UPMC PALLIATIVE AND SUPPORTIVE INSTITUTE

Palliative Care Pharmacy PHAST PHACT

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TODAY'S TOPIC:

What's New in Palliative Care Medications (2017)

Drug #4: Cariprazine (Vraylar®)

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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:

Cariprazine is an antitypical antipsychotic:

- Initial US approval: 2015
- FDA approved for:
  - Treatment of schizophrenia in adults
  - Acute treatment of manic or mixed episodes associated with bipolar I disorder in adults
- Available as 1.5mg, 3mg, 4.5mg, and 6mg capsules

Importance:

Schizophrenia and bipolar I disorder, may be disorders managed by palliative care providers. It is important for palliative care providers to be aware of all pharmacological options for these disorders. In addition, antipsychotics can be useful agents for palliative care providers to manage a myriad of symptoms including nausea, insomnia and delirium.

Pharmacology:

MoA	Exact mechanism is unknown – but could exert effects through a combination of partial agonist activity at central dopamine D_2 and serotonin 5-HT_{1A} receptors and antagonist activity at serotonin 5-HT_{2A} receptors
ADME:	A: Tmax: 3-6 hours

	D: highly protein bound M: mediated by CYP3A4 and CYP2D6; two major metabolites: desmethyl cariprazine (DCAR) and didesmethyl cariprazine (DDCAR) (which are pharmacologically equipotent to cariprazine) E: T ½: 2 to 4 days (cariprazine); 1 to 3 weeks (DDCAR)
DI:	• Strong CYP3A4 Inhibitors (e.g., ketoconazole): Reduce dose by one-half • Strong CYP3A4 Inducers: Use not recommended

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:	- Warning of use with elderly patients for dementia-induced psychosis - Neuroleptic Malignant Syndrome, Tardive Dyskinesia - Metabolic changes, risk of leukopenia, neutropenia and agranulocytosis, orthostatic hypotension - Seizures
Dosing:	- Schizophrenia: 1.5mg/day starting dose; recommended dose: 1.5-6mg/day - Bipolar Mania; 1.5mg/day; recommended dose; 3-6mg/day
ADRs:	- Most common: Peripheral edema (7% vs 2%), nausea (7% vs 4%), confusional state (6% vs 3%), hallucination (5% vs 3%), constipation (4% vs 3%), and gait disturbance (2% vs <1%)

Key: ADRs: adverse drug reactions

The Literature:

Four phase 2 or 3, 6-week, randomized controlled trials in acute schizophrenia brought caripazine to the market – although some were not formally published. Here are some good reviews though:

- J Clin Psychopharmacol. 2018 Feb;38(1):55-59.
  Efficacy and Acceptability of Cariprazine in Acute Exacerbation of Schizophrenia: Meta-Analysis of Randomized Placebo-Controlled Trials.
- Int J Clin Pract. 2017 Dec;71(12).
  Global improvement with cariprazine in the treatment of bipolar I disorder and schizophrenia: A pooled post hoc analysis.

So… What does this all mean Jenn?

- To review, cariprazine is a potential alternative to aripiprazole. Although both cariprazine and aripiprazole are dopamine receptor partial agonists, cariprazine has

a different receptor binding profile, with greater affinity for the dopamine D3 receptor as the main distinguishing feature

- In regards to tolerability: there do not appear to be clinically relevant adverse effects of cariprazine on metabolic variables, prolactin, or the ECG QT interval. To compare cariprazine to other antipsychotics:

	Cariprazine [38]	Ziprasidone [43]	Aripiprazole [44]	Iloperidone [45]	Asenapine [46]	Lurasidone [47]
Spontaneous AE with incidence ≥5% and twice placebo	Insomnia, extrapyramidal disorder, sedation, akathisia, nausea, dizziness, vomiting, anxiety, and constipation	Somnolence, respiratory tract infection	Akathisia	Dizziness, dry mouth, fatigue, nasal congestion, orthostatic hypotension, somnolence, tachycardia, and weight gain	Akathisia, oral hypoesthesia, and somnolence	Somnolence, akathisia, nausea, and parkinsonism
AE – somnolence, NNH	20–50 (sedation)	15	20	16	17	10
AE – akathisia, NNH	20–34	100	25	Rate lower than placebo	33	10
NNH weight gain ≥7%	12–35	17	20	12	35	67
Prolactin warning?	No	Yes	No	Yes	Yes	Yes
QT warning?	No	Yes	No	Yes	Yes	No

Key: AE: adverse event; NNH: number needed to harm

- As this medication has only been compared to placebo, and currently is expensive, it is unlikely you will see this anytime soon in UPMC

Geriatric Considerations:

- No specific recommendations; clinical trials did not include sufficient numbers of patients aged 65 and older to determine whether or not they respond differently from younger patients. Therefore in general, dose selection for an elderly patient should be cautious
- As still an antipsychotic, be thoughtful of BBW and other considerations

Stay tuned for future PCP Phast Phacts on cariprazine.

CLINICAL PEARL:
Cariprazine is a second generation antipsychotic with some pharmacological advantages over aripiprazole, however due to cost and lack of head-to-head trials, may be rare to see in UPMC.