UPMC PALLIATIVE AND SUPPORTIVE INSTITUTE

THE TABLET: PALLIATIVE CARE PHARMACY TIPS

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

TODAY'S TOPIC:

New Medication Review: Auvelity® (dextromethorphan HBr/bupropion HCl) for Major Depressive Disorder

Background:

Auvelity is a combination of dextromethorphan hydrobromide (HBr) and bupropion hydrochloride (HCl)
- Initial approval: 2022
- Indicated for: major depressive disorder (MDD) in adults
- Available as extended-release tablets: 45 mg/105 mg dextromethorphan HBr/ bupropion HCl

Importance:

Between 24-70% of the palliative care population is diagnosed with depression. It is important for palliative care clinicians to be aware of new potential treatment options that come to market along with the evidence to support their use for symptomatic relief.

Pharmacology:

Mechanism of Action	• Dextromethorphan HBr: uncompetitive N-methyl D-aspartate (NMDA) receptor antagonist and sigma-1 receptor agonist, serotonin reuptake inhibitor • Bupropion HCl: relatively weak inhibitor of norepinephrine and dopamine reuptake and CYP450 2D6 inhibitor ○ Bupropion increases plasma concentrations of dextromethorphan
Dosing	One tablet (45mg/105mg) PO daily x3 days then can increase to max dose: one tablet PO BID
Absorption	Tmax: dextromethorphan: 3 hours, bupropion: 2 hours
Distribution	Dextromethorphan: 60-70% protein bound, bupropion: 84% protein bound
Metabolism	dextromethorphan: Hepatic CYP2D6, bupropion: hydroxylation to 3 active metabolites
Excretion	Half-life: dextromethorphan: 22 hours, bupropion: 15 hours Primary route of excretion is urine

Other Clinical Pearls:

Contraindications	Seizure disorder, current/prior diagnosis of bulimia or anorexia nervosa, use with Monoamine Oxidase Inhibitor (MAOI), abrupt discontinuation of alcohol, benzodiazepines, barbiturates, and antiepileptics
Warnings and Precautions	• Seizure risk is dose-related • Increased blood pressure/hypertension; angle-closure glaucoma • Activation of mania or hypomania, psychosis • Dizziness • Serotonin syndrome • May cause fetal harm
Adverse Reactions	≥5%: **Dizziness**, headache, diarrhea, somnolence, dry mouth, sexual dysfunction, and hyperhydrosis
Drug Interactions	• Strong CYP2D6 inhibitors: 50% dose reduction • Strong CYP2B6 inducers: avoid use • Increases exposure of drugs that are substrates of CYP2D6 • May decrease plasms digoxin levels • Co-administration with medications that lower seizure threshold increases risk of seizure • Can cause false-positive urine test results for amphetamines
Dose Adjustments	• Dose reduce in setting of moderate renal impairment (eGFR 30-59mL/min) • Not recommended to use in severe hepatic or renal impairment (eGFR<30) • Dose reduce for CYP2D6 poor metabolizers

The Literature:

J Clin Psychiatry. 2022 May 30;83(4):21m14345.

Efficacy and Safety of AXS-05 (Dextromethorphan-Bupropion) in patients with major depressive disorder: A phase 3 randomized clinical trial (GEMINI)

Objective: To evaluate the safety and efficacy of dextromethorphan-bupropion in treatment of MDD

Methods: Double-blind, placebo-controlled phase 3 trial
- 1 tablet of dextromethorphan/bupropion (D-B) 45-105mg daily x 3 days, then BID versus placebo for 6 weeks

Outcomes:
- Primary: change in Montgomery-Asberg Depression Rating Scale (MADRS) total score
  - MADRS change from baseline at week 1 and 2, clinical remission (MADRS score ≤10), MADRS change from baseline at week 1 and 2, clinical remission (MADRS score ≤ 10), clinical response (≥ 50% reduction in MADRS score from baseline)

Results: n=327; mean age 41.2 (placebo), 42.1 (D-B); range 18-65
- Efficacy:
  - Difference in MADRS total score was -15.9 in D-B group and -12.0 in placebo [LSMD: -3.87; CI: -1.39, -6.36]
  - D-B group was superior to placebo for MADRS improvement at all time points
  - Remission was achieved by 39.5% D-B versus 17.3% placebo; clinical response by 54.0% D-B versus 34.0% placebo
- Safety:
  - D-B most common side effects: dizziness, nausea, headache, somnolence, dry mouth

Conclusion: *"In this phase 3 trial in patients with MDD, treatment with dextromethorphan-bupropion (AX-05) resulted in significant improvements in depressive symptoms compared to placebo starting 1 week after treatment initiation and was generally well tolerated."*

Am J Psychiatry. 2022 Jul;179(7):490-499.

Effect of AXS-05 (Dextromethorphan-Bupropion) in major depressive disorder: A randomized double blind controlled trial

Objective: dextromethorphan-bupropion versus active comparator sustained-release bupropion in adults (18-65 years old) with a diagnosis or moderate-severe major depressive disorder to determine overall efficacy and safety

Methods: randomized, double-blind, multicenter parallel-group clinical trial
- Dextromethorphan-bupropion 45mg/105mg tablet versus bupropion 105mg once daily x3 days then twice daily thereafter for 6 weeks

Outcomes:
- Primary: change in Montgomery-Asberg Depression Rating Scale (MADRS) total score

Results: n=80; mean age 37.7 (B) and 37.3 (D-B)
- Mean change in MADRS score was -13.7 in D-B group versus -8.8 in bupropion group (CI: -3.1, -6.8)
- D-B group mean score change was greater than bupropion at week 2 and thereafter
- Remission rates and response rates greater in D-B: 46.5% and 60.5% versus bupropion: 16.2% and 40.5%, respectively.

Safety
- D-B most common adverse effects: **dizziness**, nausea, dry mouth, decreased appetite, and anxiety

Conclusion: *"In patients with major depression, dextromethorphan-bupropion (AXS-05) significantly improved depressive symptoms compared with bupropion and was generally well tolerated."*

Discussion:

- This medication was not studied in older adults, patients with underlying psychiatric disorders
- See here for a Clinical Review
  - Active comparator trial showed promise for combination of dextromethorphan/bupropion
- We do not know long-term safety outcomes; dizziness seems to be the most common side effect, which would give me pause in prescribing for older adults or those at risk of falls
- It's expensive… Average wholesale price: $1257 for 30-day supply
- Simple dosing regimen: one tablet twice daily
- Inpatient Use at UPMC is restricted to psychiatry for new initiation; continuation from home is permitted without prior approval

CLINICAL PEARL: Dextromethorphan HBr/Bupropion HCl (Auvelity®) was approved in 2022 for major depressive disorder in adults.