

The Bipolar Child Newsletter **Winter 2003, Vol. 13**

Aripiprazole (Abilify): A Novel Atypical Antipsychotic

--Janice Papolos and Demitri F. Papolos, M.D.

Aripiprazole (Abilify): A Novel Atypical Antipsychotic

Three years ago, we published the first issue of *The Bipolar Child Newsletter*, and in the opening paragraph we outlined what we hoped to accomplish: We wrote: "We thought an e-mail newsletter would be a good forum in which to keep parents, educators, and mental health professionals abreast of the newest findings in the fields of psychopharmacology, genetics, and neurobiology as they relate to early-onset bipolar disorder.";

In keeping with that aim we'd like to focus this issue on a newly available, novel, antipsychotic medicine, aripiprazole (ari-PIP-prazole; brand name Abilify). Psychiatrists are starting to prescribe it, parents are writing to us asking for information about it, and early, anecdotal reports are promising. Much remains to be learned about this unusual new drug. Very little is known about its potential clinical utility and relative tolerability in children suffering with early-onset bipolar disorder, and scientific studies of that application are only now beginning. Still, the drug's unique properties and apparently excellent tolerability in adults offer a great deal of hope.

Let us spell out what we know about Abilify in February 2003.

Aripiprazole was discovered in Japan by Otsuka Pharmaceutical Co., Ltd. The compound entered Phase II trials for patients with schizophrenia in that country by 1995, followed by Phase III trials in Europe by 2000. In 1999, Otsuka-America arranged with Bristol-Myers Squibb to manage Phase III clinical trials and marketing of the new drug in the US. Abilify received FDA approval in November of 2002. It is so new that clinical experience with it, particularly in children, remains very limited.

The Mechanism of Action

Aripiprazole is chemically different from other atypical antipsychotic agents and is also believed to have unique pharmacological actions that are different from other atypical antipsychotic drugs, including clozapine (Clozaril), olanzapine (Zypexa), or quetiapine (Seroquel), risperidone (Risperdal), or ziprasidone (Geodon). Aripiprazole acts as a weak stimulator (so-called "partial"; agonist) at dopamine D₂ receptors, with the potential for exerting either antagonistic (inhibitory) or agonistic (stimulating) effects, depending on the sensitivity of the receptors and availability of dopamine, its natural agonist in the brain. Aripiprazole also has similar actions at serotonin 5-HT_{1A} receptors, as well as acting as an antagonist at serotonin 5-HT_{2A} receptors, and having a number of other lesser actions.

In simple terms, partial agonism refers to the ability of a drug to block a receptor if it is overstimulated or in competition with a natural agonist, such as dopamine and serotonin themselves, but also to stimulate a receptor when the natural agonist is unavailable. These unprecedented properties in a clinically effective antipsychotic agent indicate that Abilify can be considered a "next-generation"; atypical antipsychotic.

Aripiprazole is the first dopamine partial-agonist approved in the US for clinical use in adult patients with schizophrenia, although other dopamine partial-agonists (e.g., bromocriptine [Parlodel] and pramipexole [Mirapex]) have been used to treat Parkinson's disease for many years. Aripiprazole is effective in reducing both the positive and negative symptoms of schizophrenia, and is well tolerated by most patients. In

addition, promising research studies have been conducted with adults suffering with bipolar disorder. A multi-center, double-blind randomized, placebo-controlled trial included 262 adult patients diagnosed with acute mania or mixed manic-depressive states. By day four of treatment, aripiprazole was significantly better than placebo in reducing acute manic symptoms, including elevated mood, irritability, disturbed thinking, and disruptive-aggressive behavior.

These findings have prompted adult and child psychiatrists to begin to prescribe Abilify for both indicated and off-label applications, including for early-onset bipolar disorder in children and adolescents.

Advantages of Abilify

Like other atypical antipsychotics, aripiprazole has a low risk of producing extrapyramidal symptoms (EPS)—the disorders of posture and movement that some patients experience with the older neuroleptic-type antipsychotics, such as chlorpromazine (Thorazine) and haloperidol (Haldol). Typical EPS include early and later muscle contractions (dystonia), slowed movements (akinesia, or parkinsonism), motor restlessness often accompanied by severe anxiety (akathisia), and later-emerging tardive dyskinesia (TD).

In our newsletter of Fall 2000, we first sounded some concerns about a series of general medical or metabolic problems that were being increasingly reported in association with the atypical antipsychotic medications such as Clozaril, Zyprexa, Risperdal, and Seroquel. These include new-onset, type II (non-insulin dependent) diabetes mellitus, changes in lipid metabolism and blood concentrations, sometimes severe and persistent elevation of prolactin and other hormonal imbalances (milk oozes from children's nipples), and a range of adverse cardiovascular effects that include low blood pressure and abnormal functioning of the heart. The long-term implications of such adverse effects are not known, particularly for youngsters who may require such medications for decades.

Studies conducted with Abilify show that patients gain little if any weight; and the drug seems to cause no changes in the plasma glucose levels that might suggest risk of diabetes. Nor does it seem to increase serum cholesterol or other lipids. Also, the drug does not increase prolactin levels, and in fact appears to decrease them to normal levels, and there have been no reports of heart rhythm abnormalities (such as a prolonging of the electrical recovery time of the heart [QTc interval] in the electrocardiogram), hematological changes, serum chemistry changes, or thyroid problems.

Parents who wrote to us asked if there were any cases of tardive dyskinesia (TD), the late appearing movement disorder that can present with involuntary facial grimacing, lip-smacking, chewing and sucking movements, cheek puffing, and worm-like movements of the tongue, as well as quick movements of the fingers, toes, arms and legs, or dystonic, writhing postures. At this point there have been no reports, but it will be years before anyone can answer this question with any authority.

The other question we were asked was: "Does this med punk out like some of the others and will the doctor have to keep increasing the dose?"; Again, we have few answers, but the clinical trials involving patients with schizophrenia showed that Abilify sustained improvements in the positive, negative, and depressive symptoms of schizophrenia for at least a year.

The drug has been evaluated for safety in at least 5,592 adult patients who participated in multiple-dose, premarketing trials in schizophrenia, bipolar mania, and dementia of the Alzheimer's type, for a total of approximately 3,639 patient-years of exposure. A total of 1,887 aripiprazole-treated patients were treated for at least six months, and 1,251 for at least a year.

Promising--so far, but what are the side effects and how effective is it for children struggling with the symptoms of bipolar disorder?

The Side Effects

The most common adverse effects reported among adult bipolar disorder patients, specifically, included

headache (32%), nausea (14%), vomiting (12%), constipation (10%), anxiety (25%), insomnia (24%), dizziness (11%), and akathisia (10%). Sleepiness was found with higher doses. Placebo-treated patients in the same study also suffered side effects such as headache, agitation, nausea, indigestion, and anxiety. Few of the side effects for either group lasted beyond the first week.

Although many patients report few side effects with the medication, in children, specifically, we have heard of single cases: one very young child was taken off the drug due to severe constipation, one 12-year-old had new mania, and one youngster had a dystonic reaction—one of the movement disorders we spoke of above (dystonic reactions can be quickly counteracted by antihistamines such as diphenhydramine [Benadryl], or by anticholinergic drugs such as benztropine [Cogentin] or trihexyphenidyl [Artane]).

Dr. Raymond Behr, a highly respected child psychiatrist on the faculty of the Albert Einstein College of Medicine and founder of the Child Psychopharmacology Listserv for child psychiatrists is very impressed with Abilify, but has reported five cases of akathisia (out of the first 34 patients for whom he has prescribed the medication). He explained that this was not "agitation,"; but "real akathisia."; While the risk of EPS is much lower than with the older neuroleptic agents, akathisia probably has a different basis than other movement disorders associated with antipsychotic drugs, and can occur occasionally even with atypical agents. Parents should be aware of akathisia and be alert to it.

According to Ross J. Baldessarini, M.D. of Harvard Medical School, and one of the leading authorities on antipsychotic medications:

Akathisia is motor restlessness that can occur with all antipsychotics, typical or atypical, but is more likely to occur with the older typical agents and D2 blocking agents. It can occur occasionally and in subtle fashion even with clozapine. Akathisia involves extreme subjective distress with a kind of "anxiety"; that involves a physical sense of discomfort, often referred to the legs, and partially relieved by moving around, hence the restless component. Sometimes it can be treated with propranolol (Inderal) or benzodiazepines, but it may require removing the offending agent.

He added: "This common condition is often overlooked or misunderstood or mislabeled as 'agitation' and it has been associated with aggressive or even suicidal behavior.";

Since so many children with bipolar disorder suffer paradoxical reactions to all drugs (even those thought to quell mania) the hypothetical risk of inducing or worsening mania or psychosis by a dopamine partial-agonist still remains a concern for us and many clinicians, and its clarification awaits more clinical experience.

Reports from the Medical Front

Dr. Raymond Behr told us that "I have used Abilify in several kids and many of the responses have been dramatically positive. My impression is that, if it is going to work, there usually is a very quick response -- within a few days. It is very similar to the effect that one sees with Zyprexa (olanzapine) but without the sedation and weight gain.";

We corresponded extensively with Mani N. Pavuluri, M.D. the director of the Pediatric Mood Disorders Clinic at the Institute of Juvenile Research at the University of Illinois at Chicago. In one e-mail, she told us of a five- year-old child with bipolar disorder who was severely psychotic, suffering delusions of reference, raging, and refractory to three previous trials of mood stabilizers and two antipsychotics. The child is now doing well on 5 mg of Abilify a day. (A four-year-old patient, however, could not tolerate the drug due to constipation.)

Because Dr. Pavuluri and her colleagues were so impressed with their observations of the effects of aripiprazole in difficult-to-treat children who have bipolar disorder (and the results of the five clinical trials that were completed at their center in adults) they have designed a research protocol that proposes to

examine Abilify in 7-17 year-olds with bipolar disorder over a six-week period.

David Cremer, M.D. a psychiatrist from Miami, Florida informed his colleagues on the Professional Listserv of the Juvenile Bipolar Research Foundation: "I have two young patients who are bipolar and who have been on every medication for therapeutic trials and were refractory, or who stopped medications due to side effects, and they are both doing well on Abilify.";

When we contacted him and asked for some more details, he described one of his children thus:

The first patient, KM, is seven-years-old and his core symptoms were rages, sleeplessness, irritability with remorse, low frustration tolerance, fickle changes in mood, rapid speech, and an ADHD profile.

He was refractory to every medication (all the anticonvulsants), he was briefly responsive to the atypical antipsychotics and briefly responsive to lithium. On Abilify he has been able to engage in play in the office and used the time to discuss some of his feelings about how he has been feeling. The ADHD-type picture has abated with the medication.

Dr. Cremer then wrote about his other patient, a nine-and-a-half-year-old boy:

TF has severe separation anxiety, fickle moods, bursts of hyperactivity, some bizarre behavior, moodiness, and spells of rages with pressured speech. He has responded to an atypical antipsychotic, but with the side effects of puffiness and weight gain. He is on carbamazepine without side effects.

Since starting him on Abilify, he lost his puffiness almost immediately and is losing weight. His temper has stabilized. He still has his moments, but they are within the realm of average for his social delay.

Dr. Cremer mentioned that both of these children showed improvement on their mental status exams.

Reports from the Home Front

How are the children doing on Abilify—at home and in school? Several parents wrote to us and again, the stories were positive (but please bear in mind that the negative stories have not reached us yet, and that all children will not have these superb reactions or be able to tolerate the drug). One mother said:

Since Peter started the drug, things have been so much better. He is on 10mg and the first few days he was in a major "fog"; and slept a lot, and had an upset tummy. I thought we were going to have to lower the dose but waited it out and things did get better and the sleepiness went away and he no longer walks around in a fog. Things are starting to "click"; in his head as far as school work is concerned. His upsets are not rages anymore. And the constant fighting with siblings.....well, now it is just regular sibling rivalry that we have never gotten to see before. He is much more compliant and his aggression level has gone way, way down. He gets up in the morning and says: "Good morning"; instead of "I hate you!"; Not sure how long it will last, but I am enjoying it very much!

She added something that reminded us once again what this illness does not only to the child, but to the entire family, and especially the siblings: She said: "His little brother is still having a hard time understanding why Peter is being nice and not his usual self that he was used to. But we are working on that.";

We've been corresponding with the grandfather of a young boy for some time now and he wrote recently to tell us of his grandson's reactions to Abilify. He said:

His daily reports from school are all positive, and both his special-ed teachers are now able to concentrate on his education instead of his behavior. I notice there is no more cycling and no more rages. He is more calm; and when things go wrong, he doesn't explode as he did in the past. As a result of the Abilify, he is a happier 9-year old, and I no longer walk on egg shells when he is with me.

Another mother described her fourth-grader's reaction to the medication thus:

He began the Abilify and on the third to fourth day, we saw dramatic improvement. It was almost as if we were dealing with a different child. The rages stopped. He has always been an affectionate child, but now his affection shines through clearly. He's been getting wonderful reports from his special-ed teachers at school. I still find myself preparing for battle when I have to reprimand him, but I'm pleasantly surprised when he complies with my requests now and there is no problem. This medication has been truly amazing for my son and our family.

And because there is no such thing as too much good news to parents of children suffering with bipolar disorder, we conclude with this mother's description:

While it hasn't solved all of our son's problems, it has controlled his paranoia and mania, decreased his grandiosity (but not eliminated it), made it possible for him to read and focus better, and has done all of this without major side effects (once we got up to 15 mg and eliminated the other antipsychotic medications completely). He tells me that he feels much better able to control himself. He says that he can now read without his mind wandering off in different directions. He can also let negative issues drop, rather than dwelling on them.

She continued:

We have noticed a big change in him. He gets up in the morning and stays awake and alert all day (no sedation). He is generally more cooperative and although he still does annoying things, I can now confront him without feeling like I need the National Guard to back me up. His pediatrician, his therapist, and teachers at school have all noticed the change for the better.

There is something intriguing in this story and in Dr. Cremer's reports above. The children's focus and attention seem to have improved on Abilify. Indeed, Dr. Mani Pavuluri proposes to look at the drug's ability to improve cognitive functioning in her study patients. The results should be interesting for all in the field, and for all parents and educators.

Dosing

Abilify is supplied in 10, 15, 20, and 30 mg tablets--a disadvantage for children, who are typically started on lower doses. Parents can cut tablets into halves or even quarters, or bear extra costs in using the services of compounding pharmacies. We understand from Bristol-Myers Squibb that lower milligram formulations as well as a liquid formulation will be available some time "in the foreseeable future,"; but we can't be any more specific than that.

Typical adult doses for the treatment of psychotic disorders are 10-15 mg/day, with an overall range of 5-30 mg. Doses for children are not established yet, but are likely to be about half those used for adults. Moreover, the specific use of this drug to treat psychotic patients under age 18, or for those diagnosed with bipolar disorder is not approved by the FDA, though it is evidently starting to be used clinically on an off-label basis in adolescents and children and for bipolar disorder patients.

Dr. Pavuluri reports that she starts youngsters weighing less than 110 pounds at 2.5 mg, and those over 110 pounds at 5 mg initially to avoid nausea, and doubles the dose within a week if it is tolerated. Further dose increases usually are not made for another week or two as steady state, or stable, tissue concentrations are

achieved.

It is a good idea to give the medication in the morning, with a meal or some food in order to minimize risk of nausea and insomnia, which are among its most common side effects. Also, parents should ensure that the child eats fruit and vegetables, or high-fiber cereals, and drinks plenty of fluids in order to prevent constipation.

Drug-to-Drug Interactions

The anticonvulsant mood stabilizer, carbamazepine (Tegretol), induces CYP3A4 and 2D6 liver enzymes which can *increase* the ability of the body to remove Abilify, and so *decrease* Abilify's concentration in the blood. The manufacturer recommends that the dosage of Abilify be doubled as long as both drugs are taken at the same time. This consideration brings up the question as to whether Trileptal (oxcarbazepine, an analogue of carbamazepine) can cause this same increase in clearance as Trileptal also has some effect on the liver enzyme CYP3A4 that normally removes Abilify. The possibility seems to exist, but no one has a definitive answer about this yet and careful dosing and an attentive eye to the clinical picture will be required.

Antidepressants such as fluoxetine (Prozac) fluvoxamine (Luvox) and paroxetine (Paxil) can slow the body's ability to eliminate Abilify by inhibiting CYP3A4 and CYP2D6 liver enzymes, and so increasing blood levels of the drug. When any of these SSRIs are prescribed with Abilify, the manufacturer recommends that the Abilify be reduced at least to one-half of its current or usual dose.

Again, physicians who have patients on either class of these medications will have to monitor the clinical picture carefully and make adjustments as needed.

The Cost of the Medication

Abilify is very expensive. A Connecticut retail pharmacy quoted the following prices for 30 tablets at each of three dosages: 10-mg or 15-mg, \$357, and 20-mg, \$506. (We have seen cheaper prices so it behooves all parents to shop around.)

For families who don't have prescription cards or the funds to pay for Abilify, Bristol-Myers Squibb moved quickly to set up a Patient Assistance Program at 1-800-332-2056.

Conclusions

Because early anecdotal reports from researchers, clinicians, and parents seem so positive, and because the drug's safety profile has been very promising to date (and it doesn't confound a child's problems with weight gain), it is hard not to be hopeful about this new medicine. However, it is important to state again that Abilify is only beginning to be studied in children, and a more balanced picture is certain to evolve as data accumulates. (A study is currently enrolling at the NIMH comparing risperidone to aripiprazole in youngsters aged 8-18 years, with psychotic symptoms who have responded unsatisfactorily to at least one other adequate trial of an antipsychotic. To read more about this study and to see if your child qualifies, go to <http://www.ClinicalTrials.gov> and type in aripiprazole.

We are forever walking a fine line between that all-important emotion called hope, and a need to stay open-minded and await the data. One of the mothers we quoted above, put it so wisely when she wrote:

Although this medication has been wonderful for my son, I would not want to raise hopes for other bipolar parents by singing its praises too much. I know how it felt when I heard wonderful things, hopeful things, about other medications that were found to be effective with bipolar disorder. As the parent of a bipolar child, when getting overly hopeful about a medication and then going through the painful and frustrating experience of trying it only to find it did not work (or worse--it exacerbated the symptoms of the bipolar disorder), it was heartbreaking. I guess with all the variations in brain chemistries unique to individuals with bipolar disorder (or any other psychiatric illness), there can't be one medication, *the* medication, that cures bipolar disorder. I

think all parents need to be reminded of this so they're not setting themselves up for a fall

We've said it before, and it bears repeating again: If your child is doing well on his or her present medications, it is unwise to change the regimen because you read about a new drug--here or anywhere. If your child is stable, do nothing to rock that blessed boat.

We will continue to gather information about Abilify and its effect on children suffering with bipolar disorder, both on the research and the clinical fronts, and we would appreciate hearing from any of you whose children have had experience with it.

At this time of mid-winter and always, we wish you and your children the best,
Janice Papolos and Demitri F. Papolos, M.D.

Bibliography

Baldessarini, R.J. E-mail correspondence of February 5, 6, and 10, 2003.

Behr, Raymond. E-mail correspondence of February 4, 2003. Telephone Conversation Of February 10, 2003.

Burris, KD, Molski TF, et al. Aripiprazole, A novel antipsychotic is a high-affinity partial agonist at human dopamine D2 receptors. *Journal of Pharmacological Exp Ther* 2002;302:389.

Goodnick, PJ, and Jerry, JM. Aripiprazole: Profile on efficacy and safety. *Expert Opinion Pharmacotherapy* 2002; 12: 1773-1781.

Jody, Darlene, Ronald Marcus, Paul Keck, et al. "Aripiprazole vs. placebo in acute mania. (poster), Proc Am Psychiatr Assoc Annual Meeting, May 2002.

McGavin JK, Goa KL. Aripiprazole. *CNS Drugs* 2002; 16: 779-786.

Papolos, DF. and Papolos J. *The Bipolar Child*, Revised Edition. New York: Broadway Books, 2002.

Papolos, J and DF. Papolos. *The Bipolar Child Newsletters Volumes 5 and 10.* (www.bipolarchild.com)

Pavuluri, MN. E-mail correspondence of February 3 and 4, 2003.

The authors would like to thank Mani N. Pavuluri, M.D., Raymond Behr, M.D., David Cremer, M.D., Robert McQuade, Ph.D., Mort Fineberg, Mary Fineberg, Catherine Schwartz, Niki Tenn, and especially, Deborah Storms, for their contributions to this newsletter. For his abiding interest, wisdom, and friendship, as well as his specific help with this report, we acknowledge Ross J. Baldessarini, M.D.

www.bipolarchild.com