Rexulti® (brexpiprazole) and Vraylar™ (cariprazine)

DESCRIPTION

The intent of the Rexulti® and Vraylar™ drug policy is to ensure appropriate selection of patients for therapy based on product labeling, clinical guidelines and clinical studies. Rexulti is approved by the Food and Drug Administration (FDA) for the treatment of schizophrenia and as an adjunct to antidepressant medication for the treatment of major depressive disorder (MDD). Vraylar is approved for the treatment of schizophrenia and the acute treatment of manic or mixed episodes associated with bipolar disorder.

POLICY

**Rexulti®** (brexpiprazole) and **Vraylar™** (cariprazine) may be considered medically necessary for the treatment of schizophrenia in adult patients who have tried and failed at least three generically available antipsychotics.

**Vraylar™** (cariprazine) may be considered medically necessary for the treatment of bipolar disorder in adult patients who have tried and failed at least three generically available antipsychotics.

**Rexulti®** (brexpiprazole) may be considered medically necessary for the adjunctive treatment of major depressive disorder in adult patients who have inadequate response, despite demonstrated adherence with, current antidepressant therapy, when the patient has previously tried and failed the following:

- 2 or more antidepressants (e.g. selective serotonin reuptake inhibitors [SSRI], serotonin norepinephrine reuptake inhibitors [SNRI]) at target therapeutic dosing for a minimum of 4 weeks each; **AND**
- 1 or more guideline recommended, or evidence based, augmentation or combination strategies for treatment resistant depression (e.g. the addition of buspirone, mirtazapine, bupropion, triiodothyronine/liothyronine, tricyclic antidepressant, or lithium) unless all are contraindicated for use; **AND**
1. Generically available atypical antipsychotic with evidence to support use as an adjunctive treatment option for MDD (e.g., aripiprazole, quetiapine, risperidone, olanzapine, ziprasidone), unless all are contraindicated for use

The aforementioned drugs are considered not medically necessary for patients who do not meet the criteria set forth above.

Approval is for lifetime

Quantity limits apply. Rexulti 30 tablets per 30 days, Vraylar 30 capsules per 30 days

**CLINICAL RATIONALE**

The primary focus of this policy is to ensure the use of Rexulti and Vraylar are clinically appropriate, based on the current approved labeling and/or evidence based literature and/or national treatment guidelines. Given there are multiple generically available atypical antipsychotics, the policy also sets forth to ensure that more cost-effective alternatives have been tried and failed, or are inappropriate for use, prior to the approval of Rexulti and Vraylar. Neither Rexulti nor Vraylar have demonstrated significant improvements in safety nor clinical effectiveness compared to other available atypical antipsychotics. While Vraylar included risperidone and aripiprazole in two schizophrenia trials, they served as active references; there was no direct comparison. Vraylar performed similarly against placebo as did aripiprazole in one study. In the other, risperidone numerically outperformed Vraylar, but again, no statistical comparison was provided. The pivotal Rexulti trials did not include active comparators, and thus, there is no evidence to suggest Rexulti is more efficacious than other approved atypical antipsychotics for the treatment of either schizophrenia or major depressive disorder (MDD). Additionally, there is no evidence to suggest Rexulti offers improved efficacy over other adjunctive agents used in the treatment of MDD.

Based on the largest effectiveness trial in MDD to date (the National Institute of Mental Health (NIMH) funded STAR*D trial), only about one-third of patients will achieve the treatment goal of remission with their initial antidepressant trial; approximately another third of patients will remain symptomatic after four successive treatment trials. For those patients who do not respond or only partially respond to monotherapy trials, augmentation is a frequently used strategy to pursue remission. There are multiple options for combination and augmentation. Current place in therapy for atypical antipsychotics is largely unknown as the STAR*D trial, which evaluated sequenced treatment alternatives for treatment-resistant depression, investigated multiple switch and combination strategies, but did not include an arm with an adjunctive atypical antipsychotic.

While Rexulti is FDA approved for the adjunctive treatment of MDD, the addition of an atypical antipsychotic to an antidepressant is not considered a first-, or even a second-line treatment strategy. Augmentation with atypical antipsychotics has produced modest effects in short term (e.g., 6 week trials) studies. National treatment guidelines and treatment algorithms (summaries provided below) generally recommend other augmentation or combination strategies prior to atypical antipsychotics, largely as their adverse events are significant: metabolic side effects including weight gain, hyperglycemia, and hyperlipidemia, potential for cardiac conduction abnormalities, and the risk, albeit rare, for serious adverse events such neuroleptic malignant syndrome (NMS) and tardive dyskinesia (TD). Given the limited sample sizes and short duration of study these risks are not adequately understood in treatment of MDD. Additionally, discontinuation rates based on adverse effects (e.g., akathisia, weight gain, dry mouth and sedation) are discouraging; a 2009 meta-analysis concluded a 4-fold higher discontinuation rate for the atypical antipsychotic therapy compared to placebo. Optimal treatment duration with the atypical antipsychotic is unknown, which further challenges treatment decisions, particularly when the potential for considerable adverse effects exist, long term safety data are unknown and anticipated discontinuation rates high.
When depression treatment does advance to include an atypical antipsychotic, selection tends to incorporate adverse event profiles, patient preferences, and cost, with generic products offering the most cost-effective treatment options. Similar to Rexulti (brexpiprazole), aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone all have evidence to support efficacy for augmentation of an antidepressant trial that has not resulted in an adequate response/remission. The guidelines do not differentiate one agent from another, supporting the concept that all patients will require an individualized approach to treatment selection, taking into account the agent’s adverse effects and drug interaction profile and the patient’s medication regimen and individual risk factors. While the available atypicals for adjunctive MDD all have the risk of metabolic effects, the extent to which they produce these effects is variable based on the agent. The side effect profile of the individual agents may guide treatment selection for the patient with MDD (e.g., quetiapine’s ability to produce sedation may be particularly useful for a patient with insomnia, while the appetite stimulation/weight gain typically noted with olanzapine may benefit a patient with poor appetite and weight loss as of a feature of his/her depression). In major depression trials, the most common adverse effects reported with the individual agents include akathisia with Rexulti (brexpiprazole) and aripiprazole, weight gain with olanzapine, and dry mouth and sedation with quetiapine and risperidone.

NATIONAL TREATMENT GUIDELINES AND TREATMENT ALGORITHM
Texas Medication Algorithm Project (TMAP) Procedural Manual for Major Depressive Disorder Algorithms 2008
According to a well-recognized treatment algorithm for major depression without psychoses, atypical antipsychotic augmentation is a third or fourth-line option, with first and second line treatment options including monotherapy trials (SSRI, SNRI, bupropion, mirtazapine) or combination (e.g., SSRI + bupropion or buspirone, SNRI + mirtazapine, SSRI + TCA) and augmentation strategies (e.g., SSRI + triiodothyronine, TCA + lithium) other than atypical antipsychotics.

RECOMMENDED GUIDELINES
VA/DoD Clinical Practice Guideline Management of Major Depressive Disorder (MDD) 2009
According to the 2009 VA/DoD clinical practice guideline, augmentation should be considered for patients who have had a partial response following at least 6 weeks of monotherapy at a maximum therapeutic dose. The guideline recommends bupropion SR and buspirone as preferred initial agents for augmentation referencing their ease of use and lower risk of toxicity, with efficacy and tolerability findings from the STAR*D trial providing support for this recommendation. The STAR*D trial found that for patients unable to achieve remission despite an adequate trial of citalopram monotherapy, augmentation with bupropion SR or buspirone resulted in remission rates of 39% and 32.9%, respectively; augmentation with bupropion the better tolerated of the two. Similarly the guideline refers to STAR*D findings for their recommendation of lithium and T3 as augmentation agents. Lithium and T3 augmentation of bupropion SR, citalopram, sertraline and venlafaxine XR was utilized at Steps 3 and 4 of the STAR*D treatment algorithm. Remission rates were 14.5% and 25.7% for lithium and T3, respectively. Lithium was not as well tolerated as T3. The VA/DoD guidelines reviewed the evidence available for augmentation with atypical antipsychotics in 2009 and made the following recommendation in regards to their use as augmentation, “the atypical antipsychotics, with the exception of clozapine, can be considered as an alternative augmentation strategy, but should only be considered when other more established augmentation agents have either failed to result in remission or are contraindicated.” The guideline does not differentiate between the individual atypical antipsychotics indicating all mentioned within the document (aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone), with the exception of clozapine, have been reported to improve response or remission when used to augment an antidepressant.

American Psychiatric Association (APA) Practice Guideline for the Treatment of Major Depressive Disorder 2010
According to the 2010 APA practice guidelines atypical antipsychotics may increase response and remission rates for patients who have not responded to more than two medication trials. APA states “When compared with other strategies for antidepressant non-responders, augmentation with a second generation
antipsychotic carries disadvantages: the cost of the many agents, the significant risk of weight gain and other metabolic complications (e.g., dyslipidemia, hypertriglyceridemia, glucose dysregulation, diabetes mellitus) and potential risk of hyperprolactinemia, tardive dyskinesia, neuroleptic malignant syndrome and QTc prolongation. While the guideline recognizes aripiprazole’s FDA approval for adjunctive treatment of MDD (Seroquel XR and Rexulti had yet to receive approval), it references the 2009 Nelsen meta-analysis which found no significant differences between aripiprazole, olanzapine, quetiapine, and risperidone in regards to response and remission rates for this indication. In consideration of the discontinuation rates observed with the atypical antipsychotics within the meta-analysis, the guideline suggests selection of the individual agent take into consideration the individual patient and adverse effect profile of the atypical antipsychotic. Similar to the VA/DoD guidelines, the STAR*D trial is referenced as providing much of the evidentiary base for available augmentation strategies outside of the atypical antipsychotic class.

Institute for Clinical Systems Improvement (ICSI) Health Care Guideline Major Depression in Primary Care 2013
The ICSI practice guideline refers to the TMAP major depression algorithm as an appropriate treatment approach and recommends referral to a behavioral health specialist when considering augmentation strategies for treatment-resistant depression. Among the combination/augmentation options discussed, the guideline graded the following therapies as having high quality evidence: bupropion or buspirone-SSRI combination, mirtazapine-SSRI combination, and augmentation with lithium, triiodothyronine (T₃) or atypical antipsychotics. The combination of TCA-SSRI and stimulant augmentation is given mention, but evidence to support these approaches is of low quality.

**PROCEDURES AND BILLING CODES**

*To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD-CM diagnostic codes.*

- Code(s), if applicable

**REFERENCES**

- Accessed on August 20, 2015


• Accessed on August 20, 2015.

• VA/DoD Clinical Practice Guideline For Management of Major Depressive Disorder 2009.


**POLICY HISTORY**

**Policy #:** 05.01.94  
**Policy Creation:** November 2015  
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