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SUMMARY

It was a positive meeting for: Bristol-Myers Squibb's new antipsychotic, **Abilitat** (aripiprazole), Forest Labs' new SSRI **Lexapro** (escitalopram), and Johnson & Johnson's **Risperdal**, which has seen a resurgence in use due to the problems that have arisen with Lilly's **Zyprexa**. Doctors also are excited about the new IM version of risperidone (**Consta**) that is expected to be approved by the FDA later this year. Lilly appears to have several winners in development, including **atomoxetine** for ADHD, **duloxetine** (Cymbalta) for depression and the anxiolytic **mGLuR**, but the outlook for **Zyprexa** and **OFC** (combination Zyprexa+Prozac) is more iffy. Merck continues to have the lead in NK-1s with its **Substance P** for anxiety, pain and depression. Questions still remain about the oncogenicity of Pfizer's **pregabalin**. CRF antidepressants are a promising area of research, but it is not clear which company has the lead.

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The APA meeting this year conflicted with several other important medical meetings, so this report will focus on issues affecting some of the key psychiatric drugs in development, by company rather than offering a comprehensive overview of the complete conference.

Overview by Drug Class

SSRIs

A speaker predicted:

- The SSRI market will be dominated by Lexapro (escitalopram, Forest Labs) and duloxetine (Lilly's Cymbalta). They will get the same off-label use as all other SSRIs, but label expansion will expand their marketing capabilities."
- "It is the nature of these patients to switch around. Most people switch three times before deciding to stick with one therapy. Therefore, there is a lot of opportunity for cannibalization."
- "Insurers and physicians may push the generics now that there are more options."
- "There my be a backlash against generic Paxil (GlaxoSmithKline, paroxetine), with people saying that it doesn't work as well as other agents…It won't solve the problem if you stop it for two days or halt therapy."

Three issues with SSRIs continue to get attention.

1. **Weight gain**. One solution, speakers said, is switching to GlaxoSmithKline's Wellbutrin (buproprion). Another is to add an additional agent, such as Topamax (topiramate, Johnson & Johnson). A speaker said, "Over the last 10 years the population of the U.S. and the world has tended to put on a few pounds; 40%-50% of the U.S. population is overweight, and a third is obese. Our patients reflect the general population. When patients are depressed, they eat less and lose weight. When you treat the depression, they regain the weight lost." Another speaker said, "In a 12-week trial, patients on fluoxetine (Lilly's Prozac) gained 14%, and those on paroxetine gained 11%. All the studies show the same thing – an increase in weight from baseline. A six-month study found that patients on paroxetine gained more weight than those on sertraline or fluoxetine. An eight-month study of 541 patients found that, on average, patients gained three pounds with Paxil and one pound with placebo. A one-year trial of Wellbutrin, found patients actually lost weight with Wellbutrin. Wellbutrin is the only antidepressant that can potentially cause weight loss. That's why it is also being studied for patients with primary obesity – in patients who are not depressed." A third expert said, "To manage the weight gain, you can add Wellbutrin as adjunctive therapy. Or, you can use Topamax in patients who have a lot of weight gain."

2. **Withdrawal symptoms.** A speaker said, "Paroxetine and venlafaxine (Wyeth's Effexor) are most likely to cause withdrawal. Do long-acting SSRIs like fluoxetine cause less withdrawal or discontinuation? We don't know. Potentially, yes, but not necessarily. We actually can abruptly switch patients from one SSRI to another. The drug interaction story today is as uncomplicated as when fluoxetine was launched. As long as you stay away from Serzone (nefazodone, Bristol-Myers Squibb) and Prozac, you won't run into many interactions. And we can manage drug interactions by choosing antidepressants that don't affect the P-450 enzymes. Compliance is the key to long-term outcomes, and side effects are one reason for non-compliance."

3. Sexual dysfunction. A speaker said, "Our primary care colleagues underestimate the amount of sexual dysfunction from antidepressants. The prevalence is 30% with citalopram (Celexa, Forest Labs). The odds are greatest of developing sexual dysfunction with citalopram and venlafaxine XR – then sertraline, paroxetine, the fluoxetine, and buproprion SR – in that order. The antidepressants with low or no sexual dysfunction are buproprion, mirtazapine (Organon's Remeron), and nefazodone." Another speaker noted, "There is no FDA-approved medication available for treatment of antidepressant-induced sexual dysfunction – decreased libido, lubrication and ejaculation. Everything is off-label."

Treatment options for SSRI-induced sexual dysfunction include:

- Accommodation, which rarely works. Only 10% or less accommodate.
- Reducing the dose, which is very tricky and risks a recurrence of symptoms.
- Drug holidays, which can be terribly misleading to patients. A speaker said, "It is like giving them permission to play with their drug and dose, and it leads to changes in dose without supervision."
- Switching agents.
- Prescribing Viagra (sildenafil, Pfizer) or something similar.
- Trying a dopaminergic agonist or an alpha-2 antagonist.
- Add 150 mg Wellbutrin.

Antipsychotics

Newer agents have taken market share, but problems with Lilly's Zyprexa (olanzapine) have led to a return to Johnson & Johnson's Risperdal (risperidone). Speakers described it as equally as effective as Bristol-Myers Squibb's Abilitat (aripiprazole), though aripiprazole may be more effective longer-term. Risperdal is fairly equal in its side effect profile (specifically weight gain) to aripiprazole, and it has a better side-effect profile than Zyprexa.

Sources predicted that whichever company comes out with an IM depot version of its antipsychotic first will be the winner, with use expected to be high in the hospital and ER settings. One expert said, "This will be critical because there is trend of 'once you put someone on something, you keep 'em on it.'"

Overview by Condition

Sleep Disorders

Conditioned insomnia is an anxiety disorder – someone has a stressful event and then has difficulty falling asleep. Psychiatric disorders also are causes of chronic insomnia. In one study, almost 25% of insomnia cases were due to psychiatric disorders. The most common co-existent psychiatric disorder in those with insomnia is an anxiety disorder. Persistent insomnia is associated with the development of anxiety disorders.

Current options for treatment of insomnia include:

> **Benzodiazepines** (BZDs). These decreased awake time, decrease slow-wave sleep, result in inconsistent REM suppression, and increase sleep spindles. Subjectively, they also increase sleep time and sleep quality and decrease in awakenings. However, they also cause sedation and impaired coordination, especially with long half-life agents, which can result in increased motor vehicle accidents and hip fractures. There also is a potential for tolerance, rebound insomnia, and exacerbation of sleep breathing disorders. So, a speaker cautioned psychiatrists against using BZDs for insomnia." Another speaker said, "There are no long-term studies (longer than 3 weeks) on the use of BZDs for insomnia. Many of us feel that the tolerance issue has been exaggerated. We see many people able to use BZDs long term. It would be nice to identify the factors that determine who will develop tolerance and who won't."

> **Antidepressants.** These generally are not considered good for insomnia, but it is the area that has seen most of the usage growth, a speaker said. SSRIs and SNRIs increase brief arousals, decrease sleep efficiency, and suppress REM. The tricyclics and mirtazapine increase sleep. With SSRIs, the rate of emergent sedation and insomnia is roughly 10%-20%, and they can cause vivid dreams. A speaker explained, "In a patient with residual insomnia, lower the dose, change the time of administration, add a sedative-hypnotic. It is unclear whether there is any value in switching within a class. For refractory anxiety, increase the dose of the medication or add an adjunctive medication. Consider comorbid disorders, substance abuse, and sleep hygiene."

> **Atypical antipsychotics.** Olanzapine increases slow-wave sleep, and an expert said, "It has the very interesting effect of increasing slow wave sleep."

> **Anticonvulsants** such as gabapentin (Pfizer's Neurontin), tiagabine (Abbott's Gabitril), topiramate. Objectively, gabapentin decreases light sleep and increases REM, and there is some suggestion it increases slow-wave sleep. Subjectively, it improves sleep quality and helps with pain disorders.

Future developments in insomnia treatment:

- New dopaminergic agonists with FDA indication for RLS.
- Over-the-counter hypnotics. A speaker predicted, "Within two years we will have two agents with an indication for RLS, and at some point in time we may have OTC hypnotics (including neuro-steroids), and some of the agents may go OTC."
- Agents with multiple indications such as Pfizer's pregabalin, which may have indications for pain and some sleep disorders, perhaps even insomnia. Pregabalin enhances slow-wave sleep dramatically, though the functional consequences of this aren't clear, and it improves sleep efficiency.

Anxiety

Each of the traditional anxiolytics – BZDs, TCAs, MAOIs, beta blockers, buspirone – has problems, including poor tolerability (TCAs, MAOIs), limited breadth of efficacy, lack of antidepressant efficacy, and safety. A speaker said, "If BZDs weren't good, they'd be gone. And we are using very high doses. Everyone does it, but no one really talks about it. They're good, and they're safe, but they're not perfect."

SSRIs have broad spectrum anti-anxiety efficacy. They have become first-line treatment for anxiety and depression, have a favorable side effect profile, are safe in overdose, and are probably easier to take than the other agents. A speaker said, "With the SSRIs we get 60% response, but there is the nagging problem of sexual dysfunction…The SNRI venlafaxine has broad spectrum anti-anxiety efficacy, a favorable side effect profile, favorable pharmacokinetics (i.e., limited drug-drug interactions), is safe in overdose, and has a slightly different pharmacokinetic profile. There is limited information on the anti-anxiety efficacy of buproprion, and nefazodone has a patent issue. The fact is that these may be broader spectrum agents, but we just don't know – and so doctors are not as likely to use them."

Anticonvulsants also are used to treat anxiety. Sources said valproic acid is better than carbamazepine, but both are marginal antidepressants, useful mostly for problematic patients such as alcoholics with social anxiety. But, again, antidepressants are a no-no. A speaker said, "It is hard to use these agents unless there is a good reason. More recently, we are hearing about newer anticonvulsants – gabapentin, Vigabatrin (which inhibits GAMA transaminase), topiramate (which acts at ion gated channels) and tiagabine (which inhibits GABA reuptake)."

There is a pilot study of gabapentin in personality disorder and alcohol withdrawal. A speaker said, "It has some promise in alcohol withdrawal. In fact, there have been blockbuster sales – based on little data — and there may be a reason for that. But we seem to be using a lot of it, and that may portend for the future how we treat anxiety down the line. Gabapentin has fairly potent reuptake, and in high doses, it may be quite popular, so we have to be careful how we proceed with agents; you can overdo a good thing."

Other agents in development to treat anxiety include:

> CRF (*see page 4*)

> NK-1 (*see page 7*)

> Gastrin-like neuropeptides have promise, but the human testing has been equivocal so far, and there appear to be side effect problems (stomach ulcers). Work on these agents appears to have stalled.
  - Anxiogenic
  - C1-988, others

> Partial BZD agonists, including:
  - Pagoclone, which has been shown to be effective in panic disorder.
  - Abecarnil, which has shown some effect in generalized anxiety disorder (GAD), but the effect is not sustained as it is with pagoclone, so it may have died. An expert said, "It seemed to come back in the U.S. briefly after some intensive work. This is a very interesting area. It is promising, but obviously we need long-term data."

> BZD Receptor subunit agonists.

> GABA agents:
  - GABA-A1a – sedation, anxiolytic.
  - GABA-A2a – anxiolytic. There is one A2a (and probably more than one) that seems to have an anxiolytic effect. A speaker said, "These allow a new approach, without the dreaded side effects such as sedation or the physical dependence that we've seen with other agents."
  - GABA A-3a – muscle relaxation.
  - GABA-4a – memory, muscle relaxation.

> Pregabalin (*see page 8*)

> Deramciclane (Pharmacia and Orion), a 5HT2 receptor antagonist which was in Phase III trials in Europe in August 2001.

> Zatosetron (LY-191617), Lilly's 5HT3 antagonist

> Merck's L-365260, a CCK-B receptor agonist in Phase II trials

> Pfizer's CP-65003, in Phase II trials

OVERVIEW OF SPECIFIC DRUGS IN DEVELOPMENT

Corticotropin-releasing factor (CRF)
CRFs are considered one of the most promising areas of depression research. A speaker said, "CRFs are my favorite antidepressant in development. There is a lot of evidence that CRF is hyper-secretive and causes the symptoms of depression." Among the companies working on CRFs to treat depression, acute stress, depression with anxiety, childhood trauma and personality disorder are:

1. Bristol-Myers Squibb
2. Neurocrine Biosciences
3. Taisho: CRA1000 and CRA1001
4. Johnson & Johnson (R121919). The status of this agent is not clear. One expert said, "Johnson & Johnson was working with R121919, but dropped it because of some problems with (irreversible) elevations in liver function. Five other companies are working on CRFs, and all are in Phase I or II." Another speaker said, "A small study (20 patients) of J&J's R-121919 in major depression found a dose-related response (on the HAM-D scale) which is not bad at all. This is promising. It is being studied at 5 mg-40 mg and 40 mg-80 mg." It is possible that J&J is working on a follow-on compound.

ASTRAZENECA'S NAD-99. This is believed to be in Phase II development for treatment-resistant depression. An expert suggested that NAD-99 may be given with an SSRI to make that antidepressant work faster and better." At one large symposium, a speaker described it as promising but another speaker was not so sure.

BRISTOL-MYERS SQUIBB'S Abilitat (aripiprazole). Although aripiprazole has a novel/new mechanism of action that is different from other approved antipsychotics, the clinical advantages of this have yet to be determined.

On the positive side:

+ Long-term side effects are expected to be less than with other agents.
+ There is no QT issue as with Geodon.
+ It is simple to use and dose (once-daily).
+ It causes minimal weight gain.
+ It may lower prolactin levels.
+ It appears to be very effective in preventing relapse.

On the potential downside:

– Sources suggested that aripiprazole may have less efficacy than other anti-psychotics.
– There is a high incidence (~50%) of headache.
– The mid-range dose (30 mg) is the therapeutic dose, and increasing the dose does not increase efficacy. However, a Bristol official said the company is looking at doses up to 90 mg in some pilot studies. A speaker said, "It is coming out in only one dose. People are going to want to use higher doses. At this point, they have 40% activity (which is great in terms of side-effects), so it won't matter if you increase the dose or not."

Overall, aripiprazole's side effect and efficacy profile are getting a very favorable reception in the psychiatric community. Among the comments experts made:

- "In terms of efficacy and the side effect profile, it looks comparable to risperidone and olanzapine. There is no indication it is any better or any worse, but there is minimal weight gain. Whether its mechanism of action is really different from the other atypical antipsychotics is still controversial, but it looks as if it has the same ability to moderately block dopamine activity and work through the nervous system."
- "This is a very patient-friendly medicine…There are very few side effects. A minority of patients (10%) reported somnolence early on during treatment. If you use the typical template of incidence of 5% or more and twice the rate of placebo, there's really no significant side effects to deal with, so this is a very well tolerated medicine."
- "The most common side effects appear to be very time-limited."
- "Aripiprazole has been referred to as a drug that's not too hot but not too cold – a Goldilocks-type drug…There is reason to be optimistic that it could provide some very desirable and potential incremental benefit over existing treatments. It is effective therapeutically and has a very good side effect profile, so people will be willing to take it for a time. They may see, over time, the normalization of their lives."
- "Aripiprazole has great potential. And it might be effective in avoiding sexual dysfunction."

Asked if there are any problems with aripiprazole, an expert responded, "No serious problems, but it is still very early in the game right now. Only 3,000-4,000 people have been treated so far. We need to see 10,000-20,000…It is hard to say which atypical antipsychotic is most likely to be hurt by aripiprazole. There are pricing issues, but the market has been growing steadily." Another expert said, "It looks like a good profile, but doctors are hesitant to get overly excited given the limited data on the drug."

Over time, patients generally stop treatment for one of two reasons: (1) lack of efficacy or (2) intolerable side effects, regardless of whether the drug was working. A speaker said, "In our (aripiprazole) trial, most of the efficacy dropouts occur early because patients haven't responded by day 100. Thereafter, most of the dropouts are due to tolerability. What

we saw was that haloperidol produced a much higher rate of discontinuation than did aripiprazole."
There is some nausea and a little bit of sedation with aripiprazole, but rapid tolerance develops to both those side effects. Other issues that were discussed about aripiprazole include switching, tolerability, weight gain, cardiac toxicity, prolactin elevation, cholesterol effects, efficacy and use in psychiatric conditions other than schizophrenia:

Safe to switch: Bristol-Myers Squibb researchers presented data suggesting that it will be safe and effective to switch patients to aripiprazole from another antipsychotic. One said, "We see that patients switching to aripiprazole from either Zyprexa, Risperdal or haloperidol improved by another 10% or so, and that is clinically relevant and a significant improvement." Another doctor said, "Patients will be switched over to this from the drugs most commonly prescribed. I think there will be an initial spurt (of usage)."

Experts outlined three strategies for switching patients from one drug to another:

1. Abruptly – where a patient's medicine is discontinued and a new medication is started.
2. Add a new medicine at the anticipated dose and then gradually decrease the first medicine.
3. Cross-taper by changing the dose of both the old and the new medicine at the same time, decreasing one and increasing the other.

Tolerability: Aripiprazole also may have better tolerability than other antipsychotics. A major problem with many antipsychotics is neurological disorders (EPS, kinesia). Again, researchers reported that patients who switched to aripiprazole had improvement in Parkinson's symptoms, akathesia and no change in tardive dyskinesia. An expert said, "This is very favorable, telling us the kind of experience patients have with aripiprazole, that you are not causing side effects in the neurological domain." Another source said, "In terms of neurologic side effects, aripiprazole produced no EPS whatsoever, whereas haloperidol produces classic evidence."

Weight gain: This is a particularly bothersome side effect of Zyprexa, with some patients gaining as much as 50 or 100 pounds, and it appears that aripiprazole will not have the same problem. A speaker said, "We had two patients who switched to aripiprazole from either olanzapine or risperidone who had significant *decreases* in body weight – almost 5 pounds – which is a favorable health profile. There was little change with switching from haloperidol to aripiprazole – because they probably didn't gain weight with haloperidol." Another speaker said the absence of weight gain with aripiprazole is quite remarkable, and described the weight gain data as promising. A third speaker said, "There is a propensity to gain weight more with the atypical antipsychotics than the typicals. In patients we switched to aripiprazole, there was a decline in weight, indicating that with aripiprazole there's actually a weight-neutral effect. Basically, it was the same kind of effect as if the first atypical was discontinued."

Prolactin: Serum prolactin is elevated significantly with risperidone and haloperidol as well as all the other atypical antipyschotics. Elevated prolactin signals the body that you are pregnant. There is no sign of a health benefit to thinking your body is pregnant, but it may have significant negative side effects, including a decreased interest in sexual activity, decreased performance, and maybe long-term, undesirable changes and cardiovascular disease. A speaker said, "Aripiprazole may lower prolactin significantly and have an active mechanism to bring prolactin back to the normal range. Olanzapine doesn't elevate prolactin, but haloperidol and Risperdal both do so, and when patients are switched from those drugs to aripiprazole, you see a big drop."

QT prolongation: A speaker said, "This is a QTc neutral drug."

Cholesterol and fasting glucose: At this point, aripiprazole appears better than olanzapine in this area. A speaker said, "Over time, olanzapine increases total cholesterol, whereas patients on aripiprazole have a decrease in cholesterol – and it's a 20 point spread."

Efficacy: An expert said, "We've shown that aripiprazole is able to alleviate the acute symptom etiology associated with schizophrenic episodes. Another area of efficacy is that once they improve, it helps keep them well or stable on maintenance therapy. Our study was a look at maintenance treatment. Stable outpatients were randomly assigned treatment with aripiprazole as an after-treatment, and they were followed for 26 weeks. We found a substantial difference in the rate of occurrence of symptoms, with aripiprazole showing fewer recurrences than placebo…In another study, we looked at aripiprazole vs. haloperidol for acute treatment and maintenance treatment (52 weeks) together, for a continuum of care. By week 26, both treatments had started to work, with a slight edge for aripiprazole. At week 52, over half the patients had responded to aripiprazole but only 40% to haloperidol. Thus, aripiprazole works better in terms of achieving a higher level of response to treatment…We also looked at improvement in negative symptoms. Over time, the difference between aripiprazole and haloperidol widened, with aripiprazole showing greater reduction in negative symptoms."

Researchers also reported on another trial of aripiprazole in acute mania: This three-week study looked at mean change from baseline (using the Y-MRS scale), comparing aripiprazole and placebo. The study found evidence of improvement with aripiprazole as early as four days. A researcher said, "That's noteworthy because none of the three agents approved for the treatment of mania have shown efficacy this early. Their earliest efficacy was at seven days. It looks like this will result in a significant decrease in lengths of stays for manic patients."

Bipolar disorder: Bipolar depression is a great unmet need, and it looks like the way this drugs works may predict effectiveness in that area as well, but there is no clinical data

as yet. A speaker said, "There is a significant separation in the percent of responders to aripiprazole vs. placebo… Aripiprazole probably will be used with other medicines."

FOREST LABORATORIES' Lexapro (escitalopram). The company insisted there will not be a launch delay and that the launch is still scheduled for 3Q02.

By one account, Lexapro created a "huge buzz" at the APA. The company effort was more about creating awareness than about new data. Although no new data were revealed, several thought leaders strongly suggested to an audience close to 1,000 at one session that Lexapro would have a potency advantage that will give it a faster onset of action and have less side effects. One speaker pointed to several differentiating features of Lexapro that she said were supported by clinical trial data:

- twice as potent
- lower doses needed
- superior safety to Celexa
- lowest drug interactions in class.

Two new publications endorsing these claims were just released that a source suggested Forest may be able to use in its promotions: 1) Gorman; CNS Spectrum 2002:7(40) and 2) Burke; J Clin Psych 2002:63 (331).

GLAXOSMITHKLINE'S Paxil CR (paroxetine). A speaker said, "Effexor XR is better tolerated than Effexor, but they are equal in efficacy. The data submitted to the FDA on Paxil CR appears to show that it is much better tolerated than Paxil, and the drop out rates are similar, but we don't yet know whether they are equally efficacious." Another speaker said, "Paxil CR is much more tolerable than Paxil. I use it if I'm cross-tapering…I don't know if akinesia is a problem. I start Paxil CR at 12.5 mg. That gives flexibility without all the telephone calls. There is less nausea."

JOHNSON & JOHNSON'S Risperidone

Oral Risperdal: Speakers offered some tidbits about their Risperdal use and experience:

- There is fairly significant weight gain with oral Risperdal, but it is less than half the weight gain with Zyprexa.
- Patients generally are started at 25mg and then titrated up to 50mg, which becomes adequate for most patients.
- Asking patients who typically come in to the doctor's office once every four to six weeks to start coming in every two to three weeks would help the relapse rate, but it could be a hard sell with patients.
- The drug release curve has a steep slope, which much different from the smooth curve of most other atypical antipsychotics.

Depot Consta: Compliance with antipsychotic medications in schizophrenia is very poor, which is a problem for research. Many patients also will be intermittently non-compliant. Depo-Risperdal is expected to improve the ability to dose the drug. Doctors said they would like to use it in 25% of their patients, but they predicted that only 50% of these patients would accept it because they either don't like needles, would resist coming in every other week for an injection, or are put off by what they perceive as a to the treatment.

ELI LILLY

Atomoxetine for ADHD. This is expected to be a very effective drug, but one issue remains – can it be abused? Experts said that, pharmacologically, there is no reason for the FDA to view this drug as being able to be abused. There also may be a market for this agent among adults.

Cymbalta (duloxetine). The company still hopes to have FDA approval by the end of 2002. Duloxetine is expected to compete primarily with Effexor. A speaker said, "It has become very cumbersome to use the older drugs in the clinic because you have to start very low and titrate the dose up. Blood pressure, dizziness, and nausea side effects are still seen with duloxetine, but it has fewer side effects than Effexor, though there is no head-to-head study to prove this. With duloxetine, there is very little weight gain but a fair amount of dry mouth – up to 20% of patients in one study."

This dry mouth worries some doctors. One expert said, "The safety profile in regards to nausea and dry mouth is a concern. There is a high side effect profile. Drop-outs are in an acceptable range, but the advantages are slim. Therefore, this product's efficacy will have to be clear."

Other sources said the efficacy does look good. A speaker said, "I expect this to have considerable efficacy. The data submitted to the FDA looks like it separates from placebo, making it an effective antidepressant. It beat Prozac pretty well head-to-head as well as beating placebo, so I think it's going to be a major player in the market, and we always welcome new antidepressants. I expect the FDA to approve it."

Lilly is trying to start with 60 mg qd, saying that is less cumbersome. It is positioning duloxetine as relieving both depression and pain. Primary care doctors will be the primary target, which is how Lilly positioned Prozac. A speaker said, "Lilly is trying to get another Prozac. It is trying to position duloxetine as pain relief, but doctors think of Paxil and Prozac when it comes to chronic back pain."

Sources were surprised that Lilly spent the money for the pain data, but reportedly the data supports use in pain. A speaker said, "Duloxetine should work in pain, much like Effexor. There is no reason why duloxetine and pregabalin can't be used together."

Among the comments made by experts and speakers about duloxetine were:

- "This and venlafaxine together may capture 50% of the market."
- "In remission, duloxetine dominated over paroxetine, but the dose of paroxetine was only 20 mg, and if the goal was remission, then they would have gone to a higher dose (of paroxetine)."
- "There is nothing in the data that was a huge concern; but they only have part of a story for superior efficacy. The good thing is there are no cardiovascular side effects."
- "Data is needed on higher doses to complete the story on this drug, for it to be more successful in the market — but doctors are positive on this drug because of Lilly's marketing capabilities."
- "If psychiatrists believe they will get 10% more remissions, they may start with this drug and use it in initial therapy."
- "There is good convenience with duloxetine, which may make it an easier drug to use in the primary care markets."
- "Duloxetine probably will be the same as the other SSRIs in terms of sexual dysfunction."

LY-354740, an mGLuR (metabatropic glutamate receptor) agonist. mGLuR agonists work by a novel presynaptic mechanism. There appears to be a balance between the GABA and glutamate systems. LY-354740 is an mGLuR agonist that inhibits glutamatergic transmission at the metabotropic presynaptic receptor. An expert said, "This has good anxiolytic capacities, and it may be good for depression, but it is too early to tell." Another expert said, "These agents work by a novel presynaptic mechanism, decreasing excitatory effect. There appears to be a balance between the GABA and glutamate systems. There's a lot more that these agents do in the schema of glutameric neurotransmission. This agent (LY-354740) is an mGLuR agonist that inhibits glutamatergic transmission at the metabotropic presynaptic receptor. This is an exciting area with a new mechanism."

Zyprexa (olanzapine). Zyprexa causes significant (up to 50-100 pound weight gain, and it has been associated with Type 2 diabetes (with and without weight gain). Recently, Japan and the UK issued Dear Doctor letters about deaths from hyperglycemia. The concern is the likelihood of the FDA adding a black box warning or pulling this drug. One source predicted: "It is headed for a black-box warning, and it will get that in a couple of months…Black-box warnings intimidate the un-educated physicians, especially primary care physicians who don't have the time to research the black box. It is maybe silly to switch a person who is doing well on a treatment to something else because of a black box warning."

Yet, there were some critics. A speaker said, "Risperdal is equally as effective as aripiprazole, but aripiprazole will be more effective longer-term. The two are fairly equal in their side effect profile, specifically weight gain, and both have a better side effect profile than Zyprexa." Another expert said, "With women there is a real issue with osteoporosis, and in men, you get an enlargement of the breasts. On the PAN score and the negative PAN subset (both measures of severity), it did not show improvement over the year…Zyprexa is being priced too high and that is causing a problem with formularies and hospitals."

Lilly had speakers and experts out defending Zyprexa, pointing to its efficacy. Sources said, the good thing about Zyprexa is that you are able to push the dose up for very sick patients, despite the bad side effects. One expert said, "Olanzapine is a very good drug. It has a greater potential to produce lipid and glucose changes. What's going to be needed is short-term monitoring of patients who develop side effects...I would assume the FDA would be more interested in putting out an alert that there is a differential risk with this." Asked what would happen to usage if the drug was given a black box, he indicated it is a very sensitive issue but predicted it would be very bad for Zyprexa. Another speaker said, "Zyprexa makes patients feel the best, but weight gain gets to a point where the doctor has to switch patients. And there is a risk of developing diabetes."

OFC (Zyprexa+Prozac). There was some excitement about this combination pill for treatment of bipolar depression. A speaker said, "This looks like a real treatment for bipolar depression, but the question remains: Do you need dual therapy? Perhaps it will be a market extender for olanzapine. It also could be used for psychotic depressives." A Lilly official said: "OFC is the most promising new alternative for therapy for bipolar and treatment-resistant depression."

MERCK'S Neurokinin-1 (NK-1 or Substance P). Although several companies (including Pfizer and J&J/Janssen) are working on NK-1s, Merck appears to have the lead in this area with an oral, once-daily formulation of MK-869, a non–peptide NK-1 receptor antagonist being studied in anxiety, pain and depression. Merck has had several positive trials and was described as "in the home stretch with a very promising drug that is ready to submit to the FDA." A speaker said, "A study of MK-869 and paroxetine in depression was really quite successful. We saw improvement with paroxetine as a preparatory agent, then MK-869 was given in a single 300 mg dose, and we saw a nice response. In anxiety, MK-869 was given in a single dose, and we saw a very nice response compared to placebo. In anxiety, MK-869 might be a little bit better than paroxetine 20 mg. It is very promising." Another researcher said, "It's too early to say anything very useful. This is still in trials, but it hasn't tanked yet."

Other researchers were more reserved on the outlook for this and other NK-1s. One said, "These have a lot of promise. I was involved in the early studies, but larger studies haven't panned out. Three double-blind studies have failed. You need a large study to show efficacy."

PFIZER

Pagaclone. An expert said, "This partial BZD agonist is effective in panic disorder. It is promising, but obviously we need long-term data."

Pregabalin. Pregabalin works by a novel mechanism, and it is comparable to BZDs in GAD. Optimal dosing is likely to be 15-450 mg daily, with BID dosing. There is little to no abuse potential, and no evidence of dependence. The antidepressant efficacy is unclear . An expert said, "Pregabalin has good promise in treating a whole host of anxiety problems." Another source said, "Pfizer is looking at this as an antipsychotic, with no addiction problems. People don't like TID drugs because even BID drugs are a problem. The side effects are concerning, but they do clear over time. It does have a discontinuation syndrome. It is being positioned in a bunch of areas. It seems to be safe and well-tolerated. The excretion is almost all renal, which is a good thing." A third expert said, "Pregabalin will have indications for pain and some sleep disorders, perhaps even insomnia. It enhances slow-wave sleep dramatically, though the functional consequences of this aren't clear. And it improves sleep efficiency." Still another expert said, "Pregabalin has a novel mechanism. It has an inhibitory effect, reducing the release of neurotransmitters and neuro excitability through a completely different mechanism than GABA. When you prescribe pregabalin, you know for sure that release of neurotransmitters is reduced. This is a very exciting area."

Another study compared 600 mg pregabalin qd and venlafaxine 400 mg qd in GAD. A researcher said, "We have some very positive findings for this new agent. In terms of adverse events, there was mild to moderate somnolence, dizziness, dry mouth (which rarely led to discontinuation of treatment), and minimal sexual dysfunction. Discontinuation due to adverse events was approximately the same as placebo, so there are no significant problems with withdrawal. It looks as if there will be a place for this."

There do not appear to be any QTc issues with pregabalin. A source said he knows of no cardiovascular effects from it at all, and he said the safety profile is good, with no evidence of substance abuse problems so far.

The big holdup with pregabalin has been studies which showed it causes sarcoma in mice at relatively high doses. The company is still studying that, and data should be available sometime this year to help put the issue to rest. However, the company has been promising safety data for nearly two years – and the data has not been forthcoming. An expert said, "The jury is still out, but the likelihood is that it won't be more carcinogenic than placebo."

Ziprasidone (Geodon). Geodon has gotten off to a slower start than Pfizer expected or would have liked, but it is starting to catch on. Sources said concern about the QT discouraged some psychiatrists from using it, but since no serious problems have arisen, psychiatrists are becoming more comfortable with it. One source described Lilly's counter-marketing attack on Geodon's QT prolongation issue as "aggressive" and "smart," but pointed out that, so far, no one has died. Another source said, "It is tough to use Geodon in the clinic. There have been problems switching patients to Geodon, and doctors are still trying to find out the best way to use this drug."

SANOFI. The company has at least three agents in Phase II development including:

- SR-48968 (saredutant) for depression
- SR-1420801 (osanetant) for depression
- SL-651498 for anxiety

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