MS Psychopharmacology 101

Stacy Donlon M.D.
Multicare MS center
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OBJECTIVES

• Understand ways to manage depression and anxiety in MS

• Understand fatigue and various causes in MS

• Understand ways to manage fatigue in MS
Mood disorders are comorbid with Multiple Sclerosis

• Lifetime prevalence for mood disorders is much higher in MS:
  • Major depressive disorder (36%-54% vs 16.2% general population)
  • Anxiety disorders (35.7% vs 28.8% general population)
  • Adjustment disorders (22% vs 0.2-2.3% general population)
  • Psychotic disorders (2-3% vs 1.8% general population)
  • Pseudobulbar affect (6.5-46.2% in MS)
• Myriad of factors may contribute to the etiology of depression in MS
  • biological mechanisms (e.g. neuroinflammation, hippocampal microglial activation, lesion burden, regional atrophy)
  
• stressors, threats, and losses that accompany living with an unpredictable and often disabling disease
Nonpharmacologic Treatments for mood

• Cognitive behavioral therapy

• Mindfulness in Motion (combining meditation, relaxing music, and Yoga)

• Resilience training

• Routine exercise
Pharmacologic Treatment of Anxiety and Depression

• Go for a twofer

• Be mindful of coexisting mood symptoms

• Be mindful of drug interactions

• ? Side effect of DMT (interferon class)
ANTIDEPRESSANTS

• Selective Serotonin Reuptake Inhibitors (SSRIs)

• Serotonin-Norepinephrine Reuptake Inhibitors (SNRI)

• Tricyclic Antidepressants

• Monoamine oxidase inhibitors (MAOIs)

• Others
Duration of Use

• An adequate Trial: 4-8 weeks on therapeutic dose

• If partial response in 6-12 weeks, increase dose

• If no response after adequate trial, switch or augment

• Continue for 6-12 months before withdrawing

• Long term treatment if 2nd or 3rd episode of depression
SSRIs

- citalopram
- escitalopram
- fluvoxamine
- fluoxetine
- paroxetine
- sertraline
SSRI Pros

• Daily dosing

• Easy to titrate

• Safer in overdose (compared to other classes)

• Broad comorbidity coverage
  • Very good for anxiety (after titration), eating disorders, atypical depression
SSRI Cons

• Sexual side effects (up to 33%)

• RLS symptoms

• Cognitive clouding/possible anticholinergic effects

• Easy bruising

• Increased risk of gastric bleeding when combined with NSAIDs

• Discontinuation side effects (except fluoxetine)

• Possibility for worsening of anxiety with initiation

• Weight gain (5-10%, paroxetine highest risk)

• GI side effects (short term)
SNRIs

• Desvenlafaxine

• Duloxetine

• Milnacipran*

• Venlafaxine (IR, XR)
SNRI Pros

• Generally well tolerated
• Little histamine/anticholinergic effect
• Can be more fatal in overdose (compared with SSRI)
• Effective for depression, anxiety
• Possibly effective for pain reduction, migraine prevention
• Less drowsiness
• Possibly helpful for symptoms of overactive bladder (duloxetine)
SNRI Cons

• Weight gain

• Discontinuation syndrome (venlafaxine > desvenlafaxine, duloxetine)

• Hepatotoxicity (duloxetine)

• Increased heart rate, BP

• Sexual side effects (venlafaxine)
TCAs
Cross reactive/Dirty

• Serotonin, Norepinephrine---> therapeutic effects

• Histamine (H1)--->sedation, dry mouth, appetite stimulation, weight gain

• Anticholinergic (muscarinic)--->dry mouth, constipation, blurred vision, dry eyes, urinary retention, cognitive impairment, delirium

• Alpha 1 antagonist---> sedation, orthostatic hypotension
TCA Pros

• Can be very effective for severe depression

• Possibly helpful for pain, fibromyalgia, insomnia, migraine (lower doses)

• Very inexpensive
TCA Cons

• Side effects

• Lethal in overdose

• Can cause QT prolongation
TCA Adverse Effects

• Commonly reported AEs
  • Blurred vision
  • Cognitive changes
  • Constipation
  • Dry mouth
  • Orthostatic hypotension
  • Sexual side effects
  • Sedation
  • Tachycardia
  • Urinary retention
  • Weight gain

FEWER

MOST

• Desipramine
  • Nortriptyline
  • Imipramine
  • Doxepin
  • Amitriptyline
Monoamine Oxidase Inhibitors

• Tranylcypromine

• Phenelzine

• Hypericin (St. John's Wort)

• Selegiline
Possible candidates for MAOI

• Treatment refractory depression

• Depression with atypical features
  • Mood reactive, sensitive to rejection
  • Reversed neurovegetative features (hypersomnia, hyperphagia, etc)

• Depression with prominent anxiety features
Cons of MAOI

• Many drug interactions

• Dietary restrictions (avoid aged or spoiled foods)

• Risk of Hypertensive Crisis ---> death

• Risk of Serotonin Syndrome (need to wait for drug clearance when switching between SSRI, MAOI)

• Side effects include orthostatic hypotension, weight gain, dry mouth, sedation, sexual side effects, and sleep disturbance
Novel antidepressants
Mirtazapine
alpha 2 antagonist, 5HT2/3 antagonist

• Pros
  • No significant P450 effects
  • No cardiotoxicity
  • Appetite stimulant
  • Can be used as a hypnotic/helps sleep at low dose (antihistamine effects)
  • Minimal GI side effects

• Cons
  • Sedating at low doses; activating at higher doses (30mg)- may need to be taken in Am
  • Increases cholesterol
  • Weight gain
  • Rare cases of agranulocytosis
Bupropion
Mechanism likely reuptake inhibition of dopamine, norepinephrine

• Pros
  • Good for use as an augmenting agent/add on
  • No weight gain, sexual side effects, sedation, or cardiac interactions
  • Low risk of mania
  • Can be used as second line agent for ADHD
  • Helpful in smoking cessation

• Cons
  • Possible increased seizure risk at higher doses (450mg+, particularly with IR)
  • Moderate CYP2D2 inhibition
  • Dry mouth, tremor, constipation
  • Can worsen anxiety
  • Risk of psychotic symptoms at high doses
Buspirone

Pros:
• Indicated for generalized anxiety disorder
• Possibly effective as monotherapy for depression (STAR*D)
• Good augmentation strategy as add on treatment for depression
• 5HT1A agonist. It works independent of endogenous release of serotonin
• No sedation

Cons:
• Takes around 2 weeks before patients notice results
• Will not reduce anxiety in patients that are used to taking BZDs
Nefazodone

5HT receptor antagonist and weak SNDRI

• Pros
  • Very good for sleep and anxiety
  • Unlikely to cause weight gain
  • Unlikely to cause sexual side effects

• Cons
  • P450 interactions and rare risk of severe hepatotoxicity
How do you chose?

• Consider
  • Patient preference
  • FH or patient prior beneficial response to medication
  • Your familiarity of the medication
  • Potential drug interactions

• And most importantly....
  • SIDE EFFECT PROFILE
Top patient concerns

• Sedation
• Weight gain
• Sexual dysfunction
• Cost

## Activation vs Sedation

<table>
<thead>
<tr>
<th>Type</th>
<th>Medications</th>
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<tbody>
<tr>
<td>Activating</td>
<td>bupropion</td>
</tr>
<tr>
<td></td>
<td>fluoxetine</td>
</tr>
<tr>
<td></td>
<td>sertraline</td>
</tr>
<tr>
<td>Neutral or mixed sedating</td>
<td>venlafaxine</td>
</tr>
<tr>
<td></td>
<td>escitalopram</td>
</tr>
<tr>
<td></td>
<td>citalopram</td>
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<tr>
<td>Sedating</td>
<td>paroxetine</td>
</tr>
<tr>
<td></td>
<td>fluvoxamine</td>
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<tr>
<td></td>
<td>nefazodone</td>
</tr>
<tr>
<td></td>
<td>tricyclics</td>
</tr>
<tr>
<td>Strongly sedating</td>
<td>trazodone</td>
</tr>
<tr>
<td></td>
<td>mirtazepine</td>
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## Impact on weight

<table>
<thead>
<tr>
<th>Impact on Weight</th>
<th>Medication</th>
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<tbody>
<tr>
<td>No impact/?weight loss</td>
<td>Bupropion</td>
</tr>
<tr>
<td>Neutral or mixed</td>
<td>Nefazadone</td>
</tr>
<tr>
<td>Mild to moderate gain</td>
<td>SSRIs (fluoxetine &lt; paroxetine), MAOIs, Tricyclics</td>
</tr>
<tr>
<td>Significant</td>
<td>Mirtazapine</td>
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</table>
## Effect on sexual functioning

<table>
<thead>
<tr>
<th>Type</th>
<th>Examples</th>
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</thead>
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<tr>
<td>Increased</td>
<td>Bupropion</td>
</tr>
<tr>
<td>Neutral or mixed</td>
<td>Nefazadone, mirtazapine, duloxetine</td>
</tr>
<tr>
<td>Common</td>
<td>SSRIs, venlafaxine, MAOIs, Tricyclics</td>
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</table>
## Risk of discontinuation syndrome

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Medications</th>
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<tr>
<td>Very high risk</td>
<td>Tranylcypromine, phenelzine</td>
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<tr>
<td>High risk</td>
<td>Paroxetine, TCAs, venlafaxine &gt;desvenlafaxine</td>
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<tr>
<td>Moderate risk</td>
<td>Citalopram, escitalopram, sertraline, duloxetine</td>
</tr>
<tr>
<td>Low risk</td>
<td>Fluoxetine, milnacipran</td>
</tr>
<tr>
<td>Unclear risk</td>
<td>Mirtazapine, bupropion</td>
</tr>
</tbody>
</table>
Discontinuation Syndrome

• F-- Flu-like symptoms
• I-- Insomnia
• N-- Nausea
• I-- Imbalance
• S-- Sensory disturbances
• H-- Hyperarousal
Clinical Cases

• Case 1: 35 yo woman with RMS, presenting with first episode of MDD. She is on birth control and not interested in children. She denies anxiety, pain. Other medical problems include nonmedicated ADD, obesity, and fatigue.

• Target symptoms: Major depression, obesity, ADD

• After review of choices, Bupropion XL 150mg daily is started for 3 days and then increased to 300mg daily. Chosen because of its activating features and unlikelihood to cause weight gain. Plan to continue for 6-12 months followed by taper off
Case 2: 45 yo woman with RMS, migraine, interstitial cystitis, and fibromyalgia presenting with her third relapse of depression with anxious mood. She previously used sertraline in the distant past. She has some memory of its effectiveness (never fully remitted) but also remembers experiencing RLS.

Target symptoms: MDD, pain, fatigue, anxiety, overactive bladder

After review of options, duloxetine 30mg daily was started for 1 week and then increased to 60mg daily. Duloxetine was chosen as it is less likely to cause RLS and may provide benefit for symptoms of overactive bladder and pain (including migraine prevention). If tolerated, will be used longer term given prior relapses of depression.
• Case 3: 36 yo man with RMS presenting with first episode of MDD and panic disorder. He is admittedly noncompliant with medication. He has no other medical problems.

• Target symptoms: depression, panic disorder, noncompliance

• After discussion, fluoxetine 10mg daily was started and then increased to 20mg after 1 week. Fluoxetine was chosen because of its long half-life and potential benefit for panic disorder. At his follow-up in 6 weeks, he reports that symptoms have lessened but still not ideally controlled. Fluoxetine is increased to 40mg daily with better control of symptoms.
“This probably won’t work, but we do have medications that will take care of the side effects.”
STAR*D (2001-2006)
NIMH large-scale effectiveness Trial

- The largest study ever done on the pharmacotherapy for depression
- Examined ‘real-world’ patients:
  - Began with 4,041 ‘real world’ pts with major depression (up to 78% of the study group would not have qualified for a typical phase 3 clinical trial)
  - Studied these patients through 4 stages of treatment that involved switches and add-on augmentation medication if remission not achieved with current stage
  - Each stage involved up to three months of treatment. All remitters (regardless of stage) were followed for up to 1 year
  - Trial meds: Citalopram, Sertraline, Bupropion, Venlafaxine, Buspirone, Mirtazapine, Triiodothyronine (T3), Nortriptyline, Tranylcypromine, Lithium
Level 1
Citalopram 40mg
33% remit

Level 2
Switch to: Bupropion-SR, Sertraline or Venlafaxine-XR
or
Augment Citalopram with Bupropion or Buspirone
25% remit
30% remit

Level 3
Augment with:
T3
25% remit
Lithium
18% remit

Level 4
Switch to:
Venlafaxine + Mirtazapine
14% remit
or
Tranylcypromine
7% remit
Conclusions from STAR*D:

- Switching from citalopram to Bupropion SR, sertraline, or venlafaxine XR equally efficacious (remit rate for all antidepressants: about 25%)

- No difference between different classes of antidepressants

- Augmentation with bupropion (39% remission) was slightly better than buspirone (33%)

- Third and fourth level remission rates less than 20% (except T3 augmentation, 24.7%)
Fatigue

• Is the most common symptom in MS (up to 95% of patients)

• Is not related to severity of disease

• Cause is likely multifactorial:
  
  • Possibly due to a higher brain working load required to perform a given mental or physical activity, or to an internal overestimation of such load

  • Neuropsych testing and functional imaging suggest the physiopathology of fatigue may rely on dysfunction of circuits involving thalamus, basal ganglia, and frontal cortex which are possibly affected by MS lesions or disturbed in their function by the products of inflammation

  • Autoimmune thyroid disease is more common in MS- screen for thyroid disease
Nonrestorative sleep is more common in MS

• Sleep inefficiency disorders are more common in MS
  • Screen for
    • daytime hypersomnia
    • Frequent nighttime awakenings
    • Nonrestorative sleep

• Consider sleep study before implementing medication

• Daytime hypersomnia can influence cognitive functioning (evaluate first if clinically suspicious for daytime hypersomnia prior to any cognitive evaluation)
Treatments for Fatigue

• Address any underlying sleep conditions
• Exercise- endurance training (caution against certain activities if fall risk)
• CBT
• Review current medications for possible influence on fatigue and possible taper down on symptomatic treatments if no longer needed
• Consider changing time of administration of DMT (ie interferon)
• Cooling products
• Medications
  • Amantadine
  • Stimulants (amphetamines, modafinil, armodafinil)
  • LDN (up to 4.5mg QHS)
  • 4-aminopyridine
Thank you

Please also review the index slides!

QUESTIONS??


• Erlangsen A, et al “Association between Neurologic Disorders and Death by Suicide in Denmark” JAMA 2020; DOI: 10.1002/jama.2019.21834


• Helen Genova, Rosalia Dacosta-Aguayo, Yael Goverover, Angela Smith, Chris Bober, John DeLuca; Effects of an Acute Bout of Aquatic Exercise on Mood in Multiple Sclerosis: A Pilot Study. International Journal of MS Care doi: https://doi.org/10.7224/1537-2073.2018-079


Index

Extra educational information
Depression Screening Tools

• The Beck Depression Inventory-Fast Screen (BDI-FS)
  • Validated in MS population

• The Hospital Anxiety and Depression Scale (HADS)
  • Validated in MS population

• PHQ-9
  • Possibly an effective tool
Mood Stabilizers

• Indications: Bipolar, cyclothymia, schizoaffective, impulse control, and intermittent explosive disorders

• Classes: Lithium, anticonvulsants, antipsychotics

• Consider as add on therapy in patients with mood swings, frontal lobe behavior, refractory depression
Lithium

• Only medication shown to reduce rate of suicide
• Effective for long term prophylaxis of both depression and mania
• Positive predictive risk factors for response:
  • Prior positive response or family member with good response
  • Pure mania
  • Mania that is followed by depression
  • Non rapid cycling

• Always check baseline CBC, Cr, TSH, pregnancy test (is teratogenic, esp in first trimester)

• Monitoring: Steady state achieved after 5 days. check level 12 hours after last dose. Once stable check q 3 months and TSH and creatinine q 6 months.

• Goal: blood level between 0.6-1.2
Lithium side effects

• Most common are GI distress including reduced appetite, nausea/vomiting, diarrhea
• Thyroid abnormalities
• Nonsignificant leukocytosis
• Polyuria/polydypsia
• Rare risk of interstitial renal fibrosis
• Hair loss, acne
• Reduced seizure threshold, cognitive slowing, intention tremor
Lithium Toxicity

- Mild (level 1.5-2.0): vomiting, diarrhea, ataxia, dizziness, slurred speech, nystagmus

- Moderate (Level 2.0-2.5): nausea, vomiting, anorexia, blurred vision, clonic limb movements, convulsions, delirium, syncope

- Severe (Level >2.5) generalized convulsions, oliguria, and renal failure
Valproic acid

- Very effective in mania prophylaxis but not quite as effective for depression
- Factor predictive of good response:
  - Rapid cycling
  - Comorbid substance abuse
  - Patients with anxiety disorder
- Always check CBC, LFTs, pregnancy test
- Start women of childbearing age on folic acid
- Effective level typically between 50-100
Valproic acid side effects

- Thrombocytopenia and platelet dysfunction
- Nausea, vomiting, weight gain
- Transaminitis
- Sedation
- Tremor
- Increased risk of neural tube defect (secondary to reduction in folic acid)
- Hair loss
- Parkinsonism
- Hyperammonemia/encephalopathy
Lamotrigine

• Effective as mood stabilizer, possibly effective in neuropathic pain
• Safer in pregnancy (when compared to other AEDs)
• Optimal dose between 100-400mg/day
• Can be dosed once daily
• Very slow titration to prevent Stevens Johnson Syndrome (especially if adding to VPA)
• Check baseline LFTs, CBC prior to starting
Lamotrigine Side effects

• Nausea/vomiting
• Sedation
• dizziness, ataxia
• confusion
• Severe side effects include toxic epidermal necrolysis and Stevens Johnson's Syndrome. The character/severity of the rash is not a good predictor of severity of reaction so discontinue use immediately if ANY rash develops
• Blood dyscrasias (rare)
Carbamazepine

• First line medication for mania, acute mania
• Indicated for rapid cyclers
• Check baseline CBC, LFTs, pregnancy test, EKG
• Goal level 4-12 mcg/ml
• Induces its own metabolism so need to check serum level and adjust dosing after 1 month
Carbamazepine Side effects

- Rash (very common; cases of SJS reported)
- Sedation
- Confusion
- Dizziness, ataxia
- Nausea, vomiting
- Transaminitis
- AV conduction delays
- Rare risk of aplastic anemia, agranulocytosis (<0.002%)
- Water retention/risk of hyponatremia (not as pronounced as with oxcarbazepine)
- Many drug interactions
Aripiprazole: Acute mania or mixed bipolar, Psychomotor agitation due to schizophrenia

Clozapine: Treatment resistant schizophrenia, Schizophrenia or SAD with suicidal ideation

Ziprasidone: Acute mania or mixed bipolar, Schizophrenia, Acute agitation in schizophrenia (IM only)

Haloperidol: Schizophrenia and other psychotic disorders; Hyperactive behavior not responsive to psychotherapy or non-antipsychotic drugs

Risperidone: Autism with irritability; Schizophrenia: acute/active and maintenance

Quetiapine: Bipolar Depression and Mania, Maintenance therapy for Bipolar I, Acute/Active state Schizophrenia, Maintenance therapy for Schizophrenia

Trifluoperazine: Schizophrenia, all phases, Non-psychotic anxiety.

Trilafon: Schizophrenia, all phases, Nausea & Vomiting

Zyprexa: Acute mania or mixed bipolar, Psychomotor agitation due to Bipolar I or Schizophrenia, Maintenance therapy for Bipolar I and Schizophrenia
Antipsychotics

• D2 (Dopamine Type 2) receptor antagonism is a common property of all typical (first generation) antipsychotics except for clozapine
  • Associated with risk of extrapyramidal side effects (EPS)

• Atypical antipsychotics are mainly serotonin-dopamine (D2, D4) antagonists
  • Less likely to cause EPS (with exception of aripiprazole and risperidone which have a high affinity D2 blockade)
Antipsychotic Side effects

• Tardive Dyskinesia (TD)- involuntary muscle movements that may not resolve with drug discontinuation

• Neuroleptic Malignant Syndrome (NMS): Characterized by severe muscle rigidity, fever, altered mental status, autonomic instability, elevated WBC, CPK and lfts. Potentially fatal

• Extrapyramidal side effects (EPS): Acute dystonia, Parkinsonism, Akathisia
More side effects of antipsychotics

• Metabolic: weight gain, HLD, DM

• Elevated prolactin: gynecomastia in men, amenorrhea in women

• Orthostasis

• Photosensitivity

• Hematologic: agranulocytosis (1-3% risk with clozapine); CBC monitoring required
# ADA Consensus on Antipsychotic Drugs and Obesity and Diabetes

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<tr>
<th>Drug</th>
<th>Weight Gain</th>
<th>Diabetes Risk</th>
<th>Dyslipidemia</th>
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<tr>
<td>Clozapine</td>
<td>+++</td>
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<tr>
<td>Olanzapine</td>
<td>+++</td>
<td>+</td>
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<tr>
<td>Risperidone</td>
<td>++</td>
<td>D</td>
<td>D</td>
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<tr>
<td>Quetiapine</td>
<td>++</td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td>Aripiprazole*</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Ziprasidone*</td>
<td>+/-</td>
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<tr>
<td></td>
<td>Serotonin Syndrome</td>
<td>Neuroleptic Malignant Syndrome</td>
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<tr>
<td><strong>Precipitated by</strong></td>
<td>Serotonergic agents</td>
<td>Dopamine antagonists</td>
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<tr>
<td><strong>Onset</strong></td>
<td>Variable, usually &lt; 24 hours</td>
<td>Variable</td>
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<tr>
<td><strong>Similar features</strong></td>
<td><strong>Vital signs</strong></td>
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<tr>
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<td>HTN, tachycardia, tachypnea, hyperthermia (&gt;40°C)</td>
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<td></td>
<td>Mucosa</td>
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<td></td>
<td>Sialorrhea</td>
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<td><strong>Overlapping features</strong></td>
<td><strong>Skin</strong></td>
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<tr>
<td></td>
<td>Diaphoresis</td>
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<td></td>
<td><strong>Mental status</strong></td>
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<td></td>
<td>Variable: agitated state, coma</td>
<td>Variable: stupor, coma, alertiveness, delirium</td>
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<tr>
<td></td>
<td><strong>Muscles</strong></td>
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<tr>
<td></td>
<td>Increased tone, particularly in lower extremities</td>
<td>“Lead pipe” rigidity in all muscle groups</td>
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<tr>
<td><strong>Differentiating features</strong></td>
<td><strong>Reflexes</strong></td>
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<td>Hyperreflexia, clonus</td>
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<td><strong>Pupils</strong></td>
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<td>Mydriasis</td>
<td>Normal</td>
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<td><strong>Bowel sounds</strong></td>
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<tr>
<td></td>
<td>Hyperactive</td>
<td>Normal- decreased</td>
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Pseudobulbar affect

• Possibly related to disruption of corticopontocerebellar pathways

• Manifests as uncontrolled laughter or crying

• Emotion is either exaggerated or incongruent with mood

• Can also contribute to impaired cognition

• Often misdiagnosed and treated as depression
  • Anorexia, fatigue, anhedonia, feelings of hopelessness are not seen with PBA
Treatment in PBA

• Behavioral- can try interrupting the episode by changing the emotional content of the discussion (ie during a crying spell, tell a joke, etc)

• Dextromethorphan/quinidine
  • Thought to act via antiglutamatergic effects at N-methyl-d-aspartate receptors and sigma-1 receptors

  • Dextromethorphan binding is most prominent in the brainstem and cerebellum
citalopram

• Pros
  • Few drug interactions/low inhibition of P450 enzymes
  • Intermediate half-life (less risk of discontinuation syndrome)

• Cons
  • Mild antagonism at H1 receptors/sedating properties
  • GI side effects
  • Dose-dependent prolongation QT interval, doses >40mg not recommended (limit doses to 20mg in elderly)
escitalopram

• Pros
  • Few drug interactions/low inhibition of P450 enzymes
  • Intermediate half-life (less risk of discontinuation syndrome)
  • More effective in acute response/remission than citalopram

• Cons
  • Dose dependent QT interval prolongation with doses of 10-30mg/day (max dose 10mg in elderly patients)
  • Nausea, HA
Fluoxetine

• Pros
  • Long half-life so unlikely to cause discontinuation syndrome
  • Good for patients with compliance issues
  • Initially activating, can increase energy
  • Can be used for tapering off SSRIs

• Cons
  • Long half-life with active metabolite (not a great choice in hepatic disease)
  • Significant P450 interactions
  • More likely to induce mania
  • Initially activating, possible increase in insomnia and anxiety
Fluvoxamine

• Pros
  • Shortest half-life
  • Analgesic properties

• Cons
  • Shortest half life (high risk of discontinuation syndrome)
  • GI side effects, HA, sedation, weakness
  • Strong inhibitor of CYP1A2 and CYP2C19
Paroxetine

• Pros
  • Short half-life, no active metabolite
  • Sedating properties (dose at night)- can help with anxiety and insomnia

• Cons
  • Significant CYP2D6 inhibition
  • Weight gain, sedation, more anticholinergic effects
  • High risk of discontinuation syndrome
sertraline

• Pros
  • Weak P450 interactions (only slight CYP2D6 activity)
  • Short half-life, lower build up of metabolites
  • Less sedating, possible activating

• Cons
  • Increased GI side effects
  • Maximum absorption requires a full stomach
desvenlafaxine

• Pros
  • Short half-life
  • Fast renal clearance (potentially safer in elderly population)
  • Minimal drug interactions
  • Starting dose is effective dose (generally)
  • No major hepatotoxicity
  • Less risk of BP elevation (compared to venlafaxine)

• Cons
  • GI side effects common (~20%)
  • Dose related increase in BP
  • Dose related increase in cholesterol (Total, LDL, triglycerides)
  • Risk of discontinuation syndrome
duloxetine

• Pros
  • Less BP effects compared to venlafaxine
  • Possible benefit in pain
  • Possible benefit in overactive bladder

• Cons
  • CYP2D6 and CYP1A2 inhibitor
  • Increased GI side effects (early effect)
  • Possible hepatotoxicity
  • Risk of discontinuation syndrome
venlafaxine

• Pros
  • Minimal drug interactions, almost no P450 activity
  • Short half-life, fast renal clearance

• Cons
  • Increased HR and dose dependent increase in BP, 100-225 mg (3-7%), 300 mg (13%)
  • Sexual side effects (>30%)
  • Less safe in overdose, can cause QT prolongation
  • GI side effects (especially IR formulation)
  • Very high risk for discontinuation syndrome