing Abilify Maintena except for the higher dose, but it is another option. It's all a marketing play."
- "Whether I use it will depend on the side effects."
- "The only difference is the delivery technology."
- "It is nice data, but it is the same drug. It is another option. The deltoid injection is an advantage."
- "The higher dose of Abilify was worse than the lower dose [on the pivotal trial], but the FDA still approved it, so I think the FDA will approve both of these doses."
- "It has two doses, comes in a pre-filled syringe, and there is more give at the end of the month if someone misses a dose. Having that window would be nice – but when someone has been on a long-acting antipsychotic for a long time, it is not a disaster if they don't take the next dose exactly 30 days later."
- "Abilify Maintena is the only long-acting antipsychotic that I use because of the lower rate of prolactinemia…If this were available, I might use it as a first option in 20% of my patients during the first year. It would be especially good for erratic patients who have a pattern of missing shots. And the pre-filled syringe means less work for my nurses and my office."