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PHAST PHACT

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TODAY'S TOPIC:

What's New in Palliative Care Medications (2017)

Drug #2: Rexulti® (Brexpiprazole)

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If you have a topic you would like the pharmacy team to answer, please send your suggestions to: pruskowskija@upmc.edu

Background:

Brexpiprazole is an antitypical antipsychotic:

- Initial US approval: 2015
- Indicated for use as an adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD), and treatment of schizophrenia
- Available as 0.25mg, 0.5mg, 1mg, 2mg, 3mg, and 4mg tablets

Importance:

Brexpiprazole was brought to the market primarily for schizophrenia.

- The main targets in the treatment of schizophrenia are D_2, 5-HT_{2A} and α_1 receptors
- A key issue for D_2 partial agonism is to determine an optimal level of intrinsic activity at the D_2 receptors that would lead to a desirable stabilization of dopaminergic transmission. Too high leads to a lack of robust clinical activity and to adverse effects, etc.
- So far, the only D_2 partial agonist aripiprazole, with moderate D_2 intrinsic activity, has reached the market therefore there is a need for broader target

profile (e.g. on selected 5-HT receptor and α adrenoceptor subtypes) to lead to improved outcomes

It is important for palliative care providers to be aware of the available antipsychotic agents.

Pharmacology:

MoA:	Exact mechanism is unknown – but may be mediated through a combination of partial agonist activity at serotonin 5-$HT1_A$ and dopamine D_2 receptors, and antagonist activity at serotonin 5-HT_{2A} receptors
ADME:	A: peak plasma levels within 4 hours, AUC is not affected by a high fat meal D: highly protein bound M: mediated by CYP3A4 and CYP2D6; one major metabolite: DM-3411 (inactive) E: primarily feces (46%, ~14% of the total dose as unchanged drug); T ½: 91 hours
DI:	**Factors** / **Dosage Adjustments for REXULTI (2.5)** Strong CYP2D6* or CYP3A4 inhibitors — Administer half of usual dose Strong/moderate CYP2D6 with Strong/moderate CYP3A4 inhibitors — Administer a quarter of usual dose Known CYP2D6 Poor Metabolizers taking strong/moderate CYP3A4 inhibitors — Administer a quarter of usual dose Strong CYP3A4 inducers — Double the usual dose and further adjust based on clinical response

Key: MoA: Mechanism of Action; ADME: Absorption, Distribution, Metabolism, and Excretion; DI: Drug Interactions; Tmax: time until max concentration; T ½: terminal half-life; Cmax: max concentration; AUC: area under the curve

Other Clinical Points:

Contraindications:	- Hypersensitivity
Warnings and Precautions:	- Risk of cerebrovascular events in patients with dementia-related psychosis - Neuroleptic Malignant Syndrome (NMS), Tardive Dyskinesia (TD) - Metabolic changes, leukopenia, neutropenia and agranulocytosis - Orthostatic hypotension, syncope, and seizures
Dosing:	**Indication** / **Starting Dose** / **Recommended Dose** / **Maximum Dose** MDD (2.1) — 0.5 mg/day or 1 mg/day — 2 mg/day — 3 mg/day Schizophrenia (2.2) — 1 mg/day — 2 to 4 mg/day — 4 mg/day

	- Moderate to Severe Hepatic Impairment (Child-Pugh score ≥7): maximum dose is 2mg once daily for patients with MDD and 3mg once daily for patients with schizophrenia - Moderate, Severe or End-Stage Renal Impairment (CrCl <60mL/minute): maximum dose is 2mg/day for patients with MDD and 3mg/day for patients with schizophrenia - Known CYP2D6 Poor Metabolizers: Reduce the usual dosage by half
ADRs:	- Most common: • MDD: weight increased and akathisia • Schizophrenia: weight increased

Key: ADRs: adverse drug reactions

The Literature:

Brexipiprazole was brought to the market really due to its schizophrenia data, but we will focus on the data regarding the management of MDD:

- J Clin Psychiatry. 2015 Sep;76(9):1232-40.
  Adjunctive brexpiprazole 1 and 3 mg for patients with major depressive disorder following inadequate response to antidepressants: a phase 3, randomized, double-blind study.
  - Objective: To evaluate efficacy, safety, and tolerability of brexpiprazole adjunctive to antidepressant treatments (ADTs) in patients with major depressive disorder (as defined by DSM-IV-TR criteria) with inadequate response to ADTs
  - Methods: After 8-weeks of ADTs, patients were randomized to either 1mg or 3mg of brexpiprazole, or placebo. The primary efficacy end-point was change in Montgomery-Asberg Depression Rating Scale (MADRS) total score from baseline to week 6
  - Results: Brexpiprazole 3mg (n = 213) showed a greater improvement in MADRS total score versus placebo (n = 203; -8.29 vs -6.33; P = .0079), whereas brexpiprazole 1mg did not (n = 211; -7.64 vs -6.33; P = .0737)
  - Conclusion: "Brexpiprazole 3mg demonstrated efficacy versus placebo in the efficacy population per final protocol. Both doses of brexpiprazole were well tolerated."
  - *Discussion:* So far, so good…

So… What does this all mean Jenn?

- Based on the clinical trial data, brexpiprazole has shown itself to be effective as a treatment regimen for schizophrenia and as an adjunctive treatment regimen for MDD – however due to cost, its place in therapy is currently unclear (as you can imagine it is pretty expensive)
- What are the differences between brexipiprazole and aripiprazole?: Really not that much…

	Brexipiprazole	Aripiprazole
FDA Indications	• Adjunctive for MDD • Schizophrenia	• Acute agitation • Schizophrenia • Bipolar I disorder • Adjunctive for MDD
Predominant Receptor Binding	5-HT_{1A}, D_2, D_3 partial agonist and 5-HT_{2A}, 5-HT_{2B}, 5-HT_7, $alpha_{1A}$, $alpha_{1B}$, $alpha_{1D}$, and $alpha_{2C}$ antagonist	D_2 and 5-HT_{1A} partial agonist and 5-HT_{2A} antagonist
Predominant Metabolism	CYP2D6 and CYP3A4	CYP2D6 and CYP3A4
Adverse Effects	Akathisia, weight gain, constipation, fatigue, somnolence, headache, tremor, dizziness, dyspepsia, and extrapyramidal symptoms	Akathisia, headache, weight gain, sedation, somnolence, dizziness, tremor, and extrapyramidal symptoms

Geriatric Considerations:

- No dose-related considerations
- As above, consider the risk of cerebrovascular events in patients with dementia-related psychosis versus the benefits of therapy

Stay tuned for future PCP Phast Phacts on brexpiprazole.

CLINICAL PEARL:

Brexpiprazole is an atypical antipsychotic brought to the market in 2015. It may have distinct pharmacological advantages over aripiprazole, but it's use may be limited by cost.