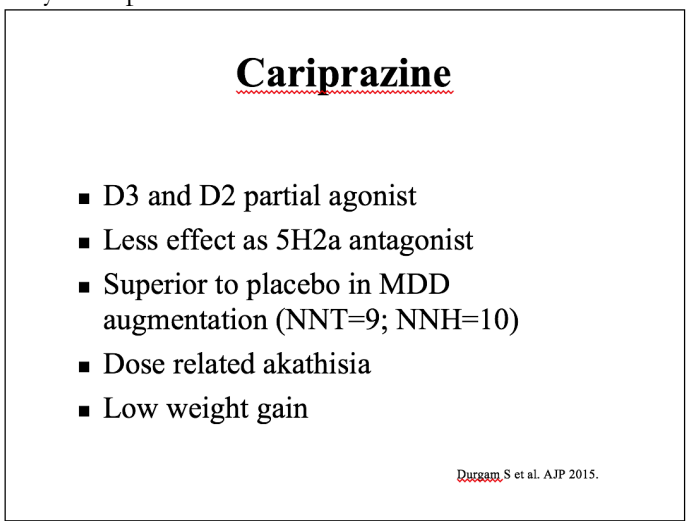
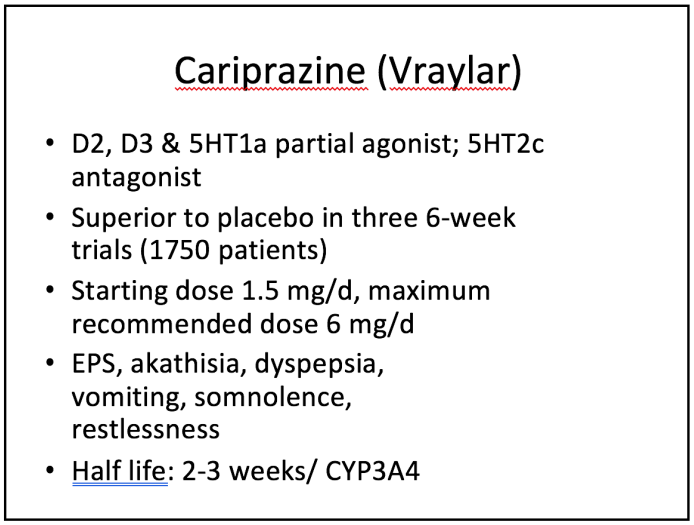
Cariprazine (Vraylar)

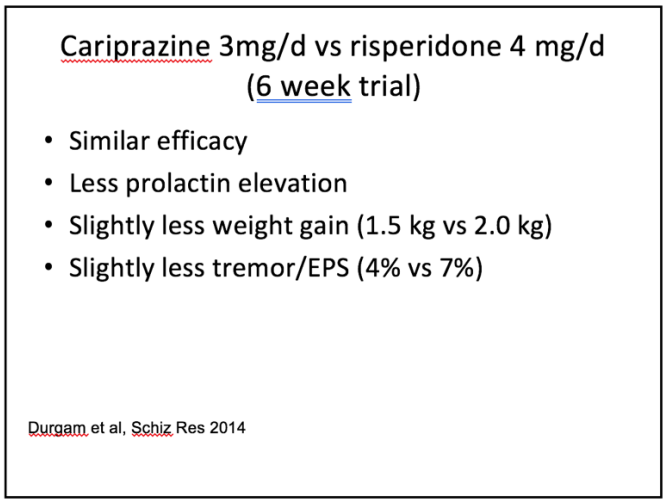
- FDA-approved for acute treatment of schizophrenia and bipolar I manic or mixed episodes (2015)
- FDA-approved for new drug application for maintenance treatment of schizophrenia 2018
- Efficacy in depression



- Efficacy in schizophrenia
  - Superior to placebo in 72-week multi-national, randomize, double-blind study of stabilized cariprazine dose of 3, 6, or 9 mg daily
    - ~2X as many subjects relapsed on placebo (49.5%) as on cariprazine (29.7%)
  - Superior to placebo in three 6-week trials (1750 patients)



  - Response rate 31% for Vraylar vs. 21% placebo
    - NNT 10
  - Relapse rate over 52 weeks 24.8% for Vraylar vs. 47.5% placebo
    - NNT 5
  - Cariprazine 3 mg/day vs. Risperdal 4 mg/day (6-week study; Durgam et al, 2014)

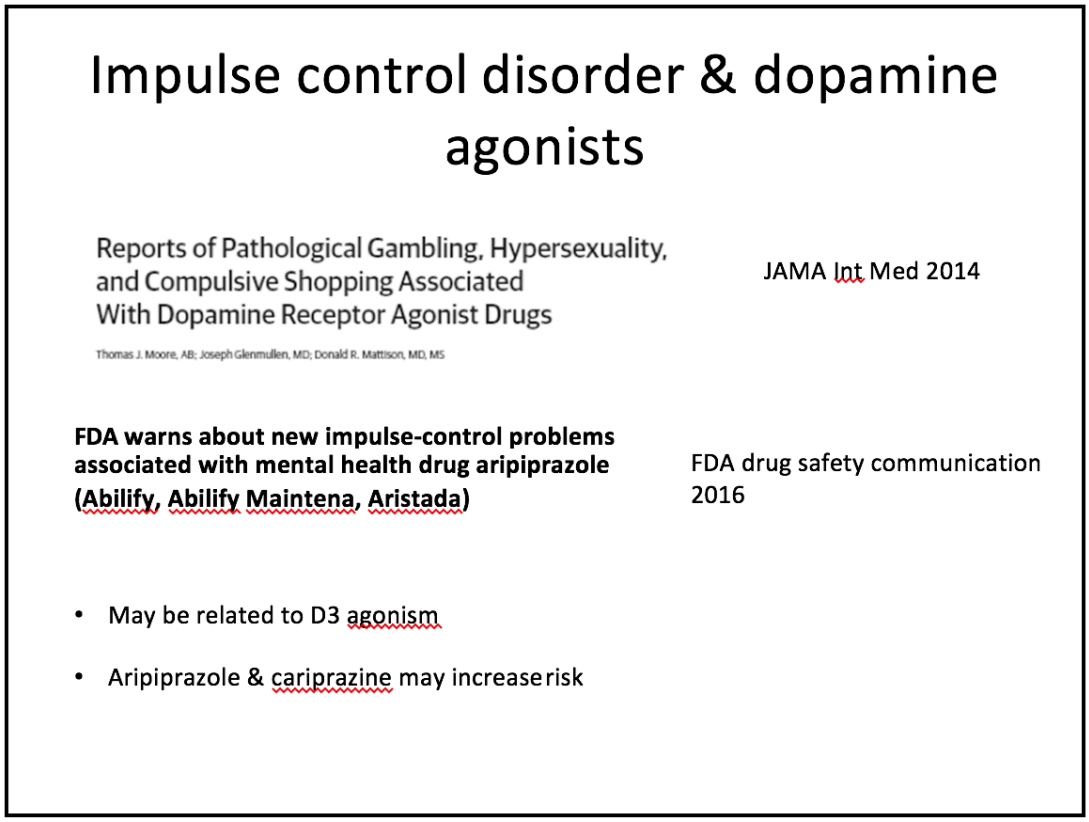


- Similar efficacy
- Cariprazine with
  - less prolactin elevation
  - slightly less weight gain (1.5 kg vs. 2 kg)
  - slightly less tremor/EPS (4% vs. 7%)

- Cariprazine vs. Risperdal and negative symptoms (461 subjects; Nemeth et al, 2017)
  - Cariprazine superior out through > 25 weeks

- Pharmacology
  - Receptor activity in decreasing order of affinity
    - High
      - Dopamine partial agonist
        - D3, 5-8X greater than D2, partial agonism
          - Abilify and Rexulti prefer D2 to D3
          - Specificity for D3 is 3-10X greater than Abilify
        - D2 (2L and 2S)
      - 5HT2b
    - Moderate
      - 5HT1a partial agonist (moderate)
      - Histamine1 (lower)
    - Even lower
      - 5HT7
      - 5HT2a (antagonist)
      - 5HT2b (antagonist)
      - 5HT2c
      - Alpha-1 noradrenergic
    - Lowest
      - Muscarinic
  - Dosing
    - 1.5-6 mg/d for schizophrenia (up to 9 mg/day)
    - 3-6 mg/d for mania

        - 1, 5, 3, 4.5, 6 mg caps
        - Once daily dosing
        - Can be taken with or without food
        - Consider every other day dosing if with 3A4 inhibitor
    - Peak is 3-4 hours if fasting, a bit longer if not
    - Half life 2-5 days (elsewhere listed as 2-4 days)
    - Metabolized by 3A4 to two active metabolites
        - The didesmethyl-cariprazine metabolite has a half-life of 1-3 weeks
- Side effects, general
    - Most common:
        - Muscle restlessness (akathisia), usually mild
            - NNH 20 at lower doses, 12 at higher
        - Parkinsonian muscle side effects (EPS), usually mild
            - NNH 15 at lower doses, 10 at higher
        - Dyspepsia
        - Vomiting
        - Somnolence
        - Restlessness
    - Favorable metabolic profile
    - Weight gain 8% vs. 5% placebo
        - NNH 34
    - Lack of anticholinergic side effects
    - Minimal effects on
        - Prolactin
        - Blood pressure
        - Cardiac conduction
    - Can cause
        - Rash
        - Pruritis
        - Urticarial
        - ?angioedema



- Evidence in Schizophrenia
  - Acute exacerbation of schizophrenia (2 phase 3 trials)
    - Kane et al, 2015
      - Side effects

Muscle restlessness	24-25% vs. 5% with placebo
Headache	14-24% vs. 17% with placebo
Insomnia	10-16% vs. 16% with placebo
Restlessness	10-15% vs. 7% with placebo
Extrapyramidal muscle symptoms	8-15% vs. 3% with placebo
Nausea OR vomiting	15-21% vs. 11% with placebo
Stomach upset	3-10% vs. 4% with placebo
Constipation	9-13% vs. 5% with placebo
Tremor	8-11% vs. 3% with placebo
Weight increase	4-8% vs. 2% with placebo
Diarrhea	6-8% vs. 2% with placebo

    - Durgam et al, 2014; acute exacerbation in schizophrenia; 732 patients
      - Cariprazine 1.5 mg, 3 mg, or 4.5 mg vs Risperdal vs. placebo
      - Overall response better with cariprazine 3 mg or 4.5 mg vs. placebo from week 1-6
      - Overall response better with cariprazine 1.5 mg vs. placebo from week 2-6
      - (Risperdal > placebo but not compared to cariprazine)
      - Response rates
        - 31-36% in cariprazine

        - 19% in placebo
        - 44% in Risperdal
    - Side effects
        - **insomnia
        - **extrapyramidal muscle side effects
        - **muscle restlessness
        - **sedation
        - **nausea
        - **dizziness
        - **constipation
        - Not associated with changes in
            - Prolactin
            - Cholesterol
            - Glucose
        - Weight was intermediate between placebo and Risperdal
- Relapse prevention (one phase 3 study)
    - 72 weeks
    - Relapse rates
        - Cariprazine: 24.8%
        - Placebo: 47.5%

- Bipolar disorder
    - Depression
        - Durgam et al, 2016
            - 571 patients
            - 1.5 mg/day (0.75-3 mg)
            - Safe and effective vs. placebo
            - Side effects
                - **Akathisia** **2.8-14.4% vs. 1.4% placebo**
                - **Insomnia** **6.8-11.6% vs. 8.3% placebo**
                - Nausea 8.2-8.5% vs. 4.8% placebo
                - Headache 6.8-7.8% vs. 11% placebo
                - Somnolence 4.3-6.8% vs. 4.1% placebo
                - Restlessness 2.7-6.2% vs. 3.4% placebo
                - Diarrhea 1.4-6.2% vs. 5.5% placebo
                - Irritability 1.4-5% vs. 0.7% placebo
                - Weight gain slight
    - Mania
        - Calabrese, et al, 2015
            - 65 adults, mania
            - 4.8-12 mg
            - Response rates
                - Cariprazine 59.3-60.6%
                - Placebo 35.5%
            - Remission rates

        - Cariprazine 44.3-44.8%
        - Placebo 29.4%
    - Side effects
        - Akathisia 20%
        - Parkinson's sx 12%
        - Nausea 10%
        - Tremor 4%
        - Wgt gain>7% 2%
- Bose et al, 2012, 151 patients, acute mania:
    - 59% response rate vs. 44% placebo
    - 52% remission rate vs. 35% placebo
    - Benefits seen by day 4
    - 3-12 mg/day, average dose 7.5 mg/day
    - Most common side effects:
        - Restless muscles
        - Muscle side effects (other): 46% vs. 12% in placebo
        - Tremor
        - Upset stomach
        - Vomiting

Efficacy and safety of adjunctive cariprazine in inadequate responders to antidepressants: a randomized, double-blind, placebo-controlled study in adult patients with major depressive disorder

Suresh Durgam, Willie Earley, Hua Guo, Dayong Li, György Németh, István Laszlovszky, Maurizio Fava, Stuart A Montgomery

Journal of Clinical Psychiatry 2016, 77 (3): 371-8

BACKGROUND: Cariprazine is an atypical antipsychotic currently under investigation as adjunctive therapy in patients with major depressive disorder (MDD) who have inadequate response to standard antidepressant therapy.

METHOD: A randomized, double-blind, placebo-controlled, flexible-dose study was conducted from December 2011 to December 2013 in adults who met DSM-IV-TR criteria for MDD and had an inadequate antidepressant response. Eligible patients were randomized to 8-week adjunctive treatment with placebo (n = 269), cariprazine 1-2 mg/d (n = 274), or cariprazine 2-4.5 mg/d (n = 276). The primary efficacy parameter was change from baseline to week 8 in Montgomery-Asberg Depression Rating Scale (MADRS) total score; P values were adjusted for multiple comparisons. Safety assessments included adverse events, clinical laboratory tests, vital signs, electrocardiograms (ECGs), and suicidality.

RESULTS: Compared with placebo, reduction in MADRS total score at week 8 was significantly greater with adjunctive cariprazine 2-4.5 mg/d (least squares mean difference [LSMD] = -2.2; adjusted P = .0114), but not with cariprazine 1-2 mg/d (LSMD = -0.9; adjusted P = .2404). Significant LSMDs for MADRS total score change were detected at all earlier study visits (weeks 2, 4, 6) in the 2- to 4.5-mg/d group and at weeks 2 and 4 in the 1- to 2-mg/d group (all P values < .05). Treatment-emergent adverse events reported in ≥ 10% of patients in either cariprazine dosage group were akathisia (22.3%), insomnia (13.6%), and nausea (12.8%) (all in 2- to 4.5-mg/d group). Mean changes in metabolic parameters, vital signs, and ECG parameters were generally similar between groups. No suicide-related adverse events were reported.

DISCUSSION: These results show that adjunctive cariprazine 2-4.5 mg/d was effective and generally well tolerated in adults with MDD who had inadequate responses to standard antidepressants. Further clinical studies to confirm these results are warranted.

Cariprazine versus risperidone monotherapy for treatment of predominant negative symptoms in patients with schizophrenia: a randomised, double-blind, controlled trial

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Lancet 2017 February 6

BACKGROUND: Although predominant negative symptoms of schizophrenia can be severe enough to cause persistent impairment, effective treatment options are lacking. We aimed to assess the new generation antipsychotic cariprazine in adult patients with predominant negative symptoms.

METHODS: In this randomised, double-blind, phase 3b trial, we enrolled adults aged 18-65 years with long-term (>2 year), stable schizophrenia and predominant negative symptoms (>6 months) at 66 study centres (mainly hospitals and university clinics, with a small number of private practices) in 11 European countries. Patients were randomly assigned (1:1) by an interactive web response system to 26 weeks of monotherapy with fixed-dose oral cariprazine (3 mg, 4·5 mg [target dose], or 6 mg per day) or risperidone (3 mg, 4 mg [target dose], or 6 mg per day); previous medication was discontinued over 2 weeks. The primary outcome was change from baseline to week 26 or end of treatment on the Positive and Negative Syndrome Scale factor score for negative symptoms (PANSS-FSNS) analysed in a modified intention-to-treat population of patients who had follow-up assessments within 5 days after

last receipt of study drugs with a mixed-effects model for repeated measures. Safety was assessed in all patients who received at least one dose of study drug. This study is registered with EudraCT, number 2012-005485-36.
FINDINGS: Between May 27, 2013, and Nov 17, 2014, 533 patients were screened and 461 (86%) patients were randomised to treatment (230 for cariprazine and 231 for risperidone); 460 were included in the safety population (one patient discontinued before study drug intake). 227 (99%) of 230 patients in the cariprazine group and 229 (99%) of 230 patients in the risperidone group were included in the modified intention-to-treat population (178 [77%] in each group completed 26 weeks of treatment). Mean daily doses were 4·2 mg (SD 0·6) for cariprazine and 3·8 mg (0·4) for risperidone. Treatment-emergent adverse events (eg, insomnia, akathisia, worsening of schizophrenia, headache, anxiety) were reported in 123 (54%) patients treated with cariprazine and 131 (57%) patients treated with risperidone. Use of cariprazine led to a greater least squares mean change in PANSS-FSNS from baseline to week 26 than did risperidone (-8·90 points for cariprazine vs -7·44 points for risperidone; least squares mean difference -1·46, 95% CI -2·39 to -0·53; p=0·0022; effect size 0·31). One patient in the risperidone group died of a cause regarded as unrelated to treatment.
INTERPRETATION: Our results support the efficacy of cariprazine in the treatment of predominant negative symptoms of schizophrenia.