- **Lurasidone (Latuda)**
  - FDA-approved for schizophrenia in 2010; FDA-approved for monotherapy or adjunctive therapy for acute bipolar I depression
  - FDA-approved for bipolar depression in youth, March, 2018
  - Evidence
    - Bipolar disorder
      - Loebel et al, 2014, Phase III PREVAIL 2
        - 6 wk, double blind, placebo controlled, multicenter trial
        - 505 patients
        - Monotherapy
        - Once daily low dose (20-60 mg/day; avg 34.9 mg/day) vs. high dose (80-120 mg/day; average 92.3 mg/day) vs. placebo
        - Results
          - Low dose
            - 15.4 point reduction in depression symptom scale
            - 19.3 point reduction in depression self-report scale
            - 53% response rate
            - 42% remission rate
            - 1 point reduction in mania scale
            - Treatment emergent mania in 1%
            - 9.5 point reduction in disability scale
          - High dose
            - 15.4 point reduction in depression symptom scale
            - 19.8 point reduction in depression self-report scale
            - 51% response rate
            - 40% remission rate
            - 0.7 point reduction in mania scale
            - Treatment emergent mania in 0%
            - 9.8 point reduction in disability scale
          - Placebo
            - 10.7 point reduction in depression symptom scale
            - 9.8 point reduction in depression self-report scale
            - 30% response rate
            - 25% remission rate
            - 1 point reduction in mania scale
            - Treatment emergent mania in 1%
            - No change in disability scale
          - Side effects
            - **nausea 59%
            - **headache 58%
            - *restless muscles
            - treatment emergent mania in 3.7% of lower dose group, 1.9% of higher dose, and 1.9% of placebo

        - slight increase in extrapyramidal muscle side effects
        - slight increase prolactin
        - weight gain about 1 pound in lower dose, 0 in higher dose, and 0 in placebo
- Loebel et al, 2014, Phase III PREVAIL 2
    - 6 wk trial, Latuda 20-120 mg/day vs. placebo added to lithium or Depakote in bipolar I depression
    - Latuda > placebo, separation from placebo beginning at week 3
    - Response rate 57% with Latuda vs. 42% placebo
    - Remission rate 50% with Latuda vs. 35% placebo
    - Significant improvement (vs. placebo) in
        - Anxiety
        - Quality of life
        - Functioning
    - Side effects
        - **nausea
        - **somnolence
        - **tremor
        - **muscle restlessness
        - **insomnia
        - treatment emergent suicidal ideation in 9% with Latuda and 6% with placebo; no suicide attempts
        - 1% in each group switched to mania
        - small increase in extrapyramidal symptoms
        - minimal effects on weight, lipids, and glucose
- Findling et al, 2015, Latuda in youth
    - Tolerability
        - Somnolence 44/105
        - Sedation 19/105
        - Nausea 18/105
        - Vomiting 16/105
        - Anxiety 6/105
        - Dystonia 6/105
        - Upper abdominal pain 6/105
        - Dyskinesia 5/105
        - Dizziness 4/105
        - Insomnia 4/105
        - Diarrhea 3/105
        - Dry mouth 3/105
        - Vision blurred 3/105
- Successful in youth 10-17 with bipolar depression, Delbello et al, 2017
    - 20-80 mg/day (avg 32.6 mg/day)
    - Response rates significantly better, but not remission rates
    - Common side effects

    - Nausea
    - Somnolence
    - Increased weight (rate of significant weight gain NOT more than placebo)
    - Insomnia
    - Akisthisia
    - Elevated prolactin
- Efficacy of Lurasidone in Adults Aged 55 Years and Older With Bipolar Depression: Post Hoc Analysis of 2 Double-Blind, Placebo-Controlled Studies; Martha Sajatovic, Brent P Forester, Joyce Tsai, Hans Kroger, Andrei Pikalov, Josephine Cucchiaro, Antony Loebel; *Journal of Clinical Psychiatry 2016 August 16*
    - **OBJECTIVE:** The aim of this post hoc analysis was to evaluate the efficacy of lurasidone in patients aged 55 years and older with bipolar depression.
    - **METHODS:** A post hoc analysis was performed on the older adult subgroup (n = 142) of outpatients meeting DSM-IV-TR criteria for bipolar I depression in 2 placebo-controlled, 6-week, randomized, double-blind studies conducted from 2009-2012: a monotherapy study comparing fixed flexible-dose ranges of lurasidone 20-60 mg/d or 80-120 mg/d with placebo and an adjunctive therapy study comparing flexible doses of lurasidone 20-120 mg/d with placebo adjunctive to either lithium or valproate. The primary endpoint was mean change at week 6 in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score.
    - **RESULTS:** In the randomized sample, the proportion of older adults was 88/505 (17.4%) in the monotherapy study and 54/348 (15.5%) in the adjunctive therapy study. In the older adult subgroup in the monotherapy study, mean change at week 6 in the MADRS was significantly greater for lurasidone versus placebo (-14.8 vs -7.1; P = .003; effect size, 0.83; pooled doses), and in the adjunctive therapy study, mean change for lurasidone was not significantly different from placebo (-13.9 vs -11.1; P = .398; effect size, 0.26). Discontinuation rates due to adverse events for lurasidone versus placebo were similar for the monotherapy (6.8% vs 6.9%) and adjunctive therapy (3.8% vs 7.1%) studies. Lurasidone had minimal effects on metabolic laboratory values.
    - **CONCLUSIONS:** The results of these post hoc analyses, which assessed the efficacy of lurasidone in older adults with bipolar disorder, found that monotherapy was effective while adjunctive therapy did not demonstrate efficacy. Both monotherapy and adjunctive therapy with lurasidone were safe and well-tolerated in this older adult population.
- ***NNT 5 for response when used as monotherapy***
    - ***NNH 15 for akathisia, 17 for nausea, 25 for sedation, -493 for clinically significant weight gain (less than placebo)***
- ***NNT 7 for response when Latuda added to mood stabilizer***
    - ***NNH 16 for nausea, 19 for sedation, 30 for akathisia, -51 for clinically significant weight gain (less than placebo)***

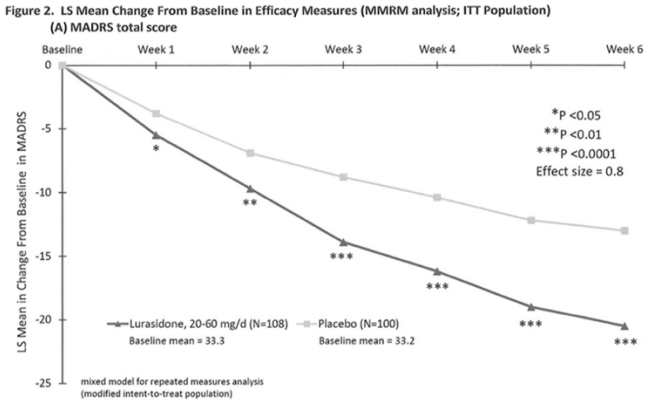
- **Depression with mixed features**

Lurasidone in MDD with Mixed Features

- DSM-5 MDD "Mixed" requires 3 manic features
- Two or three mixed features in trial
- Lurasidone 20-60 mg./day vs. placebo x 6 weeks
- NNT=3; highly effective
- Lurasidone was well tolerated; nausea 6.4% vs. 2% for placebo

Suppes P et al. AJP, in press.

Lurasidone in MDD with Mixed Features



Suppes P et al. AJP, in press.

- Tsai et al, 2018; Latuda in depression with mixed features and anxiety
  - Post-hoc analysis based on randomized, double-blind, placebo-controlled trial that lasted 6 weeks, with 209 patients (US and Europe)
  - Latuda 20-60 mg/day in pts with depression on two or three of the following manic symptoms on most days:
    - Elevated or expansive mood
    - High self-esteem or grandiosity
    - Increased talking or racing thoughts
    - Elevated energy
    - Involvement in activities with high likelihood of negative consequences

        - Decreased need for sleep
    - Avg dose 37.8 mg/day in the mild anxiety group and 35.1 in the moderate-to-severe anxiety group
    - Latuda group (compared to placebo)
        - Responder rates higher in mild anxiety group (NNT 4)
        - Responder rates higher in mod-to-sev anxiety group (NNT 3)
        - Remission rates not higher in the mild anxiety group
        - Remission rates higher in the mod-to-sev aniety group (NNT 4)
    - Controlling for anxiety, Latuda had 60.5% indirect effect and 39.5% direct effect on improvement in depressive symptoms
- Suppes et al, 2016
    - 20-60 mg/day vs. placebo, 6 weeks; 109 subjects
    - Safe and effective
    - Side effects
        - Nausea 6.4% vs. 2% with placebo
        - Somnolence 5.5% vs. 1% with placebo
        - Dizziness 3.7% vs. 3% with placebo
        - Akasthisia 3.7% vs. 2% with placebo
        - Abdominal discomfort 3.7% vs. 1% with placebo
        - Dry mouth 2.8% vs. 1% with placebo
        - Parkinsonism 2.8% vs. 1% with placebo
        - Weight gain: 1.9% vs. 1% with placebo

- **Schizophrenia**
    - May be useful for treating the cognitive and memory deficits seen in schizophrenia
        - Active at serotonin subreceptors involved in learning and memory
        - No anticholinergic side effects
    - Short term
        - Five 6-week, double blind, placebo-controlled studies (Nasrallah et al, Loebel et al, Ogasa et al, Meltzer et al, Nakamura et al)
            - All used different fixed doses b/w 40-120 mg/day, sometimes compared to active, well established antipsychotic
            - With one exception, all studied doses proved superior to placebo at 6 weeks (in the exception (Nasrallah et al), all dose increments led to clinically meaningful improvements but only 80 mg/day resulted in statistically significant improvement)
    - Long term/relapse prevention
        - Loebel et al: 12 month study Latuda vs. Seroquel XR
            - Relapse rates
                - 23.7% with Latuda
                - 33.6% with Seroquel XR
            - Probability of hospitalization
                - 9.8% with Latuda
                - 23.1% with Seroquel XR
        - Stahl et al: 6 week extension treatment: continued clinical improvement

        - Irritability in autism
            - Brams et al, 2016
                - 148 youth with ASD with irritability, agitation, or self-injurious behavior
                - Multicenter, double-blind, randomized-controlled placebo trial
                - Latuda 20 or 60 mg vs. placebo
                - Numerically greater but not statistically significant improvement vs. placebo
                - Side effects
                    - Vomiting
                    - Somnolence
                    - Nasopharyngitis
                    - Weight gain
    - Pharmacokinetics
        - Peak in 1-3 hours
        - Half-life 18 hours (elsewhere it's listed as 20-30 hours)
        - Take with food to increase absorption
        - 3A4 metabolism
        - 2 active metabolites with shorter half lives than parent compound
        - Structurally similar to Geodon
    - Pharmacodynamics
        - ***5HT2A (0.47) antagonism***
        - ***5HT7 (0.495) antagonism***
        - ***D2 (0.994) antagonism***
        - **5HT1A (6.36) partial agonism**
        - **NE alpha 2C (10.8) antagonism**
        - NE alpha 2A (40.7) antagonism
        - NE alpha 1 antagonism
        - D1 antagonism
        - 5HT2c antagonism
        - HI, muscarinic (>1000)
    - Dosing
        - 40-80 mg/day, once daily; there are 20 mg, 40 mg, and 80 mg pills
        - Take with food (at least 350 cal)
        - Doses above 80 mg not necessarily better than 40-80 mg dose range, though range is up to 160 mg/day
        - Start with 40 mg/day, better tolerated in evening
        - Available in 20, 40, 80, and 120 mg formulations
    - Side effects general
        - Weight gain appears minimal
            - Recent meta-analysis (Leucht et al, 2013) comparing 15 antipsychotic medications, second least likely to cause weight gain (only Haldol was better)
        - Effects on lipid profile appear minimal
        - Sedation moderate
            - Dose-dependent
            - Effect is immediate

        - Recent meta-analysis (Leucht et al, 2013) comparing 15 antipsychotic medications, sixth least likely to cause sedation (after paliperidone, sertindole, amisulpride, iloperidone, and Abilify)
    - Low risk of QTc prolongation
    - Extrapyramidal muscle/motor side effects
        - Recent meta-analysis (Leucht et al, 2013) comparing 15 antipsychotic medications, fourth most likely to cause muscle/motor side effects (after Haldol, zotepine, and Thorazine)
    - In elderly, like with all second generation antipsychotic medications, increased risk for stroke or transient ischemic attack
    - Very common side effects (10% or more)
        - Somnolence (immediate and dose-dependent)
        - Muscle restlessness (dose-dependent)
        - Fasting glucose increase
        - Nausea
        - Parkinson muscle side effects
- Side effects
    - **Nausea/vomiting:** **20% vs. 12% placebo**
    - **Hypersalivation:** **2% vs. less than 1% placebo**
    - **Somnolence:** **17-22% vs. 10% placebo**
      15% at 20 mg/day
      19% at 40 mg/day
      23% at 80 mg/day
      26% at 120 mg/day
    - **Restless legs:** **13-15% vs. 3% placebo**
      6% at 20 mg/day,
      11% at 40 mg/day
      15% at 80 mg/day
      22% at 120 mg/day
    - Other muscle side effects: 14%
        - Parkinsonism: 11% vs. 5% placebo
        - Dystonia: 5% vs. 1% placebo
    - Dizziness: 5% vs. 3% placebo
    - Agitation: 6% vs. 3% placebo
    - Anxiety: 6% vs. 3% placebo
    - No QTc prolongation
- Side effects in long-term study
    - Nausea 16.7% (vs. 10.9% with Risperdal)
    - Insomnia 15.8% (vs. 13.4% with Risperdal)
    - Sedation 14.6% (vs. 13.9% with Risperdal)
    - Headache 10% (vs. 14.9% with Risperdal)
    - Weight gain 9.3% (vs. 19.8% with Risperdal)
    - Discontinuation rate 21.5% (vs. 14.4% with Risperdal)

Journal of Clinical Psychiatry 2016 July 19

OBJECTIVE: To assess the effect of dose increase in adult patients with schizophrenia who demonstrate inadequate initial response to standard-dose lurasidone and to evaluate the efficacy of low-dose lurasidone in adult patients with schizophrenia.
METHODS: In this randomized, double-blind, placebo-controlled study conducted between May 2013 and June 2014, hospitalized patients with acute schizophrenia (DSM-IV-TR criteria) were randomly assigned to double-blind treatment with lurasidone 20 mg/d (n = 101), lurasidone 80 mg/d (n = 199), or placebo (n = 112). Nonresponders to lurasidone 80 mg/d (Positive and Negative Syndrome Scale [PANSS] score decrease < 20%) at 2 weeks were re-randomized to lurasidone 80 mg/d or 160 mg/d for the remaining 4 weeks of the study. The primary outcome measure was change from baseline to week 6 in PANSS total score.
RESULTS: In nonresponders to lurasidone 80 mg/d (n = 95), dose increase to 160 mg/d at week 2 significantly reduced PANSS total score at week 6 study endpoint compared with continuing 80 mg/d (-16.6 vs -8.9; P < .05 [effect size = 0.52]). While a comparable magnitude of improvement was observed in Clinical Global Impression-Severity (CGI-S) score from week 2 to week 6 endpoint for lurasidone 160 mg/d versus 80 mg/d (-1.0 vs -0.6; effect size = 0.44), the difference was not statistically significant (P = .052). Patients receiving lurasidone 20 mg/d did not demonstrate significant improvement compared with placebo at week 6 in PANSS total (-17.6 vs -14.5; P = .26) or CGI-S (-0.93 vs -0.73; P = .17) scores. Few dose-related adverse effects associated with lurasidone were observed.
CONCLUSIONS: In adult patients with schizophrenia demonstrating nonresponse to 2 weeks of treatment with lurasidone 80 mg/d, dose increase to 160 mg/d resulted in significant symptom improvement compared with continuing lurasidone 80 mg/d. Lurasidone 20 mg/d was not associated with significant improvement in psychotic symptoms in adult patients with schizophrenia.

Efficacy and Safety of Lurasidone in Adolescents with Schizophrenia: A 6-Week, Randomized Placebo-Controlled Study
Robert Goldman, Antony Loebel, Josephine Cucchiaro, Ling Deng, Robert L Findling
Journal of Child and Adolescent Psychopharmacology 2017 May 5

OBJECTIVE: To evaluate the efficacy and safety of lurasidone in acutely symptomatic adolescent patients with schizophrenia.
METHODS: Patients aged 13-17 years were randomly assigned to 6 weeks of double-blind, fixed-dose lurasidone (40 or 80mg/day) or placebo. Primary and key secondary efficacy measures were change from baseline to week 6 in the Positive and Negative Symptom Scale (PANSS) total score and Clinical Global Impressions-Severity (CGI-S) score, respectively, using mixed model for repeated measurement (MMRM) analysis. The proportion of patients achieving treatment response at endpoint, based on ≥20% reduction in PANSS total score, was analyzed using a logistic regression model.
RESULTS: Least-squares (LS) mean change in PANSS total score from baseline to week 6 was -18.6 with lurasidone 40mg/day (N=108; p<0.001 vs. placebo; effect size=0.51), -18.3 with lurasidone 80mg/day (N=106; p<0.001 vs. placebo; effect size=0.48), and -10.5 with placebo (N=112). Similarly, LS mean change in CGI-S score from baseline to week 6 was significantly greater with lurasidone 40mg/day (-1.0; p<0.001; effect size=0.49) and 80mg/day (-0.9; p=0.0015; effect size=0.45) compared with placebo (-0.5). A significantly higher proportion of patients met responder criteria on lurasidone 40 and 80mg/day versus placebo (63.9% and 65.1% vs. 42.0%; p<0.001 for both comparisons). The rate of study discontinuation was 10.3% in lurasidone-treated and 17.7% in placebo-treated patients. The most common adverse events (incidence ≥5% in either lurasidone dose group and at least twice the rate of placebo) for lurasidone 40mg/day, 80mg/day, and placebo, respectively, were nausea (12.7%, 14.4%, and 2.7%), somnolence (9.1%, 11.5%, and 5.4%), akathisia (9.1%, 8.7%, and 1.8%), vomiting (8.2%, 6.7%, and 1.8%), and sedation (5.5%, 1.9%, and 1.8%). Treatment with lurasidone was not associated with clinically meaningful effects on body weight, lipids, measures of glycemic control, or prolactin.
CONCLUSIONS: In this 6-week study, lurasidone at doses of 40 and 80mg/day demonstrated statistically significant and clinically meaningful symptom improvement in adolescent patients with schizophrenia. Lurasidone was generally well tolerated with few effects on weight and metabolic parameters, consistent with findings in adult patients with schizophrenia.

Lurasidone in Children and Adolescents: Systematic Review and Case Report
Jonathan Channing, Mary Mitchell, Samuele Cortese
Journal of Child and Adolescent Psychopharmacology 2018 July 13
OBJECTIVE: To perform a systematic review of studies of lurasidone in children and/or adolescents and to present a case report aimed to add further insights into its use in clinical practice with youth.
METHODS: We searched the following databases for empirical studies, of any design, focusing on the pharmacokinetics, efficacy, or safety of lurasidone in children and/or adolescents: Pubmed (Medline), OVID (PsycInfo, EMBASE+EMBASE classic, OVID Medline), Web of Knowledge, and ClinicalTrials.gov (last search January 23, 2018).
RESULTS: From a pool of 301 potentially relevant references, we retained 12 pertinent studies (reported in 28 references), including 1 pharmacokinetics study, 1 double blind randomized controlled trial (RCT) for bipolar depression (BD) with 1 related interim analysis study of its extension phase and 1 related external posterior predictive check study, 1 double blind RCT for schizophrenia with 3 related interim analyses of its extension phase, 1 RCT and 1 case report for autism spectrum disorder, and 2 open-label studies focusing on a variety of disorders. Overall, these studies show that lurasidone is significantly more efficacious than placebo, with moderate effect sizes, and is well tolerated for BD and schizophrenia in youth. Published studies in youth have in general used doses up to 80mg/day. Our case report suggests that high doses of lurasidone (148mg/day) were well tolerated and might have contributed to substantial functional improvement in a 14-year old girl with psychosis and a previous history of anorexia nervosa, who had not responded to previous antipsychotics (olanzapine, risperidone, aripiprazole).
CONCLUSIONS: There is increasing evidence that lurasidone may be moderately effective and well tolerated for the treatment of BD and psychosis in youth and may have procognitive effects. Our case report suggests that future RCTs should assess the efficacy and tolerability of high doses (>80mg/day) of lurasidone in youth.