Psychiatric Medication Update

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Cox North Hospital Pharmacy
Springfield Missouri
Objectives

- Discuss the meaning of New Medication
- Review new medications
- Learn to evaluate medications
A New Medication for Weight Loss

- What does that mean?
- Obesity is now “cured”?
- For some patients, obesity is “cured”?
Lose weight and keep it off

https://contrave.com/about/
CONTRAVE is a long-term approach that works when added to a diet and exercise to help you achieve sustainable results.

Three different clinical studies showed how patients taking CONTRAVE, along with diet and exercise, lost 2-4x more weight than with diet and exercise alone.

Across 3 different clinical studies, patients struggling with obesity who took CONTRAVE, along with diet and exercise, lost 2-4 times more weight over 1 year than with diet and exercise alone.
**What Happened?**

Along with diet and exercise, patients taking CONTRAVE lost more weight after 56 weeks of treatment than patients taking placebo.

<table>
<thead>
<tr>
<th>COR-I</th>
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<tbody>
<tr>
<td>COR-BMOD</td>
<td></td>
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<tr>
<td>COR-Diabetes</td>
<td></td>
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</table>
**COR-I**

The CONTRAVE group lost an average of 5.4% of their baseline body weight (or **12 pounds**) compared with the placebo group, which lost an average of 1.3% of their body weight (or **3 pounds**).

**COR-BMOD**

The CONTRAVE group lost an average of 8.1% of their baseline body weight (or **18 pounds**) compared with the placebo group, which lost an average of 4.9% of their body weight (or **11 pounds**).

**COR-Diabetes**

The CONTRAVE group lost an average of 3.7% of their baseline body weight (or **8.5 pounds**) compared with the placebo group, which lost an average of 1.7% on average (or **4 pounds**).
Usual dosage: **Two tablets** (naltrexone 16 mg/bupropion 180 mg) **twice daily**

- **Contrave**
- Contrave (bupropion/naltrexone) is a combination product used to promote and maintain weight loss in obese adults or overweight adults who have weight related medical problems. Contrave is the most popular opioid antagonist/atypical antidepressant combinations. There are currently no generic alternatives to Contrave. GoodRx:

<table>
<thead>
<tr>
<th>8mg/90mg</th>
<th>120 tablets</th>
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<tr>
<td>$356 retail</td>
<td>$297.10 with free discount</td>
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<tr>
<td>Save 16%</td>
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</tbody>
</table>

| $335 retail | $297.10 with free discount |
| Save 11%   |                          |

| $362 retail | $297.10 with free discount |
| Save 17%   |                          |

| $299 retail | $297.10 with free discount |
| Save 0%    |                          |

https://www.goodrx.com/contrave?dosage=8mg-90mg&form=tablet&label_override=Contrave&quantity=120&sort_type=popularity
How does naltrexone work?
New Drug?
A New Drug Hits The Market

The Drug Development Process

Step 1: Discovery and Development
Step 2: Preclinical Research
Step 3: Clinical Research
Step 4: FDA Drug Review
Step 5: FDA Post-Market Drug Safety Monitoring

Phase 1 Trial

- **Study Participants:** 20 to 100 healthy volunteers or people with the disease/condition.
- **Length of Study:** Several months
- **Purpose:** Safety and dosage
- Gather information about how a drug interacts with the human body
- Researchers adjust dosing schemes based on animal data to find out how much of a drug the body can tolerate and what its acute side effects are
- Discover how it works in the body, side effects associated with increased dosage, and early information about how effective it is to determine how best to administer the drug to limit risks and maximize possible benefits
Phase 2 Trial

- **Study Participants:** Up to several hundred people with the disease/condition
- **Length of Study:** Several months to 2 years
  - These studies aren't large enough to show whether the drug will be beneficial
  - Provide researchers with additional safety data
  - Researchers use these data to design new Phase 3 research protocols
Phase 3 Trial

- **Study Participants:** 300 to 3,000 volunteers who have the disease or condition
- **Length of Study:** 1 to 4 years
- **Purpose:** Efficacy and monitoring of adverse reactions
  - Demonstrate whether or not a product offers a treatment benefit to a specific population
  - Provides most of the safety data
  - Less common side effects might have gone undetected prior to Phase 3
  - These results are more likely to show long-term or rare side effects
Now? Does it hit the market now?
FDA Drug Review

- Maybe
- Before Phase 1, 2, and 3 trials Drug developers, or sponsors, must submit an Investigational New Drug (IND) application to FDA
- After Phase 1, 2, and 3 trials a New Drug Application (NDA) is filed. It tells the full story of a drug. Its purpose is to demonstrate that a drug is safe and effective.
- The FDA may approve it at this point, or it may forward it to one of its Advisory Committees to get independent, expert advice and to permit the public to make comments
Why?

It is impossible to have complete information about the safety of a drug at the time of approval.

Safety actually evolves over the months and even years.

FDA reviews reports of problems with prescription and over-the-counter drugs, and can decide to add cautions to the dosage or usage information, as well as other measures for more serious issues.
So we have a New Drug
Prilosec, then came Nexium

- Prilosec hit the market in 1988
- Esomeprazole is the S-isomer of omeprazole
- What does that mean?
- It means it’s a new drug, but not a New Drug
Think of Prilosec as a barrel, rather than a capsule. Open up the end of that barrel...

- You will see it’s full of gloves. Left handed and right handed. 50/50
- They are actually called Enantiomers
- Enantiomers are related to each other by a reflection: they are mirror images of each other
- I just think of them as gloves. Much easier to understand
Esomeprazole is the S-isomer of omeprazole

- S means left. R means right.
- It is not uncommon for companies to conduct research and see if the left glove is better than the right glove, or vice versa.
- Heartburn (Nexium OTC labeling): 20 mg once daily for 14 days
- For Prilosec: same
- Some studies have shown Esomeprazole works faster, lasts longer and is more effective
- Many hospitals have just one PPI on their formulary, and consider them interchangeable
Celexa, then came Lexapro

- Celexa (citalopram) hit the market in 1998
- Celexa’s U.S. patent expired in 2003, Lundbeck introduced Lexapro in 2002
- Lexapro (escitalopram) is the S-enantiomer of citalopram
- So, Celexa is a barrel of gloves, left handed and right handed. They did their research and found the left handed gloves are better
- To be exact: Citalopram is a racemic mixture, consisting of 50% (R)-(−)-citalopram and 50% (S)-(+)citalopram. Only the (S)-(+) enantiomer has the desired antidepressant effect
- So if the dosage range for Celexa is 20-40 mg daily, you would expect Lexapro to be dosed at 10-20 mg?
- Correct. And that’s it? Other than that, they are the same?
Lexapro Advantages

- In the clinical development of escitalopram, it was assumed that the therapeutically active enantiomer would have the same efficacy as the racemate (citalopram), but at half the dose.
- Studies indicate that escitalopram has greater efficacy and a faster onset of action than equivalent doses of citalopram.
- Escitalopram separated from placebo at week 1 on the primary efficacy parameter, whereas citalopram first separated from placebo at week 6.
- More patients responded to and achieved remission with escitalopram than to citalopram.
- May be better tolerated than citalopram.
- Few drug interactions and fewer even than with citalopram.
Why?

- We don’t know for sure what causes tissue loss and cell death
- Tangles and plaques are the main reasons according to most scientists
- Plaques made of amyloid beta proteins and neurofibrillary tangles made of tau proteins
- Some have tangles and plaques yet have no symptoms
- Some studies suggest the reason is because the toxic amyloid beta and tau proteins did not accumulate at synapses
- These individuals had a unique synaptic protein signature that made their synapses resistant to amyloid beta and tau
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<tbody>
<tr>
<td>First-line</td>
<td>Cholinesterase inhibitors for mild to moderate AD</td>
<td>Combination therapy with a cholinesterase inhibitor and memantine has been shown to be beneficial</td>
<td>Cholinesterase inhibitors for mild to severe AD</td>
<td>Cholinesterase inhibitors for mild to severe AD Evidence supports NOT stopping cholinesterase inhibitors once the patient reaches the point of severe dementia Memantine monotherapy or combination can be used in moderate to severe AD</td>
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<tr>
<td>Second-line</td>
<td>Memantine is a possible treatment for patients who cannot tolerate cholinesterase inhibitors</td>
<td>Memantine is effective in moderate to severe dementia (monotherapy and in combination)</td>
<td>Recommend to switch to another cholinesterase inhibitor if the first agent is not tolerated or effective</td>
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</tbody>
</table>

Cholinesterase Inhibitors = Aricept.

www.cpnnp.org
Pfizer exits neuroscience

- Pfizer is pulling out of neuroscience drug discovery and early development, and cutting 300 positions in its neuroscience division.

- Prior to the announcement, the company had eight neuroscience products in phase I and phase II trials. These consisted of four clinical programmes in Alzheimer disease, as well as candidates for Parkinson disease, epilepsy, schizophrenia and cognitive disorder.

- Alzheimer drug development efforts are especially fraught, with an estimated 99.6% failure rate

- Pfizer’s head of R&D Mikael Dolsten defended the move as a means “to focus and reallocate our resources into the other five areas where we think we can give the most value mid-term to shareholders and patients.”
ClinicalTrials.gov is a database of privately and publicly funded clinical studies conducted around the world.

Explore 379,601 research studies in all 50 states and in 220 countries.

See listed clinical studies related to the coronavirus disease (COVID-19)

ClinicalTrials.gov is a resource provided by the U.S. National Library of Medicine.

IMPORTANT: Listing a study does not mean it has been evaluated by the U.S. Federal Government. Read our disclaimer for details.

Before participating in a study, talk to your health care provider and learn about the risks and potential benefits.
<table>
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<tr>
<th>#</th>
<th>Status</th>
<th>Study Title</th>
<th>Conditions</th>
<th>Interventions</th>
<th>Locations</th>
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<td>1</td>
<td>Completed</td>
<td>Safety Study of Nicotinamide to Treat Alzheimer’s Disease</td>
<td>• Alzheimer’s Disease</td>
<td>• Drg: Nicotinamide</td>
<td>UCL Irvine School of Medicine, Irvine, California, United States</td>
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<tr>
<td>2</td>
<td>Recruiting</td>
<td>Nicotinamide as an Early Alzheimer’s Disease Treatment</td>
<td>• Mild Cognitive Impairment</td>
<td>• Drg: Nicotinamide</td>
<td>University of California, Irvine, California, United States</td>
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<td>3</td>
<td>Recruiting</td>
<td>Effects of Nicotinamide Riboside on Biomarkers and Oxidative Stress in Mild Cognitive Impairment/Alzheimer’s Dementia</td>
<td>• Mild Cognitive Impairment</td>
<td>• Drg: Nicotinamide riboside</td>
<td>McLean Hospital, Belmont, Massachusetts, United States</td>
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<tr>
<td>4</td>
<td>Recruiting</td>
<td>Metabolic Collector Supplementation in Alzheimer’s Disease (AD) and Parkinson’s Disease (PD) Patients</td>
<td>• Alzheimer’s Disease</td>
<td>• Drg: Metabolic Collector Supplementation</td>
<td>Alanay Alasdin Keykubat University Hospital Antalya, Turkey</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Drg: Sertibol</td>
<td>Medipol University Hospital, Istanbul, Turkey</td>
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**Study Description**

**Brief Summary:**
The purpose of this study is to determine whether nicotinamide, or vitamin B3, is safe and effective in the treatment of Alzheimer's disease.

<table>
<thead>
<tr>
<th>Condition or disease</th>
<th>Intervention/treatment</th>
<th>Phase</th>
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<tbody>
<tr>
<td>Alzheimer's Disease</td>
<td>Drug: Nicotinamide</td>
<td>Phase 1</td>
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<tr>
<td></td>
<td>Drug: Enduramide placebo</td>
<td>Phase 2</td>
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</table>

**Detailed Description:**
The goal of this proposal is to show that, nicotinamide (NA), a B3 vitamin, is safe and effective for the treatment of patients with mild to moderate Alzheimer's disease (AD). NA is known to block the ability of certain proteins to regulate other proteins by removing their acetyl groups. Recent evidence has demonstrated that inhibitors such as NA prevent nerve cell degeneration in models of Huntington's disease (HD), Parkinson's disease and Lou Gehrig's disease (or ALS). Despite these beneficial effects in many different animal models, there have been no studies to date using these inhibitors in AD. In some of our recent studies we found that the potent inhibitor, NA, significantly improves learning and memory in transgenic mice that develop AD. NA treatment also resulted in striking changes in tau, a protein that abnormally accumulates in AD. NA has been extensively used in clinical studies over the last 40 years and is generally safe and well-tolerated. As NA is a safe and readily available vitamin supplement, our recent results provide a strong argument for a study of NA in patients with AD. We therefore propose to treat 50 patients with mild to moderate AD with either NA (1500 milligrams twice a day) or an identical but inactive drug (placebo) for 24 weeks. At 6 week intervals we will assess functions such as learning and memory, and ability to carry out daily activities as well as caregiver reports using standardized tests. We will also perform spinal taps at the beginning and end of the study to measure the level of abnormal tau protein in the cerebrospinal fluid. Blood tests will periodically be done to assess liver function and complete blood counts. The results of this study may provide the basis for a more extensive study of NA for the treatment of mild to moderate AD.
A Neurologist Faces His Alzheimer's Disease

"I'm in the ring with the tiger," says Daniel Gibbs

by Judy George, Senior Staff Writer, MedPage Today May 27, 2021
This has made the headlines many times

November 4, 2020

**Alzheimer's Drug Goes Before FDA Panel With Support**

— Against expectations, agency staff review tilts in favor of anti-amyloid agent aducanumab

https://www.medpagetoday.com/neurology/alzheimersdisease/89491
Peripheral and Central Nervous System Drugs Advisory Committee
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
Building 31, Room 2417
Silver Spring, Maryland 20993-0002

October 23, 2020
Given the devastating toll of this disease, the publicly released data justifies approval accompanied by a Phase 4 post-marketing surveillance study. The alternative, requiring completion of an additional Phase 3 trial, would deny broad access up to four years while it is completed. **A four-year delay is too long to wait** for millions of Americans facing a progressive, fatal disease. A four-year delay is too long to wait for millions of American caregivers. While the trial data has led to some uncertainty among the scientific community, this must be weighed against the certainty of what this disease will do to millions of Americans absent a treatment.
The FDA's Peripheral and Central Nervous System (PCNS) Drugs Advisory Committee voted 10-0 vote, with one member abstaining.

ENGAGE and EMERGE were terminated in March 2019 when a futility analysis determined aducanumab was unlikely to outperform placebo at completion. In October 2019, the drug’s developer, Biogen, reversed its position, saying a review of previously unavailable data showed the drug actually reduced cognitive decline in EMERGE, but not in ENGAGE.

The Committee felt the positive results seen in one of two identical phase III studies could not be considered alone.

https://www.medpagetoday.com/neurology/alzheimersdisease/89544
The FDA Just Approved This Medication Against the Advice of Experts

Atie Hogan · 56 mins ago

Third member of U.S. FDA advisory panel resigns over Alzheimer's drug approval
ADUHELM™
(aducanumab-avwa)
https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761178s000lbl.pdf

The package insert is available online.

ADUHELM is indicated for the treatment of Alzheimer’s disease. This indication is approved under accelerated approval based on reduction in amyloid beta plaques observed in patients treated with ADUHELM.

To receive aducanumab from a physician, individuals must undergo an FDA-required diagnostic test.
Obtain MRIs prior to the 7th and 12th infusions. If radiographic severe ARIA-H is observed, treatment may be continued with caution only after a clinical evaluation and a follow-up MRI demonstrates radiographic stabilization (i.e., no increase in size or number of ARIA-H).
Mechanism of Action

- Aducanumab-avwa is a human, immunoglobulin gamma 1 (IgG1) monoclonal antibody directed against aggregated soluble and insoluble forms of amyloid beta.
- The accumulation of amyloid beta plaques in the brain is a defining pathophysiological feature of Alzheimer’s disease.
- ADUHELM reduces amyloid beta plaques
### Dosing

<table>
<thead>
<tr>
<th>IV Infusion (every 4 weeks)</th>
<th>ADUHELM Dosage (administered over approximately one hour)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion 1 and 2</td>
<td>1 mg/kg</td>
</tr>
<tr>
<td>Infusion 3 and 4</td>
<td>3 mg/kg</td>
</tr>
<tr>
<td>Infusion 5 and 6</td>
<td>6 mg/kg</td>
</tr>
<tr>
<td>Infusion 7 and beyond</td>
<td>10 mg/kg</td>
</tr>
</tbody>
</table>
### Side Effects

Is it over 5%

Is it double the placebo

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ADUHELM 10 mg/kg N=1105 %</th>
<th>Placebo N=1087 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARIA-E</td>
<td>35</td>
<td>3</td>
</tr>
<tr>
<td>Headache&lt;sup&gt;a&lt;/sup&gt;</td>
<td>21</td>
<td>16</td>
</tr>
<tr>
<td>ARIA-H microhemorrhage</td>
<td>19</td>
<td>7</td>
</tr>
<tr>
<td>ARIA-H superficial siderosis</td>
<td>15</td>
<td>2</td>
</tr>
<tr>
<td>Fall</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>Diarrhea&lt;sup&gt;b&lt;/sup&gt;</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Confusion/Delirium/Altered Mental Status/Disorientation&lt;sup&gt;c&lt;/sup&gt;</td>
<td>8</td>
<td>4</td>
</tr>
</tbody>
</table>

<sup>a</sup>Headache includes the adverse reaction related terms headache, head discomfort, migraine, migraine with aura, and occipital neuralgia.

<sup>b</sup>Diarrhea includes the adverse reaction related terms diarrhea and infectious diarrhea.

<sup>c</sup>Confusion/Delirium/Altered Mental Status/Disorientation includes the adverse reaction related terms confusional state, delirium, altered state of consciousness, disorientation, depressed level of consciousness, disturbance in attention, mental impairment, mental status changes, postoperative confusion, and somnolence.
AZSTARYS
(Serdexmethylphenidate and Dexamethylphenidate)

- Approved March 2, 2021
- Press Release:
  “Today’s approval by the FDA is met with great excitement for this innovative new ADHD therapy
- Ann Childress, M.D., President of the Center for Psychiatry and Behavioral Medicine and an investigator in the AZSTARYS clinical trial, commented: “The ADHD industry, and specifically the MPH space, has seen little innovation in recent years, leaving prescribers and patients desiring new treatment options. In my research and practice, three properties are repeatedly cited by patients and their caregivers as being underserved by current ADHD medications: onset of action, duration of effect and consistency of therapy. Having investigated AZSTARYS and directly observed its clinical impact on patients, I believe this product will be an important new tool for physicians to use in providing effective care for patients with ADHD.”
Jumping to Side Effects (from their package insert)

---ADVERSE REACTIONS---

Based on accumulated data from other methylphenidate products, the most common (>5% and twice the rate of placebo) adverse reactions are appetite decreased, insomnia, nausea, vomiting, dyspepsia, abdominal pain, weight decreased, anxiety, dizziness, irritability, affect lability, tachycardia, and blood pressure increased. (6)
Warnings and Precautions

- Potential for Abuse and Dependence
- Serious cardiovascular reactions, such as heart attack, stroke, and death
- Blood pressure and heart rate increases
- Psychiatric adverse reactions, such as induction of mania in bipolar patients
- Prolonged and painful erections, sometimes requiring surgical intervention
- Peripheral Vasculopathy, including Raynaud's Phenomenon
- Long-Term Suppression of Growth
Azstarys compared with Focalin XR
MECHANISM OF ACTION

- d-methylphenidate increases norepinephrine and especially dopamine actions by blocking their reuptake
- Enhancement of dopamine and norepinephrine in certain brain regions (e.g., dorsolateral prefrontal cortex) may improve attention, concentration, executive function, and wakefulness
- Enhancement of dopamine actions in other brain regions (e.g., basal ganglia) may improve hyperactivity
- Enhancement of dopamine and norepinephrine in yet other brain regions (e.g., medial prefrontal cortex, hypothalamus) may improve depression, fatigue, and sleepiness

https://www.neiglobal.com/Members/PsychEdUp/ArticleDetail/tabid/177/action/redirect/args/redirect/article/553/Default.aspx
12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Serdexamethylphenidate is a prodrug of dexamethylphenidate. Dexamethylphenidate HCl is a central nervous system (CNS) stimulant. The mode of therapeutic action in ADHD is not known.

12.2 Pharmacodynamics

Dexamethylphenidate

Dexamethylphenidate is the more pharmacologically active d-enantiomer of racemic d,l-methylphenidate. Methylphenidate blocks the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space.
Pediatric Dosing Age 6-12

- The recommended starting dosage of AZSTARYS is 39.2 mg serdexmethylphenidate/7.8 mg dexmethylphenidate once daily in the morning.

- The dosage may be increased after one week to a dosage of 52.3 mg serdexmethylphenidate/10.4 mg dexmethylphenidate per day, or decreased after one week to a dosage of 26.1 mg serdexmethylphenidate/5.2 mg dexmethylphenidate per day, depending on response and tolerability.

- Maximum recommended dosage is 52.3 mg serdexmethylphenidate/10.4 mg dexmethylphenidate once daily.
Dosing for Adults and Pediatrics Age 13-17

- The recommended starting dosage of AZSTARYS is 39.2 mg serdexmethylphenidate/7.8mg dexmethylphenidate once daily in the morning.
- Increase the dosage after one week to a dosage of 52.3 mg serdexmethylphenidate/10.4mg dexmethylphenidate per day.
- Maximum recommended dosage is 52.3 mg serdexmethylphenidate/10.4 mg dexmethylphenidate once daily.
Orexin, also known as hypocretin
Stimulates Wakefulness

Belsomra (suvorexant)

- Approved August 2014
- First In Class Status
- Dose is 5-20 mg at night
- Starts working in about an hour or maybe less
- Advantages: Primary and chronic insomnia, and for those needed long term treatment, and for those whose insomnia does not resolve with antidepressants or z drug hypnotics or benzodiazepines
- Side effects: Dizziness, nausea, abnormal dreams
More orexin blockers coming soon

- Seltorexant
  - Blocks the orexin 2 receptor only
  - It’s in phase 3 trials for depression

- JNJ-61393215 – Sorry, no name yet
  - Blocks the orexin 1 receptor only
  - It’s in trials now for panic disorder
  - Also depression and substance abuse
Lyndra
Not a new drug
A company developing a new once a week dosage form
<table>
<thead>
<tr>
<th>LYNDRA’S PIPELINE</th>
<th>RESEARCH</th>
<th>PHASE 1</th>
<th>PHASE 2</th>
<th>PIVOTAL</th>
<th>MARKET</th>
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<tr>
<td><strong>NEUROSCIENCE</strong></td>
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<tr>
<td>LYN-005 Weekly Risperidone</td>
<td>Schizophrenia</td>
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<td>LYN-157 Weekly Memantine / Donepezil</td>
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<td>Opioid Use Disorder</td>
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<td>**CARDIOVASCULAR</td>
<td>METABOLIC DISEASES**</td>
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Lyndra has continued to expand its pipeline and recently completed the LYN-005 risperidone schizophrenia Phase 2 clinical study. Greater than 200 patients and healthy volunteers have participated in Lyndra’s clinical trials to date.
**AXS-05**

Breakthrough Therapy Designation

<table>
<thead>
<tr>
<th>product candidate / MOA</th>
<th>phase 1</th>
<th>phase 2</th>
<th>phase 3</th>
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<td>Major Depressive Disorder: Breakthrough Therapy Designation</td>
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<td>Alzheimer's Disease Agitation: Breakthrough Therapy Designation</td>
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[https://www.axsome.com/axs-pipeline](https://www.axsome.com/axs-pipeline)
AXS-05
Two Drug Combination

- Bupropion (Wellbutrin)
- Dextromethorphan – the key ingredient
- The role of bupropion – its primary purpose – to increase the bioavailability of dextromethorphan.
- The drug interaction makes it possible to achieve high dextromethorphan levels for an extended period of time
Depression Response

- 18.8% of patients at Week 1
- 39.7% of patients at Week 2
- 73.2% of patients at Week 6
- 84.6% of patients at 6 months
- 82.8% of patients at 12 months
- (SSRI response = 40-60%)
Depression Remission

- 8.3% of patients at Week 1
- 21.5% of patients at Week 2
- 52.5% of patients at Week 6
- 68.7% of patients at 6 months
- 69.0% of patients at 12 months
- (SSRI remission = 30-45%)
AXS-05* (dextromethorphan-bupropion): Precision design in an oral NMDA receptor antagonist with multimodal activity

Uncompetitive NMDA receptor antagonist
NMDA receptor antagonism is thought to elicit antidepressant effects by altering the inhibitory tone of interneurons and/or having direct actions on the postsynaptic NMDA receptor, to modulate glutamate neurotransmission.

Sigma-1 receptor agonist
Sigma-1 receptor agonism modulates glutamate and monoamine signaling.

CYP2D6 inhibition
Bupropion inhibits CYP2D6 metabolism of dextromethorphan. This increases the plasma levels of dextromethorphan and prolongs its half-life, enabling antidepressant effects.

CYP2D6: cytochrome P450 2D6, ER: endoplasmic reticulum, NMDA: N-methyl-D-aspartate
*AXS-05 is an investigational treatment for depression currently under review by the U.S. Federal Drug Administration (FDA)

https://www.axsome.com/axs-pipeline/about-axs-05
**DXM**

**WHAT IS DXM?**
Dextromethorphan (DXM) is a cough suppressor found in more than 120 over-the-counter (OTC) cold medications, either alone or in combination with other drugs such as analgesics (e.g., acetaminophen), antihistamines (e.g., chlorpheniramine), decongestants (e.g., pseudephedrine), and/or expectorants (e.g., guaifenesin). The typical adult dose for cough is 15 to 30 mg taken three to four times daily. The cough-suppressing effects of DXM persist for 6 to 8 hours after ingestion. When taken as directed, side effects are rarely observed.

**WHAT IS ITS ORIGIN?**
DXM users can obtain the drug at almost any pharmacy or supermarket, seeking out the products with the highest concentration of the drug from among all the OTC cough and cold remedies that contain DXM. DXM products and powder can also be purchased on the Internet.

**What are common street names?**
Common street names include:
- CCC, Dxt, DXM, Poo Man’s PCP, Robo, Rojo, Skittles, Triple C, and Velvet

**What does it look like?**
DXM can come in the form of:
- Cough syrup, tablets, capsules, or powder

**How is it abused?**
DXM is abused in high doses to experience euphoria and visual and auditory hallucinations. Users take various amounts depending on their body weight and the effect they are attempting to achieve. Some users ingest 250 to 1,500 milligrams in a single dosage, far more than the recommended therapeutic dosages described above. Illicit use of DXM is referred to on the street as “Robo-tripping,” “skitling,” or “dosing,” derived from the products that are most commonly abused. Robitussin and Coricidin HBP. DXM abuse has traditionally involved drinking large volumes of the OTC liquid cough preparations. More recently, however, abuse of tablet and gel capsule preparations has increased.

These newer, high-dose DXM products have particular appeal for users. They are much easier to consume, eliminate the need to drink large volumes of unpleasant-tasting syrup, and are easily portable and concealed, allowing an abuser to continue to abuse DXM throughout the day, whether at school or work.

DXM powder, sold over the Internet, is also a source of DXM for abuse. (The powdered form of DXM poses additional risks to the user due to the uncertainty of composition and dose.)

DXM is also distributed in illicitly manufactured tablets containing only DXM or mixed with...
other drugs such as pseudoephedrine and/or methamphetamine.

DXM is abused by individuals of all ages, but its abuse by teenagers and young adults is of particular concern. This abuse is fueled by DXM's OTC availability and extensive “how to” abuse information on various websites.

What is its effect on the mind?
Some of the many psychoactive effects associated with high-dose DXM include:

- Confusion, inappropriate laughter, agitation, paranoia, euphoria, and hallucinations
- Other sensory changes, including the feeling of floating and changes in hearing and touch

Long-term abuse of DXM is associated with severe psychological dependence. Abusers of DXM describe the following three dose-dependent “plateaus”:

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<th>DOSE (MG)</th>
<th>BEHAVIORAL EFFECTS</th>
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<tr>
<td>100-200</td>
<td>Mild stimulation</td>
</tr>
<tr>
<td>200-400</td>
<td>Euphoria and hallucinations</td>
</tr>
<tr>
<td>300-1500</td>
<td>Distorted visual perceptions, loss of motor coordination, out of body sensations</td>
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What is its effect on the body?
DXM intoxication involves:

- Over-activity, lethargy, loss of coordination, slurred speech, sweating, hypertension, nausea, vomiting, and involuntary spasmodic movement of the eyelids

The use of high doses of DXM in combination with alcohol or other drugs is particularly dangerous, and deaths have been reported. Approximately 5-10 percent of Caucasians are poor DXM metabolizers and at increased risk for overdoses and deaths. DXM taken with antidepressants can be life threatening.

OTC products that contain DXM often contain other ingredients such as acetaminophen, chlorpheniramine, and guaifenesin that have their own effects, such as:

- Liver damage, rapid heart rate, lack of coordination, vomiting, seizures, and coma

To circumvent the many side effects associated with these other ingredients, a simple chemical extraction procedure has been developed and published on the Internet that removes most of these other ingredients in cough syrup.

What are the overdose effects?
DXM overdose can be treated in an emergency room setting and generally does not result in severe medical consequences or death. Most DXM-related deaths are caused by ingesting the drug in combination with other drugs. DXM-related deaths also occur from impairment of the senses, which can lead to accidents.

In 2003, a 14-year-old boy in Colorado who abused DXM died when he was hit by two cars as he attempted to cross a highway. State law enforcement investigators suspect that the drug affected the boy’s depth perception and caused him to misjudge the distance and speed of the oncoming vehicles.

Which drugs cause similar effects?
Depending on the dose, DXM can have effects similar to marijuana or ecstasy. In moderate to high doses its out-of-body effects are similar to those of ketamine or PCP.

What is its legal status in the United States?
DXM is a legally marketed cough suppressant that is neither a controlled substance nor a regulated chemical under the Controlled Substances Act.
Cannabis AKA Marijuana

- Cannabis is the umbrella
- Cannabis contains over 400 known compounds
- Two of those compounds:
  - Tetrahydrocannabinol (THC) and cannabidiol (CBD)
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<th>Disorder</th>
<th>CBD</th>
<th>CBD+THC</th>
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<tr>
<td>Depression (42 studies)</td>
<td>• No improvement in symptoms</td>
<td>• No improvement in symptoms</td>
</tr>
<tr>
<td>Anxiety (31 studies)</td>
<td>• No improvement in symptoms</td>
<td>• Reduction in symptoms</td>
</tr>
<tr>
<td>Psychosis (11 studies)</td>
<td>• No improvement in symptoms</td>
<td>• No improvement in positive symptoms</td>
</tr>
<tr>
<td></td>
<td>• Improvement in global functioning</td>
<td>• Worsening of negative symptoms</td>
</tr>
<tr>
<td>ADHD (3 studies)</td>
<td></td>
<td>• No improvement in symptoms</td>
</tr>
<tr>
<td>PTSD (12 studies)</td>
<td></td>
<td>• Improvement in global functioning and nightmare frequency</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• No effect on sleep quality</td>
</tr>
<tr>
<td>Tourette syndrome (8 studies)</td>
<td></td>
<td>• No improvement in symptoms</td>
</tr>
<tr>
<td>All Studies</td>
<td></td>
<td>• More adverse events</td>
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There is scarce evidence to suggest that cannabinoids improve depressive disorders and symptoms, anxiety disorders, attention-deficit hyperactivity disorder, Tourette syndrome, post-traumatic stress disorder, or psychosis.

There is very low quality evidence that pharmaceutical THC (with or without CBD) leads to a small improvement in symptoms of anxiety among individuals with other medical conditions.

There remains insufficient evidence to provide guidance on the use of cannabinoids for treating mental disorders within a regulatory framework.
Thank You!

Questions?

Who put the alphabet in alphabetical order?

What color are mirrors?

If I try to fail, but succeed, which one did I do?

Is it true that five out of four people have trouble with fractions?