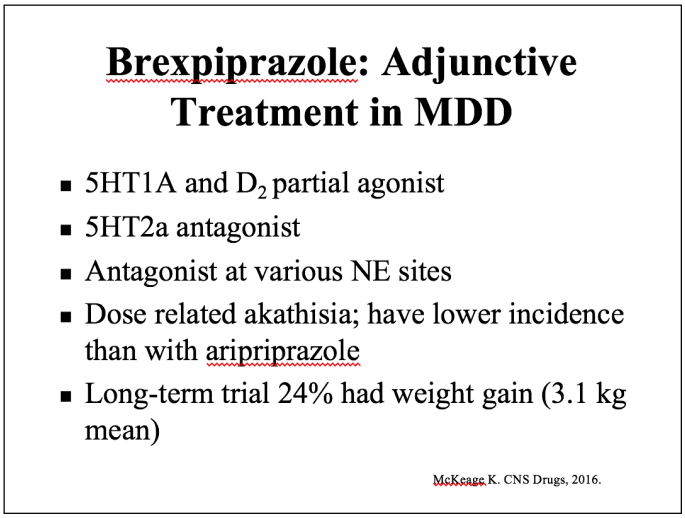
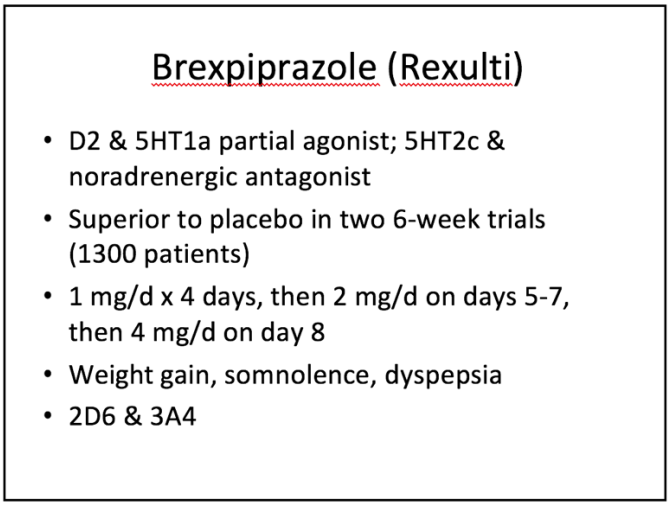
Rexulti (brexpiprazole)

- Rexulti is an atypical antipsychotic (serotonin-dopamine activity modulator) indicated for:
  - Use as an adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD)
    - 

  - Treatment of schizophrenia
    - 2 acute trials
      - 

    - 1 study of relapse prevention
    - 46% response rate for Rexulti vs. 31% placebo
    - 13.5% relapse rate over 52 weeks vs. 38.5% placebo
    - NNT of 4
- Dosage and administration
  - Administer REXULTI once daily with or without food
  - Dosing (increase at weekly intervals)
    - MDD
      - Start at 0.5-1 mg/day
      - Recommended dose 2 mg/day
      - Max dose 4 mg/day
    - Schizophrenia
      - Start at 1 mg/day
      - Recommended dose 2-4 mg/day
      - Max dose 4 mg/day
  - Tablets: 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg

- Side effects
  - **Weight increase**
    - **In MDD studies:**
      - **Weight increased 6-8% vs. 2% placebo**
      - **2.86-3.6 lbs vs. 0.66 lb placebo**
      - **Percentage > or = 7% total weight 2-5% vs. 2% placebo**
    - **In schizophrenia studies:**
      - **Weight increased 3-4% vs. 2% placebo**
      - **2.2-2.64 lbs vs. 0.44 lb placebo**
      - **Percentage > or = 7% total weight 10-11% vs. 4% placebo**
      - **Percentage > or = 7% total weight over 52 weeks 20% vs. 10% placebo**
  - Triglycerides
    - Shift of triglycerides from normal to high: 5-13% vs. 6% placebo
    - Shift of triglycerides from normal/borderline to very high: 0-0.7% vs. 0% placebo
  - MDD studies
    - **Muscle restlessness** **4-14% vs. 2% placebo**
    - **Somnolence OR fatigue** **6-11% vs. 2.5% placebo**
    - **Headache** **4-9% vs. 6% placebo**
    - **Nasopharyngitis** **1-7% vs. 2% placebo**
    - **Somnolence** **4-6% vs. 0.5% placebo**
    - Fatigue 2-5% vs. 2% placebo
    - Tremor 2-5% vs. 2% placebo
    - Dizziness 1-5% vs. 1% placebo
    - Restlessness 2-4% vs. 0% placebo
    - Anxiety 2-4% vs. 1% placebo
    - Increased appetite 2-3% vs. 2% placebo
    - Constipation 1-3% vs. 1% placebo
  - Schizophrenia studies
    - **Muscle restlessness** **4-7% vs. 5% placebo**
    - **Stomach upset** **2-6% vs. 2% placebo**
    - **Blood CPK increased** **2-4% vs. 1% placebo**
    - **Sedation** **2-3% vs. 1% placebo**
    - Tremor 2-3% vs. 1% placebo
    - Diarrhea 1-3% vs. 2% placebo
    - Minimal effects on prolactin
    - No clinically relevant effects on QTc
- Pharmacology
  - Partial dopamine agonist (15-20%)
  - Receptor activity in decreasing order of affinity
    - 5HT1a (partial agonist)
    - alpha 1b (antagonist)
    - D2 (2L) (partial agonist); similar to Abilify
      - 43% intrinsic activity
      - compared to 100% for dopamine itself
      - compared to 61% for Abilify
      - compared to 84% for bifeprunox
      -
    - 5HT2a (antagonist); slightly less than D2 receptors
    - D3
    - 5HT2b (antagonist)
    - 5HT2c (antagonist)

        - 5HT7 (antagonist)
        - alpha 1a (antagonist)
        - histamine H1
        - and also
            - alpha 2b (antagonist)
            - alpha 2c (antagonist)
            - alpha 1d (antagonist)
            - muscarinic M1
    - Half life 91 hours
    - After single dose administration of REXULTI tablets, the peak plasma brexpiprazole concentrations occurred within 4 hours after administration
    - Steady-state concentrations were attained within 10-12 days of dosing.
    - Metabolized to an inactive metabolite
    - 2D6 and 3A4; use ½ usual dose if with strong 2D6 or 3A4 inhibitor, ¼ both or with poor 2D6 metabolizer AND 3A4 inhibitor

Adjunctive Brexpiprazole in Patients With Major Depressive Disorder and Irritability: An Exploratory Study

Maurizio Fava, François Ménard, Charlotte Kampp Davidsen, Ross A Baker

Journal of Clinical Psychiatry 2016 July 5

OBJECTIVE: To evaluate the effects of adjunctive brexpiprazole on symptoms of irritability in patients with major depressive disorder (MDD).
METHODS: Patients diagnosed with MDD according to DSM-IV-TR criteria who had inadequate response to antidepressant treatment continued treatment with their current antidepressant for 2 weeks. Patients still having inadequate response, and with irritability, received 6 weeks of open-label treatment with their current antidepressant at the same dose and adjunctive brexpiprazole (target dose: 3 mg/d). Brexpiprazole was discontinued at week 6, and the patients continued with their antidepressant until week 10. Changes from baseline to week 6 and week 6 to week 10 were analyzed.
RESULTS: This study was conducted between October 7, 2013, and July 30, 2014. Fifty-four patients were treated with adjunctive brexpiprazole. At week 6, clinically relevant improvements were observed in Sheehan Irritability Scale total (-21.1) and item 1 (irritable mood) (-3.5) scores, Kellner Symptom Questionnaire total (-24.4) and anger-hostility subscale (-7.7) scores, and 30-item Inventory of Depressive Symptomatology, clinician version (IDS-C_{30}), item 6 (irritable mood) score (-1.2). More (15 patients) stopped than developed (5 patients) anger attacks during treatment, as measured by the Anger Attacks Questionnaire. The Clinical Global Impressions-Severity of Illness score improved (-1.4), as did the depressive symptoms (IDS-C_{30} total score, -17.8; Kellner Symptom Questionnaire depression subscale score, -7.7; and Montgomery-Asberg Depression Rating Scale total score, -14.2). Irritability symptoms worsened after brexpiprazole discontinuation, assessed at week 10. Adjunctive brexpiprazole was well tolerated.
CONCLUSIONS: Adjunctive treatment with brexpiprazole may represent a strategy for patients with MDD and inadequate response to antidepressant treatment who have symptoms of irritability.

Cognitive Effects of MIN-101 in Patients With Schizophrenia and Negative Symptoms: Results From a Randomized Controlled Trial

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OBJECTIVE: Current dopamine-blocking antipsychotic drugs have little impact on the cognitive deficits associated with schizophrenia. We evaluated whether MIN-101, a molecule that combines sigma-2 antagonism and 5-HT2A antagonism, might improve cognitive deficits in individuals with moderate to severe negative symptoms in schizophrenia.
METHODS: Individuals (N = 244) aged 18 to 60 years with stable symptoms of DSM-5-defined schizophrenia and moderate to severe negative symptoms were randomized to placebo (n = 83), MIN-101 32 mg (n = 78), or MIN-101 64 mg (n = 83) in a 12-week, phase 2b, prospective, double-blind, placebo-controlled, parallel-group trial between May 2015 and December 2015. In a post hoc analysis, mean z and T score changes from baseline at 12 weeks of treatment in the cognitive composite score and individual tests on the Brief Assessment of Cognition in Schizophrenia (BACS) Battery were compared between MIN-101 and placebo.
RESULTS: A total of 79 patients (95.2%) from the placebo group, 76 (97.4%) from the MIN-101 32 mg group, and 79 (95.2%) from the MIN-101 64 mg group completed the BACS at baseline. The BACS token motor (P = .04), verbal fluency (P = .01), and composite z scores (P = .05) showed significant improvements in the MIN-101 32 mg group compared to the placebo group. At week 4, the clinical improvements from baseline in the Positive and Negative Syndrome Scale (PANSS) negative factor showed a significant correlation with improvements from baseline on the BACS composite in the 64 mg group (r = -0.292, P = .020). At week 12, improvement in the PANSS negative factor showed significant correlations with improvements in the BACS composite (r = -0.408, P = .002), Trail Making Test (r = -0.394, P = .003), and verbal memory (r = -0.322, P = .017) for the 64 mg group.
CONCLUSIONS: Results suggest a possible benefit of MIN-101 on cognitive performance in individuals with schizophrenia with stable positive symptoms and concurrent clinically significant negative symptoms.

A Randomized, Placebo-Controlled Study of the Efficacy and Safety of Fixed-Dose Brexpiprazole 2 mg/d as Adjunctive Treatment of Adults With Major Depressive Disorder

Mary Hobart, Aleksandar Skuban, Peter Zhang, Carole Augustine, Claudette Brewer, Nanco Hefting, Raymond Sanchez, Robert D McQuade

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OBJECTIVE: To assess the efficacy, safety, and tolerability of brexpiprazole as adjunct to antidepressant treatment (ADT) in adults with major depressive disorder (MDD) and inadequate response to ADTs.
METHODS: Outpatients with inadequate response to 1-3 ADTs during their current depressive episode (DSM-IV-TR criteria) were administered prospective, open-label ADT. Those patients with inadequate response to prospective ADT were randomized to double-blind, adjunctive brexpiprazole 2 mg/d or placebo. The primary efficacy end point was the change from baseline (randomization) to week 6 in Montgomery-Åsberg Depression Rating Scale (MADRS) total score. Key secondary efficacy end points were the change in Sheehan Disability Scale (SDS) mean score for all patients and the change in MADRS total score for subgroups with minimal response to prospective ADT and DSM-5-defined anxious distress. The study was conducted from July 2014 to May 2016.
RESULTS: Adjunctive brexpiprazole (n = 191) improved MADRS total score from baseline to week 6 versus placebo (n = 202; least squares mean difference [95% confidence limits]: -2.30 [-3.97, -0.62]; P = .0074). There was no separation between groups for the SDS mean score (-0.22 [-0.66, 0.23]; P = .33). Adjunctive brexpiprazole also improved MADRS total score versus placebo in the subgroups with minimal response to prospective ADT (-2.25 [-4.23, -0.27]; P = .026) and anxious distress (-2.98 [-5.24, -0.72]; P = .0099). Treatment with adjunctive brexpiprazole was well tolerated with no unexpected side effects.
CONCLUSIONS: This study adds to the substantial body of evidence for the efficacy and tolerability of brexpiprazole as adjunctive treatment in patients with MDD and inadequate response to ADTs.