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Palliative Care Pharmacy PHAST PHACT

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TODAY'S TOPIC:

What's New in Palliative Care Medications (2017) – Drug #6 Brexpiprazole (Rexulti®)

Palliative Care Pharmacy Team:

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Background:

New medications are constantly being approved by the FDA for the treatment of Indications commonly seen in palliative care

Drug #6: Brexpiprazole (Rexulti®)

- Approved: 2015
- FDA Approved Indication(s):
  - Use as an adjunctive therapy to anti-depressants for the treatment of major depressive disorder
  - Treatment of schizophrenia

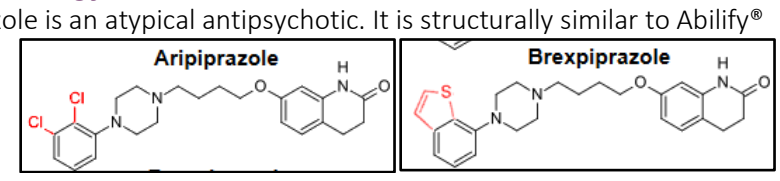
Importance:

Antipsychotics are often used in the palliative care population for the management of delirium, nausea, anxiety, insomnia and/or cachexia. It is important for palliative care providers to be aware of this new agent and its role for our patients.

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

Pharmacology:

Brexipiprazole is an atypical antipsychotic. It is structurally similar to Abilify®



MoA:	Although not completely known, may be mediated through a combination of partial agonist activity at serotonin 5-HT1A and dopamine D2 receptors, and antagonist activity at serotonin 5-HT2A receptors.
ADME:	- Cmax: 4 hours - Highly protein bound to both α1-acid glycoprotein and albumin - Metabolism mediated by CYP3A4 and CYP2D6. One inactive metabolite: DM-3411 - T ½: 91 (for brexiprazole) and 86 (for DM-3411) hours
DIs:	***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, excretion; DIs: drug interactions; Cmax: concentration max; T ½: terminal half-life

Other Clinical Points:

Warnings and Precautions:	BBW: increased mortality in elderly patients with dementia-related psychosis (as in all antipsychotics) Warnings: - NMS and TD - Metabolic changes - Leukopenia, neutropenia and agranulocytosis - Orthostatic hypotension and syncope - Seizures
Dosing:	Based on indication: **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 - In moderate to severe hepatic impairment (CPS ≥ 7), and In moderate to severe or end stage renal impairment (CrCl <60 mL/min): maximum dose is 2mg and 3mg for MDD and schizophrenia respectively - In known CYP2D6 poor metabolizers: reduce usual dose by half
ADRs:	Again based on indication: - MDD: Weight increased and akathisia (≥5% and at least twice the rate for placebo) - Schizophrenia: Weight increased (≥4% and at least twice the rate for placebo)

Key: ADRs: adverse drug reactions; NMS: neuroleptic malignant syndrome; TD: tardive dyskinesia; MDD: major depressive disorder; CPS: child pugh score; CrCl: creatinine clearance

The Literature:

The efficacy and safety of brexpiprazole were assessed in several published placebo controlled clinical trials. The first two studies explored the drug's efficacy and safety in the treatment of schizophrenia and the last two trials discuss its efficacy and safety as an adjunctive treatment for MDD. Here is one in its entirety:

- J Clin Psychiatry. 2015 Sep;76(9):1224-31.
  Efficacy and safety of adjunctive brexpiprazole 2 mg in major depressive disorder: a phase 3, randomized, placebo-controlled study in patients with inadequate response to antidepressants.
  - Objective: To assess the efficacy, tolerability, and safety of brexpiprazole as adjunctive therapy to antidepressant treatments (ADTs) in adults with major depressive disorder (as defined by DSM-IV-TR criteria) and inadequate response to

ADTs

- Methods: phase 3, randomized, placebo-controlled trial. Patients first entered a prospective 8-week phase on physician-determined, open-label ADT. Those with inadequate response were randomized to ADT + brexpiprazole 2 mg/d or ADT + placebo for 6 weeks
- Results: Brexpiprazole (n = 175) reduced mean MADRS total score versus placebo (n = 178) at week 6 in the efficacy population per final protocol (-8.36 vs -5.15, P = .0002). Brexpiprazole improved SDS mean score versus placebo (-1.35 vs -0.89, P = .0349). The most common treatment-related adverse events were weight gain (brexpiprazole, 8.0%; placebo, 3.1%) and akathisia (7.4% vs 1.0%).
- Conclusions: "Adjunctive brexpiprazole therapy demonstrated efficacy and was well tolerated in patients with major depressive disorder and inadequate response to ADTs."
- *Discussion:* So remember this medication has only been studied against placebo

So… What does this all mean Jenn?:

- Yes there is a new atypical antipsychotic on the market – but its role in the palliative care population is small currently
- Despite its generic name, this medication has a different receptor profile and adverse drug reaction profile than aripiprazole (Abilify®)
- When comparing brexipriprazole to other atypical antipsychotics, it appears to have a similar adverse drug reaction profile as aripiprazole – although more studies are needed to confirm
- Currently this medication is not available throughout UPMC
- The cost of brexpiprazole is currently $1122/30 day supply. Most insurance companies do not approve unless the patient has tried at least 2-3 other therapies for schizophrenia or MDD (depending on which indication you are prescribing for)

That concludes "What's New in Palliative Care Medications"

CLINICAL PEARL:

Brexipiprazole (Rexulti) is a new second generation atypical antipsychotic for the management of schizophrenia and major depressive disorder. Its role in palliative care is unclear at this time.