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Abilify

- Generic name is aripiprazole
- Introduced 2002
- FDA-approval
    - Treatment of irritability in autism
    - Treatment of manic and mixed episodes associated with bipolar I in youth as young as 10 in 2008
    - Augmentation of antidepressant treatment in unipolar depression, 2007
    - Bipolar disorder, maintenance, adults in 2005
    - Bipolar mania in adults in 2004
    - Schizophrenia
- Pharmacology
    - Partial dopamine agonist (25-30%)
    - Half life is 75 hours (50-80 hours; elsewhere listed as 72-94 hours)
    - Time to max is 3-5 hours
    - Metabolized to an active metabolite, which represents 40% of the parent drug exposure
    - Metabolized by 2D6, 3A4; use ½ usual dose in poor 2D6 metabolizers and ¼ if poor 2D6 metabolizer AND with a 3A4 inhibitor
    - Receptor activity in decreasing order of affinity
        - D2 partial agonist at the D2; presynaptic D2 agonist
            - 61% intrinsic activity
                - compared to 100% for dopamine itself
                - compared to 43% for Rexulti
                - compared to 84% for bifeprunox
        - 5HT2b
        - D3
        - 5HT1a
        - 5HT2a (10-fold less than with D2); antagonist
        - Also:
            - 5HT2c
            - alpha-1a
            - alpha-1b
            - 5HT7
            - Histamine1
            - D1
            - muscarinic M1
- Other
    - Supplied in 2, 5, 10, 15, 20 and 30 mg tabs and recently available in DISCMELT (orally disintegrating) 10 and 15 mg pills); liquid
    - Typical adult dose ranges are 10-15 mg/D, though 5-30 mg is the full range for adults.
    - Children should start at 2.5 mg and increase the dose every 1-2 weeks to a range between 2.5-15 mg/d, though doses as high as 30 mg/day are sometimes used
- Evidence
    - General
        - May be useful in unipolar depression, especially atypical depression.
        - Appears effective in adults with schizophrenia or bipolar disorder; may be useful in treatment-resistant mood and anxiety disorders.
        - Compared to Zyprexa, Abilify is associated with greater improvements in working memory, sequencing, fluency, problem-solving, and verbal learning (Kern, in review).
    - Adults
        - Mania

- Keck, et al, JCP, 2006, randomized, double-blind, placebo-controlled 26 week trial of Abilify in recently manic patients with bipolar I disorder; 76 centers, 3 countries:
    - Relapses: 25% Abilify vs. 43% placebo
        - Superior in delaying time to manic relapse
        - Not superior in delaying time to depressive relapse
    - Side effects (combining Keck's study and Kane et al, 2007:
        - **Anxiety/nervousness** 10.5-27.3% vs. ***20.5% placebo***
        - Insomnia 15.6-24.2% vs. ***19.3% placebo***
        - **Weight gain** 13% vs. 0% placebo; usually less than other medicines in this class
        - Depression 11.7% vs. ***14.5% placebo***
        - **Stomach upset 10.5%**
        - **Tremor** 9.1% vs. 1.2% placebo
        - Headache 7.8-16% vs. ***16.9% placebo***
        - Agitation 7.8-16.3% vs. ***10.8% placebo***
        - Physical lassitude 7.8% vs. ***8.4% placebo***
        - **Muscle restlessness** 3.9-6.5% vs. 1.2% placebo
        - Manic reaction 6.5% vs. 13.3% placebo
        - Sleepiness 5.3% vs. ***7.2% placebo***
        - Depersonalization 9.6% vs. 4% placebo
- Vieta, 2005: 12-week, double blind, randomized, Haldol-compared, trial in adult, acute bipolar mania. 347 patients, multicenter.
    - 49.7% response rate with Abilify versus 28.4% with Haldol.
    - Continuation (of medication) rates at week 12: 50.9% with Abilify, 29.1% with Haldol.
    - Muscle side effects: 24% with Abilify (high) versus 62.7% with Haldol
- Keck, 2003 and Sachs, 2004: two three-week placebo-controlled RCTS for adults with mania: Abilify (average dose 28 mg/day)
    - Response rates 40-53% and placebo 19-32% respectively.

- Bipolar depression
    - Two negative randomized control trials in bipolar depression (Thase et al, 2008)
    - Kemp et al, 2007: chart review, 12 patients, Abilify augmentation for bipolar depression, all were treatment resistant
        - 33% responded after 8 weeks; one had to stop Abilify due to a relapse of depression
        - Side effects:
            - one had two stop Abilify due to akithisia
- Maintenance treatment in bipolar disorder
    - McIntyre et al, 2006: 2 year study
        - successfully delayed relapse into manic or mixed manic episodes (though not clearly preventing relapse of depression)
    - McQuade, 2004: Abilify (15-30 mg) versus placebo for maintenance:
        - Percent of ***relapses***
            - **Mania**—8% Abilify, 23% placebo
            - Depression—12% Abilify, 13% placebo
            - Mixed—5% Abilify, 6% placebo
            - Unknown relapses—0% Abilify, 1% placebo
- Treatment-resistant depression
    - Berman et al, 2007: Abilify (vs. placebo) augmentation of standard antidepressant therapy in patients with major depression who had an incomplete response to 1 prospective antidepressant trial and 1-3 historical course of antidepressant therapy within the current episode. This involved a 7-28 day screening phase, an 8-week prospective antidepressant treatment phase, and a 6 week RCT, DB Abilify vs. placebo augmentation phase;

antidepressants included Lexapro, Prozac, Paxil CR, Zoloft, and Effexor XR; 178 patients
        - Response rates: 33.7% vs. 23.8% placebo
        - Reduction of symptoms was significantly (~50%) better in the Abilify group
        - Remission rates: 26% vs. 15.7% placebo
            - By week 1: 3.4 vs. 1.8
            - By week 2: 10.5 vs. 5.8
            - By week 3: 18.8 vs. 8.7
            - By week 4: 22.7 vs. 11
            - By week 5: 26 vs. 14
            - By week 6: 26 vs. 15.7
        - Side effects:
            - Restless legs/muscles 23.1% vs. 4.5% placebo
            - Headache 6% vs. 10.8% placebo
            - Subjective restlessness 14.3% vs. 3.4%
    - Rutherford et al, 2007: Abilify augmentation of Lexapro helpful in geriatric patients with depression (study has some methodological flaws)
    - Papakostas et al, 2006, Abilify augmentation of SSRIs in treatment resistant depression: 56-58% response rate
    - Simon, 2005: adjunctive Abilify for treatment-resistant depression in 15 adults; safe and effective.
    - Marcus et al
    - Cases studies find efficacy with doses from 2.5-10 mg/day
- OCD
    - Sayyah et al, 2012: 39 adults, placebo controlled RCT, Abilify 10 mg vs. placebo added to ongoing SSRI, 12 weeks; safe and effective
    - Higuma et al, 2012: 13 patients, Abilify 2-12 mg/day added to ongoing SSRI; safe and effective
    - Matsunaga et al, 2011: 11 adults, 8-14 mg/day, safe and effective (70% response rate)
    - Selvi et al, 2011, 90 adults, Abilify 15 mg/day vs. Risperdal 3 mg/day added to ongoing SSRI, safe and effective (50% response rate); Risperdal more effective (72% response rate)
    - Muscatello et al, 2011: 30 adults, Abilify added to SSRI or clomipramine; safe and effective
    - Ak et al, 2011: 23 adults, 10 weeks, Abilify added to SSRI, safe and effective (but only 30% response rate)
    - Delle Chiaie et al, 2011 20 adults, Abilify added to SSRI, 12 weeks, safe and effective
    - Masi et al, 2010: 39 adolescents, Abilify 9-15 mg/day, safe and effective
    - Uguz, 2010: 3 adults with OCD and bipolar disorder; safe and effective
    - Pessina et al, 2009: 12 adults, Abilify 5-20 mg/day added to SSRI, safe and effective
    - Storch et al 2008: one teen, Abilify added to SSRI and CBT; safe and effective
    - Connor et al, 2005: 7 adults, Abilify monotherapy, 10-30 mg/day, effective
- Borderline personality disorder
    - Egger et al, 2006; Nickel et al, 2006; Nickel et al 2007; : Abilify safe and effective
- Psychosis/schizophrenia/schizoaffective disorder
    - General (5 placebo-controlled studies)
    - Relapse prevention (26-week study of 297 patients)
    - Abilify vs. Risperdal (12-week study) in first episode psychosis (Robinson et al, 2016)

12 week RCT of risperidone vs aripiprazole in 198 FEP subjects

- Aripiprazole (mean dose 15 mg/d) vs risperidone (mean dose 3.2 mg/d)
- Comparable retention & efficacy
- Aripiprazole: more effective for neg sx, more akathisia
- Risperidone: more dyslipidemia, elevated FBS, hyperprolactinemia

Robinson et al, Schiz Bull 2016

        -
        - Average dose of Abilify 15 mg/d vs. Risperdal 3.2 mg/d
        - Comparable overall efficacy
        - Comparable over all retention/discontinuation rates
        - Abilify more effective for negative symptoms, but more akathisia
        - Risperdal associated with more problems with lipids/cholesterol, elevated glucose, and elevated prolactin
    - Useful in treatment-resistant schizophrenia (Kane et al, 2007)
    - Useful in acute schizophrenia with high agitation (Marder et al, 2007)
    - Efficacious against hostility in schizophrenia and schizoaffective disorder; 1476 patients; as effective as Haldol
- Youths
    - General
        - Valicenti, 2005: reduced symptoms of aggression, hyperactivity, impulsivity in 56% of 32 children with developmental disabilities; doses ranged from 7-10.5 mg/day
        - Findling, 2003: Small open-label study (23 kids) demonstrated safety and efficacy in the short-term (15 days) treatment of aggressive behavior in children
    - Mania
        - A Double-Blind and Placebo-Controlled Trial of Aripiprazole in Symptomatic Youths at Genetic High Risk for Bipolar Disorder
          Robert L Findling, Eric A Youngstrom, Brieana M Rowles, Elizabeth Deyling, Jacqui Lingler, Robert J Stansbrey, Molly McVoy, Sarah Lytle, Joseph R Calabrese, Nora K McNamara
          Journal of Child and Adolescent Psychopharmacology 2017 July 31
          OBJECTIVE: To determine if acute treatment with aripiprazole (APZ) would be superior to treatment with placebo in reducing dysfunctional symptoms of elevated mood and/or irritability in symptomatic children and adolescents at familial high risk for bipolar disorder (BPD) whose mood episodes occur spontaneously. These are patients we have previously referred to as suffering from "cyclotaxia."
          METHODS: This was single-site, randomized, double-blind, placebo-controlled outpatient clinical trial in which youths aged 5-17 years who met diagnostic criteria for either cyclothymic disorder (CYC) or BPD not otherwise specified (BP-NOS) were randomly assigned to receive either APZ or placebo. Eligible participants had at least one parent with BPD, another first- or second-degree relative afflicted with a mood disorder, and also had not responded to psychotherapy. Treatment with APZ was

initiated at a dose of approximately 0.1 mg/kg/day and could be increased by approximately 0.05 mg/kg/day at each study visit. Patients were seen weekly for 4 weeks and then every other week thereafter for 12 weeks. The primary outcome measure was mean change from baseline on Young Mania Rating Scale (YMRS) total score.

RESULTS: A total of 59 patients (30 APZ, 29 placebo) aged 11.8 (SD = 2.7) years were randomized and returned for at least one postbaseline assessment. The mean total daily doses of active APZ and placebo were 7.1 mg (SD = 3.7) and 7.4 mg (SD = 4.2), respectively. At the 12-week time point, APZ was superior to placebo on the primary outcome measure ($p < 0.005$). Most adverse events were mild and transient in nature. There was a significant difference in weight gain from baseline between patients who received APZ (2.3 kg [SD = 3.3]) and those who received placebo (0.7 kg [SD = 1.8]).

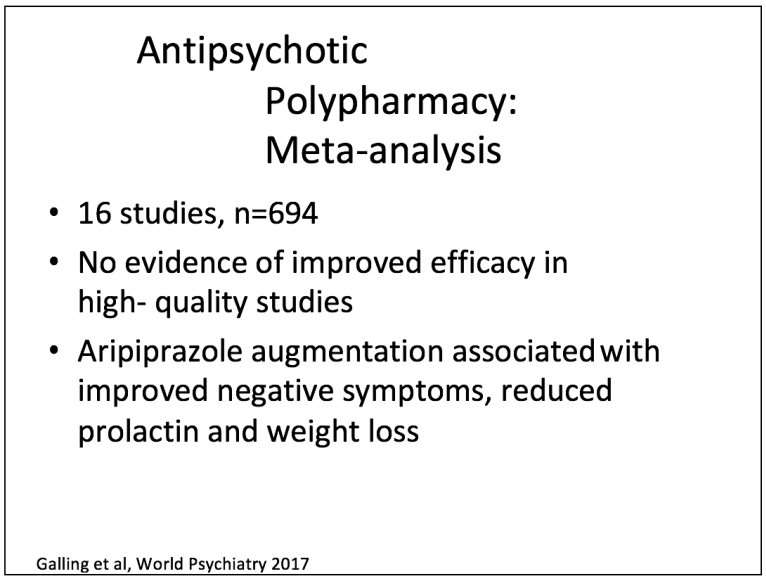
CONCLUSION: This double-blind trial found that APZ was significantly more efficacious than placebo in reducing symptoms of mania in children and adolescents with cyclotaxia.

- Biederman et al, 2005: chart review of 71 youths aged 7-15 yo, average dose 10 mg (range 2.5-30 mg), over an average of 4.4-4.6 mo
  - 67-71% response rate
  - Side effects
    - Sedation 33%
    - Restless muscles 23%
    - Weight change range from 5 kg to -21 kg
- Barzman, 2004: chart review; 30 kids with psychotic disorders (bipolar and schizoaffective); 5-15 mg/day; 67% response rate. Side effects: sedation, akithisia, stomach upset, 12/14 lost weight.

- Bipolar maintenance (OR schizophrenia)
  - Findling, et al, 2013, pediatric bipolar I disorder; 30 week placebo-controlled RCT, Abilify 10 vs. Abilify 30 vs. placebo; safe and effective.
  - Findling, et al, 2011, pediatric bipolar disorder (I, II, NOS, cyclothymia)
    - 16 weeks open-label treatment with Abilify (96 patients)
    - 72 weeks, double-blind: Abilify continuation (30 patients) vs. taper to placebo (30 patients)
    - mean dose 6.4 mg/day
    - Abilify > placebo
    - Side effects:
      - Stomach pain 33% vs. 3% placebo
      - Headaches 30% vs. 20% placebo
      - Increased appetite 30% vs. 43% placebo
      - Musculoskelatal pain 27% vs. 0% placebo
      - Cold symptoms 27% vs. 7% placebo
      - Vomiting 23% vs. 20% placebo
      - Weight gain 20% vs. 17% placebo
      - Urinary wetting 13% vs. 7% placebo
      - Sedation 10% vs. 7% placebo
      - Prolactin, triglycerides, cholesterol, glucose, blood pressure, pulse all unaffected by Abilify (or improved)
  - Findling, 2005 (funded by maker of Abilify): well-tolerated and effective (5-30 mg/day) in pediatric bipolar disorder and schizophrenia
- Tic disorders/Tourette syndrome
  - Budman et al 2008: 37 youth with Tourette's, effective
  - Yoo et al, 2007: open-label, youth with tic disorders; 8 week study
    - 52.8% reduction in tic symptoms; 79.2% much to very much improved
    - Side effects
      - 25% discontinued trial due mostly to muscle restlessness
      - sleepiness 37.5%
      - nausea 20.8%
      - headache 16.6%

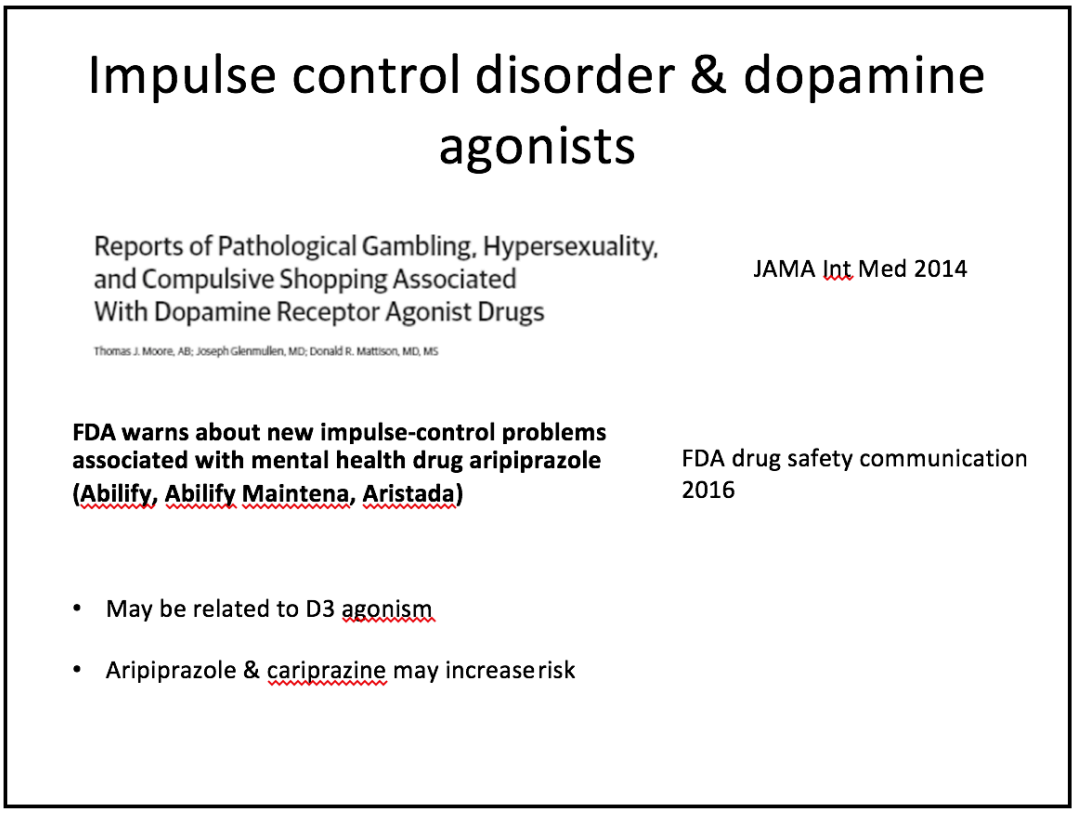
        - Muscle side effects 8.3%
    - Davis, 2006: efficacious and safe in case series of a small number of adults and children with Tourette syndrome
    - Case reports showing safety and efficacy
- Conduct disorder
    - Oren, 2003
- Pervasive developmental disorders
    - Owen et al, 2009; 98 youth with autism, 6-17 yo, with significant irritability, 8 wk double-blind, placebo-controlled, 2-15 mg/day
        - Abilify (~8.5 mg/day) > placebo for irritability
        - Discontinuation rates:
            - Placebo: 5.9%
            - Abilify: 10.6
        - Side effects
            - Fatigue
            - Somnolence
            - Weight gain 2.1 kg (vs. 1 kg placebo)
    - Marcus et al, 2009; 218 youth with autism spectrum disorder, 6-17 yo, with significant irritability, 8 weeks, randomized double blind, placebo-controlled, 5 or 10 or 15 mg/day doses
        - Abilify at all doses > placebo for irritability
        - Discontinuation rates
            - Placebo: 7.7%
            - Abilify 5 mg: 9.4%
            - Abilify 10 mg: 13.6%
            - Abilify 15 mg: 7.4%
        - Common side effects leading to discontinuation
            - Sedation
            - Drooling
            - Tremor
            - Restless muscles (akathisia)
            - Other muscle side effects
        - Weight gain
            - Placebo: 0.3 kg
            - Abilify 5 mg: 1.3 kg
            - Abilify 10 mg: 1.3 kg
            - Abilify 15 mg: 1.4 kg
    - Valicenti-McDermott, 2006: chart review; 56% response rate; worse if autistic spectrum
    - Stigler et al, 2006; prospective, 14-week, open-label, 25 kids, only 13 of which, to date, aged 5-17 yo, have finished the study; dose range 2.5-15 mg (average 7.5 mg);
        - 92.3% response; side effects:
        - Side effects:
            - 10 of 13 with mild tiredness
            - Weight
                - 2 of 13 lost weight
                - 4 of 13 had no change in weight
                - 7 of 13 gained weight
                - Average ~5 pound weight gain
- Schizophrenia
    - Maintenance treatment in adolescent schizophrenia, 52 week randomized, placebo controlled study (Correll et al, 2017)
        - 201 enrolled folks, 146 randomized to Abilify (98) or placebo (48) in the 52-week maintenance phase

- Treatment with Abilify was associated with longer time to exacerbation of psychotic symptoms/impending relapse (hazard ratio 0.46)
- Abilify associated with lower risks of
  - treatment-emergent adverse events (TEAE's) vs. placebo (3.1% Abilify vs. 12.5% placebo)
  - severe TEAE's (2% Abilify vs. 10.4% placebo)
  - discontinuation due to TEAE's (20.4% Abilify vs. 39.6% placebo)
  - muscle side effects, weight gain, and somnolence vs. placebo



- Side effects, overall:
  - General
    - Low risk of motor/muscle side effects
    - Does not appear to cause
      - tardive dyskinesia
      - weight gain
      - glucose intolerance/diabetes
      - high cholesterol or lipid abnormalities
      - increase the hormone prolactin (and in fact appears to lower it)
      - heart or heart rhythm problems
      - thyroid problems
      - blood cells problems
      - kidney problems
  - headache (32%)
  - insomnia (24-27%)
  - abdominal pain (14%)
  - muscle side effects (EPS) (12%)
  - vomiting (10-12%; ~18% in youth)
  - constipation (10%)
  - diarrhea (8%)
  - headache (8%)
  - agitation (8%)
  - nausea (4-14%; ~16% in youth)
  - dizziness (4-11%)
  - anxiety (2-25%)
  - akathisia (motor/muscle restlessness) (2-10%)
  - sleepiness (0-37.5% in youth)

- tremor
- hypertension in two patients (with other cases noted in the literature); blood pressure dropped after discontinuation of Abilify
- lowers prolactin, usually asymptomatically, but risk of hypoprolactinemia:
  - failure to lactate
  - subtle menstrual changes, infertility
  - decreased spermatogenesis
  - decreased breast development
  - decreased adrenal secretion of DHEA
  - decreased pubic, axillary hair
  - immunodeficiency
  - lack of parental behavior



- a number of other side effects and risks in multiple organ systems
- Pregnancy
  - One case of unexplained fetal tachycardia (Mendhekar et al, 2006)
  - To date, not associated with congenital anomalies

Aripiprazole for the treatment of pediatric bipolar I disorder: a 30-week, randomized, placebo-controlled study

from Bipolar Disorders by Robert L Findling, Christoph U Correll, Margaretta Nyilas, Robert A Forbes, Robert D McQuade, Na Jin, Svetlana Ivanova, Raymond Mankoski, William H Carson, Gabrielle A Carlson

Objective: To evaluate the long-term efficacy, safety, and tolerability of aripiprazole in pediatric subjects with bipolar I disorder.

Methods: A randomized, double-blind, 30-week, placebo-controlled study of aripiprazole (10 or 30 mg/day) in youths (10–17 years) with bipolar I disorder (manic or mixed) ± psychotic features (n = 296) was performed. After four weeks, acute treatment completers continued receiving ≤26 weeks of double-blind treatment (n = 210). The primary outcome was Young Mania Rating Scale (YMRS) total score change.

Results: Of the 210 subjects who entered the 26-week extension phase, 32.4% completed the study (45.3% for aripiprazole 10 mg/day, 31.0% for aripiprazole 30 mg/day, and 18.8% for placebo). Both aripiprazole doses demonstrated significantly ($p < 0.001$) greater improvements in YMRS total score at endpoint compared with placebo in protocol-specified last observation carried forward analyses, but not in observed case or mixed-model repeated measures at week 30. Overall time to all-cause discontinuation was longer for aripiprazole 10 mg/day (15.6 weeks) and aripiprazole 30 mg/day (9.5 weeks) compared with placebo (5.3 weeks; both $p < 0.05$ versus placebo). Both aripiprazole doses were significantly superior to placebo regarding response rates, Children's Global Assessment of Functioning and Clinical Global Impressions-Bipolar severity of overall and mania scores at endpoint in all analyses. Commonly reported adverse events included headache, somnolence, and extrapyramidal disorder.

Conclusions: Aripiprazole 10 mg/day and 30 mg/day were superior to placebo and generally well tolerated in pediatric subjects with bipolar I disorder up to 30 weeks. Despite the benefits of treatment, completion rates were low in all treatment arm

The Effectiveness of Aripiprazole for Tics, Social Adjustment, and Parental Stress in Children and Adolescents with Tourette's Disorder

Liang-Jen Wang, Wen-Jiun Chou, Miao-Chun Chou, Susan Shur-Fen Gau

Journal of Child and Adolescent Psychopharmacology 2016, 26 (5): 442-8

OBJECTIVE: Tourette's syndrome (TS) frequently results in a negative impact on multiple functional domains. This prospective open-label study investigated the potential effectiveness of aripiprazole for tics, social adjustment, and parental stress in children and adolescents with TS.

METHODS: Study participants consisted of 26 patients (mean age 10.4±3.0 years; 22 boys and 4 girls) who were prescribed aripiprazole, with each dose ranging from 2.5 to 15mg/day. At baseline and 2, 4, and 8 weeks from baseline, tic symptoms, social adjustment, and parenting stress were assessed using the Yale Global Tic Severity Scale (YGTSS), the Social Adjustment Inventory for Children and Adolescents (SAICA), and the Parenting Stress Index (PSI). Aripiprazole could be optionally titrated from 2.5 to 30mg/day at each visit.

RESULTS: Of the 26 patients at the initial visit, 22 (84.6%) completed the study. The mean dose of aripiprazole at the endpoint was 8.0±4.0mg/day. During the 8-week aripiprazole treatment period, motor tics, phonic tics, and impairment on the YGTSS all showed significant improvement. Home behaviors on the SAICA and child domain on the PSI also showed significant improvement. Patients' phonic tics, but not motor tics, showed a positive correlation with their school function and peer relationships. The child domain on the PSI was positively correlated with motor tics, phonic tics, and impairment, as measured by the YGTSS.

CONCLUSIONS: An 8-week aripiprazole treatment program for children and adolescents with TS was beneficial to their tic symptoms, behaviors at home, and caregivers' stress with regard to fulfilling parenting roles. A long-term placebo-controlled trial with larger samples is warranted to confirm the effectiveness of aripiprazole for social adjustment and parental stress.

Effectiveness and Tolerability of Aripiprazole in Children and Adolescents with Tourette's Disorder: A Meta-Analysis

Yueying Liu, Hong Ni, Chunhong Wang, Lili Li, Zaohuo Cheng, Zhen Weng

Journal of Child and Adolescent Psychopharmacology 2016, 26 (5): 436-41

OBJECTIVE: Aripiprazole, an atypical antipsychotic drug, has shown potential as a promising candidate for the treatment of Tourette's disorder (TD). However, the effectiveness and the tolerability profile of aripiprazole in the reduction of tics in children and adolescents with TD have not been systematically analyzed. This meta-analysis aimed to evaluate the effectiveness and tolerability of aripiprazole in children and adolescents with TD.

METHODS: We searched for clinical trials that investigated the effect of aripiprazole in children and adolescents with TD in PubMed and Web of Science. The outcomes of interest comprised the Yale Global Tic Severity Score (YGTSS) total tic scores and the Clinical Global Impressions Scale for Tic Severity (CGI-S) scores. The pooled effect size (ES) and 95% confidence interval (CI) were calculated to assess the effectiveness of aripiprazole in children and adolescents with TD.

RESULTS: Ten studies were retrieved from 122 citations for the analysis, and in total, 302 patients (mean age, 11.6 years; median follow-up, 9 weeks) were included in the analysis. After synthesis of the data, the meta-analysis showed significantly greater improvement in the mean change in the YGTSS total tic scores (ES=-1.99, 95% CI=[-2.26]-[-1.72]; p=0.001) and the mean CGI-S scores (ES=-2.34, 95% CI=[-2.96]-[-1.73]; p=0.001) from pretreatment to posttreatment. Adverse events were reported in nine trials. Drowsiness (28.5%), nausea (20.2%), and headache (13.8%) were common adverse events.

CONCLUSIONS: The use of aripiprazole is safe, and shows therapeutic effectiveness in children and adolescents with TD.

Efficacy and Safety of Aripiprazole Once-Monthly in the Maintenance Treatment of Bipolar I Disorder: A Double-Blind, Placebo-Controlled, 52-Week Randomized Withdrawal Study

Joseph R Calabrese, Raymond Sanchez, Na Jin, Joan Amatniek, Kevin Cox, Brian Johnson, Pamela Perry, Peter Hertel, Pedro Such, Phyllis M Salzman, Robert D McQuade, Margaretta Nyilas, William H Carson

Journal of Clinical Psychiatry 2017 January 31

OBJECTIVE: To evaluate efficacy, safety, and tolerability of long-acting injectable antipsychotic aripiprazole once-monthly 400 mg (AOM 400) as maintenance treatment for bipolar I disorder (BP-I).

METHODS: In a double-blind, placebo-controlled, 52-week randomized withdrawal study conducted from August 2012 to April 2016, patients with a DSM-IV-TR diagnosis of BP-I currently experiencing a manic episode were stabilized sequentially on oral aripiprazole and AOM 400 and then randomized to AOM 400 or placebo. The primary end point was time from randomization to recurrence of any mood episode. Other end points included proportion of patients with recurrence of any mood episode and recurrence by mood episode type.
RESULTS: Of 266 randomized patients, 64 (48.1%) of 133 in the AOM 400 group and 38 (28.6%) of 133 in the placebo group completed the study. AOM 400 significantly delayed the time to recurrence of any mood episode compared with placebo (hazard ratio: 0.45; 95% CI, 0.30 to 0.68; P < .0001). Significantly fewer patients (P < .0001) experienced recurrence of any mood episode with AOM 400 (35/132; 26.5%) compared with placebo (68/133; 51.1%), with the effects observed predominantly on manic episodes (P < .0001). Patients were not depressed at study entry, and between-group differences in depressive episodes were not significant (P < .864). The treatment-emergent adverse events (incidence > 5%) that were reported at higher rates with AOM 400 than placebo were weight increase, akathisia, insomnia, and anxiety.
CONCLUSIONS: AOM 400 delayed the time to and reduced the rate of recurrence of mood episodes and was generally safe and well tolerated. These findings support the use of AOM 400 for maintenance treatment of BP-I.

From Papolos and Papolos: Aripiprazole (Abilify): A Novel Atypical Antipsychotic, 2/03 (shortened by Wilson)

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 clopazine (Clozaril), olanzapine (Zypexa), or quetiapine (Seroquel), risperidone (Risperdal), or ziprasidone (Geodon). Aripiprazole acts as a weak stimulator (so-called "partial" agonist) at dopamine D_2 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-agonsists (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 haloperidal (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 mislabled 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 collegues 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 ad 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.

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.

Effect of Aripiprazole Lauroxil on Metabolic and Endocrine Profiles and Related Safety Considerations Among Patients With Acute Schizophrenia

Henry A Nasrallah, John W Newcomer, Robert Risinger, Yangchun Du, Jacqueline Zummo, Anjana Bose, Srdjan Stankovic, Bernard L Silverman, Elliot W Ehrich
Journal of Clinical Psychiatry 2016 August 30
OBJECTIVE: Aripiprazole lauroxil, a long-acting injectable antipsychotic, demonstrated safety and efficacy in treating symptoms of schizophrenia in a double-blind, placebo-controlled trial. Because the metabolic profile of antipsychotics is an important safety feature, the effects of aripiprazole lauroxil on body weight, endocrine and metabolic profiles, and safety were examined in a secondary analysis.
METHODS: Patients with schizophrenia (DSM-IV-TR criteria) were randomly assigned to aripiprazole lauroxil 441 mg, aripiprazole lauroxil 882 mg, or placebo intramuscularly once monthly between December 2011 and March 2014. Changes in body weight, body mass index, fasting blood glucose and serum lipids, glycosylated hemoglobin (HbA1c), and prolactin over 12 weeks were assessed. The incidence of treatment-emergent adverse events (AEs) was evaluated.
RESULTS: Among 622 randomized patients, no clinically relevant changes from baseline to week 12 were observed for any serum lipid, lipoprotein, plasma glucose, or HbA1c value with placebo or either dose of aripiprazole lauroxil. Both doses of aripiprazole lauroxil were associated with reductions in mean prolactin levels, whereas placebo treatment was not. The mean (standard deviation) change from baseline for body weight was 0.74 (3.9) kg, 0.86 (3.7) kg, and 0.01 (3.6) kg for aripiprazole lauroxil 441 mg, aripiprazole lauroxil 882 mg, and placebo groups, respectively. AEs related to metabolic parameters were reported in 2.4%, 1.4%, and 2.4% of patients in the aripiprazole lauroxil 441 mg, aripiprazole lauroxil 882 mg, and placebo groups, respectively.

CONCLUSIONS: Aripiprazole lauroxil was well tolerated, with a low-risk metabolic profile relative to published data for other antipsychotics. Changes similar to those observed with placebo were observed in the aripiprazole lauroxil groups for metabolic parameters, with modest weight gain in the active treatment groups over the 12-week course.

Aripiprazole Reduces Severity of Tics in Children with Tourette's Disorder

New Rochelle, NY, July 20, 2016—A meta-analysis of clinical trials evaluating the effectiveness of aripiprazole for the treatment of Tourette's disorder (TD) in children and adolescents showed a significantly greater overall improvement in total tics and tic severity from pretreatment to post-treatment for the aripiprazole compared to the placebo group. The drug was safe, with drowsiness, nausea, and headache being the most common adverse effects, according to the study published in ***Journal of Child and Adolescent Psychopharmacology***, a peer-reviewed journal from **Mary Ann Liebert, Inc., publishers**. The article is available free on the ***Journal of Child and Adolescent Psychopharmacology*** website until August 20, 2016.

The article "Effectiveness and Tolerability of Aripiprazole in Children and Adolescents with Tourette's Disorder: A Meta-Analysis" describes an assessment of ten studies that included 302 patients with a mean age of 11.6 years. Coauthors **Yueying Liu, MD** and **Chunhong Wang, MD**, Jiangnan University (Wuxi), **Hong Ni, MD** and **Lili Li, MD**, Soochow University Affiliated Children's Hospital (Suzhou), **Zaohuo Chen, MD**, Nanjing Medical University (Wuxi), and **Zhen Weng, PhD**, Chinese Academy of Sciences (Suzhou), China, report on the therapeutic potential of aripiprazole, an atypical antipsychotic drug, for treating TD in a pediatric population.

"Treatment of children with Tourette's remains challenging for many clinicians. This study highlights the effectiveness of aripiprazole for this group of patients," says **Harold S. Koplewicz, MD**, Editor-in-Chief of the***Journal of Child and Adolescent Psychopharmacology*** and President of the Child Mind Institute in New York.

Randomized, Double-Blind, Placebo-Controlled Trial Demonstrates the Efficacy and Safety of Oral Aripiprazole for the Treatment of Tourette's Disorder in Children and Adolescents
Floyd Sallee, Eva Kohegyi, Joan Zhao, Robert McQuade, Kevin Cox, Raymond Sanchez, Alet van Beek, Margaretta Nyilas, William Carson, Roger Kurlan
Journal of Child and Adolescent Psychopharmacology 2017 July 7
OBJECTIVES: Aripiprazole modulates dopaminergic and serotonergic pathways that may play a role in the pathogenesis of Tourette's disorder (TD). This trial evaluated the efficacy and safety of oral aripiprazole in the suppression of tics in children and adolescents with TD.
METHODS: This phase 3, randomized, double-blind, placebo-controlled trial (ClinicalTrials.gov , NCT01727700) recruited patients who were 7-17 years old with a diagnosis of TD from hospitals, private practices, and research clinics at 76 sites in the United States, Canada, Hungary, and Italy. Patients were randomized in a 1:1:1 ratio by using an interactive voice/web-response system to low-dose aripiprazole (5 mg/day if <50 kg; 10 mg/day if ≥50 kg), high-dose aripiprazole (10 mg/day if <50 kg; 20 mg/day if ≥50 kg), or placebo for 8 weeks. Randomization was stratified by region (North America or Europe) and baseline body weight (<50 kg vs. ≥50 kg). The primary efficacy endpoint was mean change from baseline to week 8 in the Yale Global Tic Severity Scale Total Tic Score (YGTSS-TTS) for the intent-to-treat population.
RESULTS: Between November 2012 and May 2013, 133 patients were recruited and randomized to low-dose aripiprazole (n = 44), high-dose aripiprazole (n = 45), or placebo (n = 44). Least-squares mean treatment differences versus placebo in change from baseline to week 8 in the YGTSS-TTS were statistically significant (high dose, -9.9 [95% confidence interval, CI, -13.8 to -5.9], low dose, -6.3 [95% CI, -10.2 to -2.3]). At week 8, 69% (29/42) of patients in the low-dose and 74% (26/35) of patients in the high-dose aripiprazole groups demonstrated a Clinical Global Impression-Tourette's Syndrome improvement score of 1 (very much improved) or 2 (much improved) compared with 38% (16/42) in the placebo group. The most common adverse events (AEs) were sedation (low dose, 8/44 [18.2%], high dose, 4/45 [8.9%], placebo, 1/44 [2.3%]), somnolence (low dose, 5/44 [11.4%], high dose, 7/45 [15.6%], placebo, 1/44 [2.3%]), and fatigue (low dose, 3/44 [6.8%], high dose, 7/45 [15.6%], placebo, 0). No serious AEs or deaths occurred.
CONCLUSIONS: This study indicates that oral aripiprazole is a safe and effective treatment for tics in children and adolescents with TD.

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Durability of Therapeutic Response With Long-Term Aripiprazole Lauroxil Treatment Following Successful Resolution of an Acute Episode of Schizophrenia
Joseph P McEvoy, Robert Risinger, Serhiy Mykhnyak, Yangchun Du, Chih-Chin Liu, Arielle D Stanford, Peter J Weiden
Journal of Clinical Psychiatry 2017 September 19
OBJECTIVE: To evaluate durability of therapeutic effect of long-term treatment with aripiprazole lauroxil in patients with schizophrenia following successful treatment of an acute psychotic episode.
METHODS: This post hoc analysis assessed long-term outcomes for a subgroup of patients who entered a 52-week extension study after being successfully stabilized with one of 2 doses of aripiprazole lauroxil (441 or 882 mg) in a pivotal 12-week, placebo-controlled, randomized clinical trial. Durability of therapeutic effect was measured by the proportion of patients completing the 1-year course of aripiprazole lauroxil, the trajectories of the Positive and Negative Syndrome Scale (PANSS) total and the Clinical Global Impression-Severity (CGI-S) item scores beyond the first 12 weeks, and the likelihood of remission at any follow-up point.
RESULTS: In total, 181 patients treated with aripiprazole lauroxil entered the extension study; 73% and 66% of patients from the 441 mg and 882 mg groups, respectively, completed all 13 aripiprazole lauroxil treatments scheduled every 4 weeks over 52 weeks. Both groups continued on a positive trajectory of symptom improvements ($P < .0001$ for reductions in PANSS total and CGI-S scores from week 12 to end of follow-up). Most patients (74% and 68% in the aripiprazole lauroxil 441 mg and 882 mg groups, respectively) achieved remission during follow-up.
CONCLUSIONS: These post hoc analyses of a subgroup of patients demonstrate the continued therapeutic efficacy of aripiprazole lauroxil after successful treatment of an acute episode of schizophrenia. Both the 441 mg and 882 mg groups had similar retention rates, degree of symptom improvement, and likelihood of remission.

Aripiprazole for Irritability in Asian Children and Adolescents with Autistic Disorder: A 12-Week, Multinational, Multicenter, Prospective Open-Label Study
Hyo-Won Kim, Eun-Jin Park, Ji-Hoon Kim, Vitharon Boon-Yasidhi, Jariya Tarugsa, Alexis Reyes, Stella Manalo, Yoo-Sook Joung
Journal of Child and Adolescent Psychopharmacology 2018 April 24
OBJECTIVES: We investigated the effectiveness and tolerability of aripiprazole in the treatment of irritability in Asian children and adolescents (6-17 years) with autistic disorder in a 12-week, multinational, multicenter, open-label study.
METHODS: Sixty-seven subjects (10.0 ± 3.1 years old, 52 boys) were enrolled and treated with flexibly dosed aripiprazole for 12 weeks (mean dose, 5.1 ± 2.5 mg; range 2-15 mg).
RESULTS: Aripiprazole significantly reduced the mean caregiver-rated scores for the Irritability, Lethargy/Social Withdrawal, Stereotypy, Hyperactivity, and Inappropriate Speech subscales of the Aberrant Behavior Checklist from baseline to week 12 ($p < 0.001$ for all subscales). Clinician-rated Clinical Global Impression Severity of Illness scale score also improved from baseline through week 12 ($p < 0.001$). The most common adverse event was weight gain and no serious adverse event related to aripiprazole treatment was noted.
CONCLUSION: Our results suggest that aripiprazole is effective and generally tolerable in the treatment of irritability in Asian children and adolescents with autistic disorder. Further studies with larger sample sizes and longer treatment durations are required.

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