UPDATE ON NEURO/PSYCH MEDICATIONS

Steve Williams, Pharm.D. - clinical pharmacist, clinical professor
DEMENTIA

Federal Gov't Expenditures

<table>
<thead>
<tr>
<th>Year</th>
<th>$bn</th>
<th>Number of Americans with AD (millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>$184bn</td>
<td>5.1mn</td>
</tr>
<tr>
<td>2015</td>
<td>$216bn</td>
<td>5.3mn</td>
</tr>
<tr>
<td>2020</td>
<td>$261bn</td>
<td>5.7mn</td>
</tr>
<tr>
<td>2025</td>
<td>$332bn</td>
<td>6.5mn</td>
</tr>
<tr>
<td>2030</td>
<td>$443bn</td>
<td>7.8mn</td>
</tr>
<tr>
<td>2035</td>
<td>$613bn</td>
<td>9.5mn</td>
</tr>
<tr>
<td>2040</td>
<td>$778bn</td>
<td>11.1mn</td>
</tr>
<tr>
<td>2045</td>
<td>$980bn</td>
<td>12.6mn</td>
</tr>
<tr>
<td>2050</td>
<td>$1,167bn</td>
<td>13.4mn</td>
</tr>
</tbody>
</table>

Researchers estimate that 5-8% of Americans aged 65+ have dementia.

- Cognitively Normal: 92-95%
- All dementias: 5-8%

Pie chart showing the distribution of dementia types:
- Alzheimer's Disease: 55%
- Dementia with Lewy Bodies: 20%
- Stroke/Mixed Dementia: 15%
- Traumatic Brain Injury: 6%
- Other/Fronto-temporal Dementia: 4%
<table>
<thead>
<tr>
<th>Type of Dementia</th>
<th>% of Dementias</th>
<th>Symptoms</th>
<th>Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer’s</td>
<td>55</td>
<td>Memory: names, recent events, language deficits (aphasia, apraxia), Late: mood/aggression</td>
<td>Atrophy generalized, esp. temporal, pit.</td>
</tr>
<tr>
<td>Lewy Body</td>
<td>20</td>
<td>Visual hallucinations, cognition fluctuation Parkinsonian: gait, tremor, rigid tone, falls – sensitive to antipsychotics, PD meds</td>
<td>Atrophy, Lewy bodies cortex</td>
</tr>
<tr>
<td>Vascular</td>
<td>15</td>
<td>Focal signs, stepwise decline</td>
<td>Stroke, diabetes</td>
</tr>
<tr>
<td>Pseudo</td>
<td>*</td>
<td>Mimics dementia</td>
<td>Depression, bipolar,</td>
</tr>
<tr>
<td>Other</td>
<td>10</td>
<td>Nutritional, trauma, AIDS, thyroid, drugs/alcohol</td>
<td>Fe, B12, folate,</td>
</tr>
</tbody>
</table>
The diagram illustrates the interactions between different neuronal systems, focusing on the role of glutamatergic neurons. Key components include Cholinergic neurons, glutamatergic neurons, and presynaptic neurons or glial cells.

**Glutamatergic Neuron:**
- Memantine
- NMDAR
- AMPAR
- Acetate
- Choline
- Donepezil
- Rivastigmine
- Galantamine
- Phenserine
- BNC
- Huperzine A
- Dimebolin
- AC-1202
- Ketone bodies
- Improved energy utilization
- Enhanced insulin sensitivity and glucose metabolism
- Postsynaptic neuron
- Ion influx
- Glutamate
- Phosphate group
- Deactivation/Inhibition
- PPAR-\(\gamma\)
- Rosiglitazone
- Valproate
- GSK 3\(\beta\)
- Microtubule
- Nucleus
- CNS

**Presynaptic Neuron or Glial Cell:**
- Secretase \(\beta\)
- APP
- Ab oligomers
- Ab aggregates
- Tramiprosate
- Clioquinol
- AN-1792 IVIg

The diagram also highlights the role of AC-1202 in enhancing insulin sensitivity and glucose metabolism through improved energy utilization.
**FDA-approved drugs**

The U.S. Food and Drug Administration (FDA) has approved five medications (listed below) to treat the symptoms of Alzheimer's disease.

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Brand name</th>
<th>Approved For</th>
<th>FDA Approved</th>
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</thead>
<tbody>
<tr>
<td>1. donepezil</td>
<td>Aricept</td>
<td>All stages</td>
<td>1996</td>
</tr>
<tr>
<td>2. galantamine</td>
<td>Razadyne</td>
<td>Mild to moderate</td>
<td>2001</td>
</tr>
<tr>
<td>3. memantine</td>
<td>Namenda</td>
<td>Moderate to severe</td>
<td>2003</td>
</tr>
<tr>
<td>4. rivastigmine</td>
<td>Exelon</td>
<td>All stages</td>
<td>2000</td>
</tr>
<tr>
<td>5. donepezil and memantine</td>
<td>Namzaric</td>
<td>Moderate to severe</td>
<td>2014</td>
</tr>
</tbody>
</table>
ADUCANUMAB

- Sept 1 2016 Nature
- MAB targeting amyloid plaque
- Scientists may have ‘game changer’ drug to treat Alzheimer’s
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</table>
A. Normal

- Cholinergic interneuron
- Spiny Neuron
- Glutamate
- Dopamine
- Substantia Nigra
- GPe/GPi/SNr

B. Parkinson’s disease

- Cholinergic interneuron
- Spiny Neuron
- Glutamate
- Dopamine
- Acetylcholine
- Substantia Nigra
- GPe/GPi/SNr
WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. RISPERDAL® (risperidone) is not approved for the treatment of patients with dementia-related psychosis. [See Warnings and Precautions (5.1)]
NUPLAZID (PIMAVANSELRIN)

- Parkinson’s Disease - Psychosis
  - Caused by low dopamine
  - Medications increasing dopamine can cause hallucinations
  - Clozapine and Quetiapine used – mechanism is serotonin (5-HT$_{2A}$) receptor blockade
  - Pimavanserin 5HT$_{2A}$ inverse agonist
  - 2016
Atypical Antipsychotics
second generation

Clozapine (Clozaril)

Olanzapine (Zyprexa)

Quetiapine (Seroquel)

Aripiprazole (Abilify)

Brexpiprazole (Rexulti)

Cariprazine (Vraylar)

Asenapine (Saphris)

Risperidone (Risperdal)

Ziprasidone (Geodon)

Lurasidone (Latuda)

Paliperidone (Invega)

Iloperidone (Fanapt)
<table>
<thead>
<tr>
<th>SEDATION</th>
<th>WEIGHT GAIN</th>
<th>EPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>Aripiprazole</td>
<td>Clozapine</td>
</tr>
<tr>
<td>Iloperidone</td>
<td>Lurasidone</td>
<td>Iloperidone</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>Ziprasidone</td>
<td>Quetiapine</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>Asenapine</td>
<td>Asenapine</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Iloperidone</td>
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<tr>
<td>Ziprasidone</td>
<td>Paliperidone</td>
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</tr>
<tr>
<td>Asenapine</td>
<td>Risperidone</td>
<td>Ziprasidone</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Quetiapine</td>
<td>Olanzapine</td>
</tr>
<tr>
<td>Clozapine</td>
<td>Olanzapine</td>
<td>Risperidone</td>
</tr>
<tr>
<td>Quetiapine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Best choice to worst choice.
Weight Gain from Antipsychotic Drugs after 2.5 Months

- Clozaril (clozapine): 9.9 lbs
- Haldol (haloperidol): 7.0 lbs
- Thorazine (chlorpromazine): 6.5 lbs
- Zyprexa (olanzapine): 5.0 lbs
- Stelazine (chlorpromazine): 4.6 lbs
- Thorazine (chlorpromazine): 4.4 lbs
- Seroquel (quetiapine): 4.6 lbs
- Neurontin (gabapentin): 4.1 lbs
- Geodon (ziprasidone): 1.9 lbs
- Abilify (aripiprazole): 1.5 lbs
- Clozaril (clozapine): 1.3 lbs
- Placebo: -0.7 lbs
Genetic factors → Severe mental illness → ↑ Ingestion; ↓ Exertion → Weight gain; Visceral adiposity → Insulin resistance → Reduced glucose tolerance → Hyperinsulinaemic response → β-cell failure → Fasting hyperglycaemia corresponding to diabetes → Antipsychotics → Increased cardiovascular risk → Ketoacidosis
# Extrapyramidal Symptoms

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Onset</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute dystonia</td>
<td>Hours to 5 days</td>
<td>Spasm of tongue, neck, face &amp; back</td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>5 – 30 days</td>
<td>Tremor, shuffling gait, drooling, stooped posture, instability</td>
</tr>
<tr>
<td>Akathesia</td>
<td>5 – 60 days</td>
<td>Compulsive, repetitive motions; agitation</td>
</tr>
<tr>
<td>Tardive dyskinesia</td>
<td>Months to years</td>
<td>Lip-smacking, worm-like tongue movement, ‘fly-catching’</td>
</tr>
</tbody>
</table>
Epilepsy
Absence (Petit Mal) Seizures

Between seizures patient normal

Seizure: vacant stare, eyes roll upward, eyelids flutter (3/sec), cessation of activity, lack of response

EEG normal between seizures
(3/sec generalized spike-and-wave discharges)

Fp1-A1
Fp2-A2
F3-A1
F4-A2
C3-A1
C4-A2
P3-A1
P4-A2

Patient is unresponsive, blinks eyes

200 µV
1 sec
Impairment of consciousness:
cognitive, affective symptoms

Dreamy state; blank, vacant
expression; déjà vu; jamais vu; or fear

Complex Partial Seizures

Frontal lobe
Parietal lobe
Posterior temporal gyrus
Occipital lobe
Superior temporal gyrus

Formed auditory hallucinations. Hears music, etc

Formed visual hallucinations. Sees house, trees that are not there

Bad or unusual smell

Olfactory hallucinations

Psychomotor phenomena. Chewing movements, wetting lips, automatisms (picking at clothing)

Dysphasia

EEG: left temporal lobe seizure

Fp1-F7
F7-T3
T3-T5
T5-O1
Fp2-F8
F8-T4
T4-T6
T6-O2

Repetitive sharp waves over left temporal region
Simple Partial Seizures

Somatosensory: Tingling of contralateral limb, face, or side of body
Postcentral gyrus
Central sulcus
Precentral gyrus
Leg
Trunk
Arm
Face

Focal motor: Tonic-clonic movements of upper (or lower) limb

EEG: focal motor seizure, left arm and hand
Fp1 - F3
F3 - C3
C3 - P3
P3 - O1
P4 - O2
Fp2 - F4
F4 - C4
C4 - P4
Repetitive sharp waves over right central region

Visual: Sees flashes of light, scotomas, unilateral or bilateral blurring

Auditory: Hears ringing, hissing or noises

Grimacing
Contraversive: Head and eyes turned to opposite side
Autonomic: Sweating, flushing or pallor, and/or epigastric sensations

HSS... HSS...
- 1857- Bromides
- 1912-Phenobarbital
- 1938-Phenytoin (Dilantin)
- 1954- Primidone
- 1960- Ethosuximide (Zarontin)

- 1974-Carbamazepine (Tegretol)
- 1975 Clonazepam (Klonopin)
- 1978- Valproate (Depakote)
1993- Felbamate (Felbatol)
1993- Gabapentin (Neurontin)
1995- Lamotrigine (Lamictal)
1997- Topiramate (Topamax)
         Tiagabine (Gabitril)
1999- Levetiracetam (Keppra)
2000- Oxcarbazepine (Trileptal)
2000- Zonisamide (Zonegran)
2005- Pregabalin (Lyrica)
2009- Lacosamide (Vimpat)
2009- Rufinamide (Banzel)
2010- ACTH (Acthar)
2011- Clobazam (Onfi)
2012 - Ezogabine (Potiga)
2012-Perampanel (Fycompa)
2013- Oxcarbazepine (Oxtellar XR)
• Vigabatrin (Sabril) 2009
• Topiramate (Topamax XR) 2013
• Eslicarbazepine (Aptiom) 2014
• Brivaracetam (Briviact) 2016
ANTIDEPRESSANTS

Mechanisms, differences, uses,
Selective serotonin reuptake inhibitors (SSRIs)

• Citalopram (Celexa)
• Escitalopram (Lexapro, Cipralex)
• Paroxetine (Paxil, Seroxat)
• Fluoxetine (Prozac)
• Fluvoxamine (Luvox)
• Sertraline (Zoloft, Lustral)
Serotonin-norepinephrine reuptake inhibitors (SNRIs)

- Desvenlafaxine (Pristiq)
- Duloxetine (Cymbalta)
- Levomilnacipran (Fetzima)
- Milnacipran (Ixel, Savella)
- Tofenacin (Elamol, Tofacine)
- Venlafaxine (Effexor)
Serotonin modulators and stimulators (SMSs)

- **Vilazodone** (Viibryd)
- **Vortioxetine** (Trintellix)
VORTIOXETINE

• serotonin modulator and stimulator
• September 30, 2013, the Food and Drug Administration approved (Brintillex) to avoid confusion with the blood-thinning medication Brilinta in the United States, but on May 2, 2016, the US FDA approved a name change to Trintellix
Serotonin antagonists and reuptake inhibitors (SARIs)

• Reboxetine (Edronax)

• Viloxazine (Vivalan)

• Atomoxetine (Strattera)
Tetracyclic antidepressants (TeCAs)

- **Amoxapine** (Asendin)
- **Maprotiline** (Ludiomil)
- **Mianserin** (Bolvidon, Norval, Tolvon)
- **Mirtazapine** (Remeron)
- **Setiptiline** (Tecipul)
Tricyclic antidepressants (TCAs)

- Amitriptyline (Elavil, Endep)
- Amitriptylinoxide (Amioxid, Ambivalon, Equilibrin)
- Clomipramine (Anafranil)
- Desipramine (Norpramin, Pertofrane)
- Dibenzepin (Noveril, Victoril)
- Dimetacrine (Istonil)
- Dosulepin (Prothiaden)
- Doxepin (Adapin, Sinequan)
- Imipramine (Tofranil)
- Lofepramine (Lomont, Gamanil)
- Melitracen (Dixeran, Melixeran, Trausabun)
- Nitroxazepine (Sintamil)
- Nortriptyline (Pamelor, Aventyl)
- Noxiptiline (Agedal, Elronon, Nogedal)
- Pipofezine (Azafen/Azaphen)
- Protriptyline (Vivactil)
- Trimipramine (Surmontil)
Atypical antipsychotics

- **Aripiprazole** (Abilify) – specifically approved as an *adjunct* for major depressive disorder
- **Brexpiprazole** (Rexulti) – specifically approved as an adjunct for major depressive disorder
- **Lurasidone** (Latuda) – specifically approved as an adjunct for depressive episodes in bipolar disorder
- **Olanzapine** (Zyprexa) – specifically approved as an adjunct for major depressive disorder
- **Quetiapine** (Seroquel) – approved as an adjunct for both major depressive disorder and depressive episodes in bipolar disorder
MAJOR DEPRESSIVE DISORDER

• Which is the best?
• Individualizing effects and side effects

Selecting Medication

Many safe, efficacious, inexpensive medications are available

• SSRIs and SNRIs are first line; SSRIs are most commonly used; some SSRIs are approved for anxiety disorders
• Many generic formulations available; no absolute class advantage
• Little data to guide selection of medication for individual patients
• Medications differ mainly in adverse effect profiles
Additional Considerations

Considerations

- Prior successful use or family history of use
- Patient concerns discussed during the clinical interview (e.g., sexual adverse effects)
- Breast-feeding: consult LactMed®

Specific recommendations

- Insomnia: mirtazapine
- Fatigue, amotivation: SNRI or bupropion
- Pain: duloxetine
- Cognitive impairment: vortioxetine
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MDD Treatment in Primary Care

PCPs manage approximately one-third to one-half of nonelderly adults\textsuperscript{a,b} and nearly two-thirds of older adults\textsuperscript{c} who receive treatment for MDD.

\begin{itemize}
  \item Prescription for antidepressants written by PCPs\textsuperscript{d}
  \item Percentage written by psychiatrists and addiction specialists
  \item Other
\end{itemize}

\begin{itemize}
  \item Patients, %
  \item \[\text{PCPs}\]
  \item \[\text{68}\]
  \item \[\text{21}\]
  \item \[\text{11}\]
\end{itemize}

\textit{PCPs include pediatricians, obstetrician/gynecologists, physician assistants, and nurse practitioners.}

Undertreatment of Patients With MDD

12.5% of primary care patients have had MDD in the past year

Of those with MDD
- 47% are recognized clinically
- 24% receive any treatment
- 9% receive adequate treatment
- 6% achieve remission of symptoms

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<th>ALTERED MENTAL STATUS + ELEVATED TEMPERATURE</th>
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<td>(CULPRIT IS OFTEN POLYPHARMACY)</td>
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<table>
<thead>
<tr>
<th></th>
<th>EXPOSURE</th>
<th>MUSCLE TONE</th>
<th>MUCOSA &amp; SKIN</th>
<th>PUPILS</th>
<th>BOWEL SOUNDS</th>
<th>REFLEXES</th>
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<tr>
<td>NEUROLEPTIC MALIGNANT SYNDROME</td>
<td>ANTIPSYCHOTICS</td>
<td>RIGID</td>
<td>WET</td>
<td>NORMAL</td>
<td></td>
<td>BRADYREFLEXIA</td>
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<tr>
<td>SEROTONIN SYNDROME</td>
<td>SEROTONERGICS (antidepressants, fentanyl, linezolid, sumatriptan, ondansetron)</td>
<td>RIGID</td>
<td>WET</td>
<td></td>
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<td>ANTICHOLINERGIC TOXIDROME</td>
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<td>MALIGNANT HYPERTHERMIA</td>
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<td>RIGID</td>
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Hyperreflexia (greater in lower extremities)

Tremor (greater in lower extremities)

Clonus (greater in lower extremities)

Increased bowel sounds; may have diarrhea

Agitation

Diaphoresis

Mydriasis

Tachycardia

Autonomic instability; often hypertensive
Are they really new?

**PATENT EXTENSION**

- Long acting
- Chiral change
- New route (nasal)
- New indication (age, disease)
- Combinations

- Slightly change chemical