Disclosure

Relevant Financial Relationships
None

Off-Label/Investigational Uses
Off-label use of medications for autoimmune encephalitis, sleep disorders, dementia-related psychosis
Learning Objectives

• Functional neurological disorders
  • Gain insight into possible pathophysiology of functional movement and other conversion disorders and updates on their diagnosis and management

• Cognitive/behavioral disorders
  • Recognize features of autoimmune and degenerative neurological disorders that can present with predominantly psychiatric symptoms

• Sleep disorders
  • Review diagnosis and management of selected sleep disorders that may be associated with neurologic or psychiatric symptoms or disease
Functional Neurologic Symptom Disorders

- The neurologist’s perspective
- Diagnostic developments
- Pathophysiological insights
- Management updates
Tragic Case
Which management strategy is most likely to be successful?

A. Psychoanalysis
B. Cognitive behavioral therapy
C. Physical and speech therapy
D. Medication
E. Confrontation of malingering
F. Hyperbaric oxygen and amino acids
Happy Ending
Which of the following is NOT one of the diagnostic criteria for Conversion Disorder (Functional Neurological Symptom Disorder) in the DSM-5?

A. One or more symptoms of altered voluntary motor or sensory function.

B. The symptom or deficit causes clinically significant distress or impairment in social, occupational, or other important areas of functioning or warrants medical evaluation.

C. Clinical findings provide evidence of incompatibility between the symptom and recognized neurological or medical conditions.

D. Psychological factors are judged to be associated with the symptom or deficit because the initiation or exacerbation of the symptom or deficit is preceded by conflicts or other stressors.
Functional Neurologic Symptom Disorders

• Bodily symptoms or disorders that are genuine but not related to defined disease processes
• Not a synonym for psychogenic
• A functional rather than structural disturbance in nervous system functioning
Functional Neurologic Symptom Disorders

• Common
  • 2\textsuperscript{nd} most common diagnosis (14\%) after headache in outpatient neurology consults\textsuperscript{1}
  • Much higher in tertiary movement disorder, epilepsy, or symptom-based clinics (~50\%)

• High rates of disability and occupational impairment

• Higher rates of psychiatric comorbidity

\textsuperscript{1}Stone et al. Clin Neurol Nsurg 2010
Functional Neurologic Symptom Disorders

• Low profile in neurology training curricula, textbooks, research

• Neurologists extensively investigate and exclude neurologic disease
  • Rarely make positive diagnoses or manage functional disorders

• Psychiatric models (conversion) for classification, etiology, and treatment often provide little benefit to psychiatrists or patients

• Gray area where no one takes charge

• Result: patients are overtested and poorly managed
## Common Terms and Implications

<table>
<thead>
<tr>
<th>Psychogenic</th>
<th>Functional</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Suggests psychological causation</td>
<td>• Broad term suggesting a functional rather than a structural deficit, which could apply to several neurological disorders not regarded as psychogenic but where structural pathology is absent, eg, migraine</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Conversion disorder</th>
<th>Hysteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Operationalised within DSM: requires an identified psychological triggering factor for diagnosis</td>
<td>• Historical term that carries substantial stigma in society and implies a link between symptoms and the uterus</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Somatisation disorder</th>
<th>Non-organic</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Operationalised within DSM: requires presence of multiple physical symptoms including one conversion neurological symptom</td>
<td>• Defines the condition by what it is not; the term organic is itself not well defined</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medically unexplained symptoms</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Suggests that a medical explanation might one day be apparent</td>
<td></td>
</tr>
<tr>
<td>• Could refer to many medical symptoms that are not thought to be psychogenic, but still are not of a known cause</td>
<td></td>
</tr>
</tbody>
</table>

- **Symptomatic labels:** chronic fatigue, low back pain
- **Symptom syndromes:** chronic fatigue syndrome, chronic pain syndrome
- **Non-diagnoses:** non-epileptic spells, non-cardiac chest pain, non-organic…
Labels Matter to Patients

What should we say to patients with symptoms unexplained by disease? The “number needed to offend”

Jon Stone, Wojtek Wojcik, Daniel Durrance, Alan Carson, Steff Lewis, Lesley MacKenzie, Charles P Warlow, Michael Sharpe

<table>
<thead>
<tr>
<th>Diagnoses (X)</th>
<th>Putting it on (yes)</th>
<th>Mad (yes)</th>
<th>Imagining symptoms (yes)</th>
<th>Medical condition (no)</th>
<th>Good reason to be off sick from work (no)</th>
<th>Offence score (%)*</th>
<th>Number needed to offend (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms all in the mind</td>
<td>71 (83)</td>
<td>27 (31)</td>
<td>75 (87)</td>
<td>57 (66)</td>
<td>60 (70)</td>
<td>93</td>
<td>2 (2 to 2)</td>
</tr>
<tr>
<td>Hysterical weakness</td>
<td>39 (45)</td>
<td>21 (24)</td>
<td>39 (45)</td>
<td>28 (33)</td>
<td>36 (42)</td>
<td>52</td>
<td>2 (2 to 3)</td>
</tr>
<tr>
<td>Psychosomatic weakness</td>
<td>21 (24)</td>
<td>10 (12)</td>
<td>34 (40)</td>
<td>18 (21)</td>
<td>24 (28)</td>
<td>42</td>
<td>3 (2 to 4)</td>
</tr>
<tr>
<td>Medically unexplained weakness</td>
<td>21 (24)</td>
<td>10 (12)</td>
<td>27 (31)</td>
<td>32 (37)</td>
<td>35 (41)</td>
<td>35</td>
<td>3 (3 to 5)</td>
</tr>
<tr>
<td>Depression associated weakness</td>
<td>18 (21)</td>
<td>6 (7)</td>
<td>17 (20)</td>
<td>13 (15)</td>
<td>24 (28)</td>
<td>33</td>
<td>4 (3 to 5)</td>
</tr>
<tr>
<td>Stress related weakness</td>
<td>8 (9)</td>
<td>3 (6)</td>
<td>12 (14)</td>
<td>14 (16)</td>
<td>20 (23)</td>
<td>20</td>
<td>6 (4 to 9)</td>
</tr>
<tr>
<td>Chronic fatigue</td>
<td>8 (9)</td>
<td>1 (2)</td>
<td>9 (10)</td>
<td>16 (19)</td>
<td>12 (14)</td>
<td>15</td>
<td>7 (5 to 13)</td>
</tr>
<tr>
<td>Functional weakness</td>
<td>6 (7)</td>
<td>2 (2)</td>
<td>7 (8)</td>
<td>7 (8)</td>
<td>17 (20)</td>
<td>12</td>
<td>9 (5 to 21)</td>
</tr>
<tr>
<td>Stroke</td>
<td>2 (2)</td>
<td>4 (5)</td>
<td>4 (5)</td>
<td>5 (6)</td>
<td>10 (12)</td>
<td>12</td>
<td>9 (5 to 21)</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>3 (3)</td>
<td>3 (3)</td>
<td>7 (8)</td>
<td>5</td>
<td>22 (9 to ∞)</td>
</tr>
</tbody>
</table>

*Proportion of patients who responded “yes” to one or more of “putting it on,” “mad,” or “imagining symptoms.”
†Calculated according to the offence score.

Didn’t assess “psychogenic” or “conversion disorder”
Naming Functional Disorders (Somatic symptom and related disorders)

**DSM-IV**
- Conversion disorder
- Somatoform disorder NOS
- Somatization disorder
- Hypochondriasis
- Factitious disorder
- Malingering

**DSM-5**
- Conversion disorder (Functional neurological symptom disorder)
- Somatic symptom disorder
  - Specify: if pain, persistent, severity
- Illness anxiety disorder
- Factitious disorder on self or another
- Malingering
FMD Proposed Diagnostic Criteria

By movement disorder specialists

Fahn-Williams criteria

Documented
Persistent relief by psychotherapy, suggestion, or placebo has been demonstrated, which may be helped by physiotherapy; or the patient was seen without the movement disorder when believing himself or herself unobserved.

Clinically established
The movement disorder is incongruent with a classical movement disorder or there are inconsistencies in the examination, plus at least one of the following three: other psychogenic signs, multiple somatisations, or an obvious psychiatric disturbance.

Probable
The movement disorder is incongruent or inconsistent with typical movement disorders or there are psychogenic signs or multiple somatisations.

Possible
Evidence of an emotional disturbance.

Laboratory supported definite
Not included in this classification.

Gupta and Lang proposed revisions

Clinically definite
Includes Fahn-Williams documented and clinically established categories, and also includes movement disorders that are incongruent with a classical movement disorder or for which there are inconsistencies in the examination, without the need for the additional presence of psychogenic signs, multiple somatisations, or an obvious psychiatric disturbance.

Probable
Not included in this classification.

Possible
Gupta and Lang question the utility of this category. They suggest it could be used to include those with movement disorders congruent or consistent with a classical movement disorder but where there are additional psychogenic signs, somatisations, or evidence of emotional disturbance. However, they suggest that this category may then include patients who are different pathophysiologically from those with true psychogenic movement disorders.

Laboratory supported definite
Presence of data from electrophysiological tests that prove the presence of a psychogenic movement disorder (primarily evidence of pre-movement potentials before jerks or data from tremor studies).
DSM-5: Conversion Disorder (Functional Neurological Symptom Disorder)

A. One or more symptoms of altered voluntary motor or sensory function

B. Clinical findings provide evidence of incompatibility between the symptom and recognized neurological or medical conditions [internal inconsistency]

C. The symptom or deficit is not better explained by another medical or mental disorder

D. The symptom or deficit causes clinically significant distress or impairment in social, occupational, or other important areas of functioning

• Specify symptom type: weakness, paralysis, abnormal movements, swallowing, speech, attacks, sensory loss, special senses, mixed

• With or without psychological stressor
Conversion Disorder (Functional Neurological Symptom Disorder)

<table>
<thead>
<tr>
<th>Criterion</th>
<th>DSM-IV</th>
<th>DSM-5</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor or sensory symptom...</td>
<td>✔</td>
<td>✔</td>
<td></td>
</tr>
<tr>
<td>...causing distress or difficulty for the patient</td>
<td>✔</td>
<td>✔</td>
<td></td>
</tr>
<tr>
<td>Positive physical signs of internal inconsistency or incongruity with recognized disease</td>
<td>X</td>
<td>✔</td>
<td>Emphasizes how these disorders should be diagnosed.</td>
</tr>
<tr>
<td>Patient must have a psychological stressor</td>
<td>✔</td>
<td>X</td>
<td>Often not present. As a consequence, many patients without stressors rejected by psychiatry.</td>
</tr>
<tr>
<td>Patient must be determined as “not feigning”</td>
<td>✔</td>
<td>X</td>
<td>Feigned symptoms are probably rare, are separately classified, and should not be considered a functional disorder. Proving feigning is hard. Proving “not feigning” is clinically impossible.</td>
</tr>
</tbody>
</table>

DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition;  
DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.  
\(^a\) Data from American Psychiatric Association.\(^7,9\)
New DSM-5 criteria should hopefully…

- Allow neurologists and other physicians to make diagnoses positively based on the exam
- Enable neurologists and psychiatrists to develop a better mutual understanding of how the diagnosis is made
- Encourage psychiatrists to learn relevant exam techniques
- Avoid common situation where absence of an identifiable psychological stressor leads to concluding that the diagnosis is incorrect
- Reduce risk of neurological disease being misdiagnosed as functional due to concomitant stressor
- Encourage use of shared common language
- ICD-11 beta draft includes functional disorders in both the psychiatry and neurology sections
Clinical Pearls to Diagnosis

• Hinges on demonstration of positive physical signs of internal inconsistency or incongruity with recognized physical disease
• “Functional” is the preferred term
• Does not require psychological stressor or comorbidity
Do patients with functional neurological disorders have greater stress or more stressors?

A. Yes
B. No
C. Maybe
D. I don’t know
E. Could you repeat the question?
Stressors?

- FMD pts have same stress levels as healthy controls based on circulating basal cortisol
  - But had ~3x higher rates of mood & anxiety d/o
- Other studies show no difference in number of stressful life events in prior year
- Self-rated depression/anxiety (SCL-90) & dissociation/personality disorder (PDQ-4) normal in:
  - 39% of Functional MD
  - 38% of Neurologic MD
  - 89% healthy controls
The Spectrum
Functional symptoms and syndromes

- Neurology
- Gastroenterology
- Gynecology
- ENT
- Cardiology
- Rheumatology
- Infectious disease
- Immunology

Functional weakness, sensory disturbances, non-epileptic spells, gait and movement disorders

IBS, non-ulcer dyspepsia, chronic abdominal pain

Rome IV criteria

Chronic pelvic pain

Functional dysphonia, globus (hystericus)

Atypical chest pain, palpitations

Fibromyalgia

Post-viral chronic fatigue syndrome

Multiple chemical sensitivity syndrome

<table>
<thead>
<tr>
<th>Table 1: Functional Gastrointestinal Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Esophageal Disorders</strong></td>
</tr>
<tr>
<td>A1. Functional chest pain</td>
</tr>
<tr>
<td>A2. Functional heartburn</td>
</tr>
<tr>
<td>A3. Reflux hypersensitivity</td>
</tr>
<tr>
<td>A4. Globus</td>
</tr>
<tr>
<td>A5. Functional dysphagia</td>
</tr>
<tr>
<td><strong>B. Gastrointestinal Disorders</strong></td>
</tr>
<tr>
<td>B1. Functional dysphagia</td>
</tr>
<tr>
<td>B1a. Postprandial distress syndrome (PDS)</td>
</tr>
<tr>
<td>B1b. Epigastric pain syndrome (EPS)</td>
</tr>
<tr>
<td>B2. Belching disorders</td>
</tr>
<tr>
<td>B2a. Excessive supragastric belching</td>
</tr>
<tr>
<td>B2b. Excessive epigastric belching</td>
</tr>
<tr>
<td>B3. Nausea and vomiting disorders</td>
</tr>
<tr>
<td>B3a. Chronic nausea vomiting syndrome (CNVS)</td>
</tr>
<tr>
<td>B3b. Cyclic vomiting syndrome (CVS)</td>
</tr>
<tr>
<td>B3c. Cerebellar hyperemesis syndrome (CHS)</td>
</tr>
<tr>
<td>B4. Nausea</td>
</tr>
<tr>
<td>B5. Vomiting</td>
</tr>
<tr>
<td>B6. Irritable bowel syndrome (IBS)</td>
</tr>
<tr>
<td>B6a. Irritable bowel syndrome (IBS)</td>
</tr>
<tr>
<td>B6b. Irritable bowel syndrome (IBS-C)</td>
</tr>
<tr>
<td>B6c. Irritable bowel syndrome (IBS-D)</td>
</tr>
<tr>
<td>B6d. Irritable bowel syndrome (IBS-M)</td>
</tr>
<tr>
<td>B6e. Irritable bowel syndrome (IBS-L)</td>
</tr>
<tr>
<td>B6f. Irritable bowel syndrome (IBS-L-A)</td>
</tr>
<tr>
<td>B6g. Irritable bowel syndrome (IBS-L-B)</td>
</tr>
<tr>
<td>C. Bowel Disorders</td>
</tr>
<tr>
<td>C1. Intestinal pain</td>
</tr>
<tr>
<td>C2. Functional constipation</td>
</tr>
<tr>
<td>C3. Functional diahrhea</td>
</tr>
<tr>
<td>C4. Functional abdominal bloating/Silence</td>
</tr>
<tr>
<td>C5. Unspecified functional bowel disorder</td>
</tr>
<tr>
<td>C6. Opoid induced constipation</td>
</tr>
<tr>
<td><strong>D. Centrally Mediated Disorders of Gastrointestinal Pain</strong></td>
</tr>
<tr>
<td>D1. Centrally mediated abdominal pain syndrome (CAP)</td>
</tr>
<tr>
<td>D2. Nociceptive bowel syndrome (NEP) / Opoid-induced GI hyperalgesia</td>
</tr>
<tr>
<td><strong>E. Gallbladder and Sphincter of Odd (SO) Disorders</strong></td>
</tr>
<tr>
<td>E1. Biliary pain</td>
</tr>
<tr>
<td>E2. Functional gallbladder disorder</td>
</tr>
<tr>
<td>E3. Functional bowel SO disorder</td>
</tr>
<tr>
<td>E4. Functional pancreatic SO disorder</td>
</tr>
<tr>
<td><strong>F. Anorectal Disorders</strong></td>
</tr>
<tr>
<td>F1. Fecal incontinence</td>
</tr>
<tr>
<td>F2. Functional anal pain</td>
</tr>
<tr>
<td>F3. Latent anorectal pain</td>
</tr>
<tr>
<td>F4. Unspecified functional anal pain</td>
</tr>
<tr>
<td>F5a. Proctalgia herpes</td>
</tr>
<tr>
<td>F5b. Functional defecation disorders</td>
</tr>
<tr>
<td>F5c. Inadequate defecatory propulsion</td>
</tr>
<tr>
<td>F5d. Dysdyssynergic defecation</td>
</tr>
<tr>
<td><strong>G. Childhood Functional GI Disorders: Neonate/Toddler</strong></td>
</tr>
<tr>
<td>G1. Infant regurgitation</td>
</tr>
<tr>
<td>G2. Functional regurgitation</td>
</tr>
<tr>
<td>G3. Nausea and vomiting disorders</td>
</tr>
<tr>
<td>G4. Infant colic</td>
</tr>
<tr>
<td>G5. Functional diarrhea</td>
</tr>
<tr>
<td>G6. Infant dysphagia</td>
</tr>
<tr>
<td><strong>H. Childhood Functional GI Disorders: Child/Adolescent</strong></td>
</tr>
<tr>
<td>H1. Functional nausea and vomiting disorders</td>
</tr>
<tr>
<td>H2. Functional abdominal pain disorders</td>
</tr>
<tr>
<td>H3a. Postprandial distress syndrome</td>
</tr>
<tr>
<td>H3b. Epigastric pain syndrome (EPS)</td>
</tr>
<tr>
<td>H3c. Abdominal migraine</td>
</tr>
<tr>
<td>H3d. Functional abdominal pain - NOS</td>
</tr>
<tr>
<td>H3e. Functional defecation disorders</td>
</tr>
<tr>
<td>H3f. Functional constipation</td>
</tr>
<tr>
<td>H3g. Nonessential infantile incontinence</td>
</tr>
</tbody>
</table>

Stone et al. JNNP 2005
Biopsychosocial Model

• Predisposing vulnerabilities
  • **Bio:** Genetic
  • **Psych:** Childhood adversity, personality traits
  • **Social:** Symptom modeling of others

• Precipitating mechanisms
  • **Bio:** Abnormal physiologic event/state, physical pain
  • **Psych:** Emotional d/o
  • **Social:** Major life event

• Perpetuating
  • **Bio:** Deconditioning, CNS Plasticity(?)
  • **Psych:** Illness beliefs, perception of damaging/irreversible symptoms, avoiding provocation
  • **Social:** Reinforcement by family, money, MDs
Recent Insights

- Right temporoparietal junction
  - Critical role in self-agency network as a mismatch detector
  - Processes discrepancies between motor intentions and consequences
- 35 pts with FMD vs. 35 normal controls
- RS fMRI shows decreased functional connectivity between rTPJ and bilateral sensorimotor regions (SMA) needed for intentional binding of motor intention with sensory feedback
Functional Imaging in conversion disorder

- Greater functional connectivity between the right amygdala (limbic) and supplementary motor area (motor preparatory) during both fearful versus neutral, and happy versus neutral ‘stimuli’

- Potential neural mechanism that may explain why psychological or physiological stressors can trigger or exacerbate conversion disorder
# Taking the initial HPI

<table>
<thead>
<tr>
<th>Historical Elements</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptom list</strong></td>
<td>Ensure that you have elicited all the patient’s physical symptoms. This is important not only for diagnosis but also in building trust and confidence with a patient. Consider asking about fatigue, sleep, concentration, and pain in every patient.</td>
</tr>
<tr>
<td><strong>Day-to-day function</strong></td>
<td>Build a picture of what the patient can and cannot do. The patient may be focused on what they cannot do, but finding out what they can do gives clues about mood and anxiety.</td>
</tr>
<tr>
<td><strong>Onset: Weakness and movement disorder</strong></td>
<td>Sudden onset (approximately 50% of patients): Look for physical injury, panic attack, episode of dissociation, migraine, general anesthetic, drug side effect, viral illness, or another physiologic trigger that may help you explain back a mechanism to the patient. Gradual onset: Often associated with asymmetrical pain and fatigue.</td>
</tr>
<tr>
<td><strong>Onset: Dissociative (nonepileptic attacks)</strong></td>
<td>Ask patients carefully about prodromal symptoms. They are typically reluctant to discuss them, but they often describe panic, autonomic arousal symptoms, or dissociation if questioned sympathetically. The first event may have been either clear-cut syncope or a mechanical fall.</td>
</tr>
<tr>
<td><strong>Other functional disorders</strong></td>
<td>Consider if the patient has other diagnoses such as irritable bowel syndrome, fibromyalgia, or chronic fatigue syndrome, which are often considered functional disorders.</td>
</tr>
<tr>
<td><strong>Illness beliefs</strong></td>
<td>Consider what the patient thinks may be wrong. Consider if the patient or others think doctors have missed something (eg, Do they think they have nerve damage or do they think it is possible their symptoms could improve? What treatments do they think would help?).</td>
</tr>
<tr>
<td><strong>Experience with other doctors</strong></td>
<td>Enquire about the outcome of visits with other doctors. Allow the patient to vent their frustration if relevant.</td>
</tr>
</tbody>
</table>

Tread carefully or leave for future history:
- Childhood trauma
- Anxiety, depression
Examination: Positive features, not exclusion

- **Weakness**
  - Variability, collapsing, give-way, co-contraction

- **Movement disorders**
  - Very challenging: tremor entrainment, fixed dystonic posture, distractability, chorea, myoclonus

- **Sensory loss**
  - Hemisensory syndrome, shoulder/groin demarcation, midline splitting, ipsilateral vision/hearing loss

- **Visual disorders**
  - Tubular visual field. Many exam techniques and tricks
Which of the following examples are functional gait/movement disorders, and which are due to neurological disease?
Exam Pitfalls

• Some tests have poor discriminating value between organic and “non-organic” disease
  • Only Hoover test and give-way weakness validated

• Combination of organic disease + symptom exaggeration, exam elaboration or functional overlay

• Pain may confound effort or movement

• Exam findings don’t discriminate among psychiatric causes
Examine Strength, Reflexes, Tone
Examine Gait

- Exaggerated effort
- Extreme slowness
- Excessive truncal sway
Functional Gait Features

• Exaggerated effort or fatigue: “huffing-puffing”
• Extreme slowness or hesitation
• Fluctuations over short time or distractibility
• Uneconomic postures / wasted energy
• Sudden knee buckling
• Monoplegic dragging gait
• Walking-on-ice
• Tightrope walking, excess truncal sway, near falls
• Convulsive shaking
• Psychogenic Romberg or pull test
• Improvement with novel tasks (beware of dystonia)
• Bizarre ≠ psychogenic

Stone et al. JNNP 2005
Lempert et al. J Neurol 1991
Laub et al. Mov Dis CP 2016
## Spell Characteristics

### Table 2
Attack features that can help to distinguish non-epileptic attacks from epileptic seizures. Reproduced from Reuber and Elger, with permission

<table>
<thead>
<tr>
<th>Observation</th>
<th>Non-epileptic seizures</th>
<th>Epileptic seizures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Situational onset</td>
<td>Occasional</td>
<td>Rare</td>
</tr>
<tr>
<td>Gradual onset</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Precipitated by stimuli (noise, light)</td>
<td>Occasional</td>
<td>Rare</td>
</tr>
<tr>
<td>Undulating motor activity</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Asynchronous limb movements</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Purposeful movements</td>
<td>Occasional</td>
<td>Very rare</td>
</tr>
<tr>
<td>Rhythmic pelvic movements</td>
<td>Occasional</td>
<td>Rare</td>
</tr>
<tr>
<td>Opisthotonus, “arc de cercle”</td>
<td>Occasional</td>
<td>Very rare</td>
</tr>
<tr>
<td>Side-to-side head shaking</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Tongue biting (tip)</td>
<td>Occasional</td>
<td>Rare</td>
</tr>
<tr>
<td>Tongue biting (side)</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Prolonged ictal atonia</td>
<td>Occasional</td>
<td>Very rare</td>
</tr>
<tr>
<td>Ictal crying</td>
<td>Occasional</td>
<td>Very rare</td>
</tr>
<tr>
<td>Closed mouth in “tonic phase”</td>
<td>Occasional</td>
<td>Very rare</td>
</tr>
<tr>
<td>Vocalisation during “tonic-clonic” phase</td>
<td>Occasional</td>
<td>Very rare</td>
</tr>
<tr>
<td>Closed eyelids</td>
<td>Very common</td>
<td>Rare</td>
</tr>
<tr>
<td>Convulsion &gt;2 minutes</td>
<td>Common</td>
<td>Very rare</td>
</tr>
<tr>
<td>Resistance to eyelid opening</td>
<td>Common</td>
<td>Very rare</td>
</tr>
<tr>
<td>Pupillary light reflex</td>
<td>Usually retained</td>
<td>Commonly absent</td>
</tr>
<tr>
<td>Reactivity during “unconsciousness”</td>
<td>Occasional</td>
<td>Very rare</td>
</tr>
<tr>
<td>Lack of cyanosis</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Rapid postictal reorientation</td>
<td>Common</td>
<td>Rare</td>
</tr>
</tbody>
</table>

Stone et al. JNNP 2005
Non-epileptic behavioral event (PNES)
No EEG correlate while monitoring

• Pushes alert button
• Head tips forward
• Initially responds to questions
• Goes limp, half asleep
• Repositions self
• Able to squeeze
• No tonic phase
• Stimulus starts the convulsions
• Irregular pelvic thrusts
• Variable muscle tone

Courtesy of Dr. Greg Cascino
Diagnostic investigations

• Typically necessary even with clear cut functional disorder (imaging, EMG, EEG, etc)
  • Looking for comorbid neurological disease
• Perform quickly with defined endpoint
• Prepare patient that you suspect a functional disorder and to anticipate normal test results
Counseling the patient: The talk

- Use vocabulary carefully
  - Brain, not mind
  - Functional, not psychogenic
  - Software vs. hardware

- Define the diagnosis
  - Brain memorizes maladaptive motor program

- Reassure the patient
  - Real, common, unconscious, disabling, no permanent structural damage, reversible
Counseling the patient: The talk

- Give a positive diagnosis rather than saying “you don’t have anything”
  - Supported by clinical features, exam findings
    - Analogous to Parkinson disease
  - Demonstrate them to the patient
Multidisciplinary team: neurology, physiatry, physical therapy, psychiatry, psychology

Doctor (testing weak hip extension): “Try to keep your foot flat on the floor for me.”

Patient (in a sitting position): “I can’t do it.”

Doctor (testing contralateral hip flexion against resistance): “Now, concentrate on lifting up your good right leg. Look at that right leg and focus on keeping it up in the air. Now can you feel that when you do that the power in your left leg has come back to normal? I can’t get that left foot off the floor now.”

Patient (and the partner): “That’s weird.”

Doctor: “I can see that you were really trying to keep your left foot on the floor but your leg was weak. But because the movement comes back to normal when you move your other leg that shows me that the weakness can’t be due to damage anywhere in the nervous system. This test is called Hoover’s sign and it’s a positive sign of a problem called functional weakness. Your brain is having trouble sending a message to your leg to make it move, but when you are distracted the message can get through. This test shows me there is a problem with the function of your nervous system, not damage to it. Shall I show you again?”
Counseling Pitfalls

• Expecting patient to be satisfied by saying “you do not have neurologic disease”.
  • “Then what is wrong with me?”

• Prematurely attributing functional symptoms to psychological factors
  • Rarely straightforward. Interpreted as accusatory.

• Emphasizing a negative neurologic workup as rationale for a functional diagnosis
Counseling the patient: The talk

- Explain why they got this
  - Honest answer: We don’t know (We, not I)
  - Address “psychogenic” directly
    - Explain psychogenic vs. functional controversy
      - Allows them to understand previous negative experiences with MDs
  - 30%-40% have “significant psychologic trauma” in their life
    - Opens door to non-threatening discussion
    - Allows 60-70% without an apparent psychologic issue
Prognosis

- Poor prognosis in 40-90% without appropriate treatment
- 66 PMD vs 704 PD
- Similar disability and physical QOL to PD in spite of 17 years younger and shorter disease duration (4 yrs vs 7 yrs)
- Higher levels of distress, anxiety, depression, somatization
Role of psychiatric assessment and psychological therapy

• Patients with functional disorders have higher rates of comorbid psychiatric conditions
  • Anxiety, panic disorder, depression, OCD, personality disorders, PTSD
  • Assessment and management of these is critical
  • Factitious or malingering?

• For non-epileptic (dissociative) spells
  • Cognitive behavioral therapy*
  • Model of attacks overlapping with panic disorder
    • Conditioned dissociative response to autonomic arousal

*LaFrance et al. Epilepsia 2013
*Goldstein et al. Neurology 2010
*LaFrance et al. JAMA Psych 2014
Psychiatric interview

• Experienced psychosomatic medicine psychiatrist evaluated 36 FMD pts

• Open-ended qualitative 30-60 min interview

• 22 current & 6 past psychiatric disorders; 5 of other 8 had clear emotional processing problems

• Themes
  1. Minimization of emotional effect of trauma
  2. Symbolic conversion of psychological stressors into a specific movement disorder
  3. Emotional states converted into physical symptoms and expressed in somatic language
  4. Avoidance of or inability to recognize emotional states
  5. Secondary gain from symptoms
Which management strategy is most likely to be successful for functional weakness, gait, speech, or movement disorders?

A. Psychoanalysis
B. Cognitive behavioral therapy
C. Physical and speech therapy
D. Medication
E. Confrontation of malingering
F. Hyperbaric oxygen and amino acids
BEST (Behavioral Shaping Therapy) Program for functional movement disorders

- One-week intensive outpatient motor reprogramming program
  - Emphasizes principles of PT/OT
    - 2 sessions PT daily
    - 2 sessions OT daily
  - Meet Psychology for one appointment to explore further, but PT is emphasized
Functional movement disorders: Successful treatment with a physical therapy rehabilitation protocol

Kathrin Czarnecki, Jeffrey M. Thompson, Richard Seime, Yonas E. Geda, Joseph R. Duffy, J. Eric Ahlskog

- 60 consecutive FMD patients treated
- Controls: 60 sex and age-matched FMD patients with treatment-as-usual
- 70% back to normal or near-normal after 1 week
- 60% still normal or markedly improved after 2 years vs. 22% of controls; need ongoing therapy
BEST Program

• Focus on abnormal movements
• Break down movements into individual motor components
• Gradually reconstruct normal motor movements
• Ignore inappropriate movements
• Distract (bounce ball when working on trunk, tap when working on tremor)
• Reinforce
• Plan for self-management home therapy
BEST Program

• Tremor examples
  • Actively do the tremor- speed it up, slow it down
  • Contract muscles, then relax. Repeat to teach relaxation
  • Change the posture of the limb where tremor is most present
  • Competing movement- clap to a rhythm

• Gait examples
  • Slow down gait- speed up
  • Walk by sliding feet forward- progress from there
  • Take baby steps (even crawl), sway, then slowly increase to normal gait
Poor Candidates

• Episodic movement disorders (or spells)
• Severe pain so they can not focus on rehab
• Multiple somatizations so they can not focus on rehab
• Factitious or malingering (secondary gain)
• Significant Psychiatric disease
• Doubtful of diagnosis
Physiotherapy for Motor Disorders

Review
Physiotherapy for functional (psychogenic) motor symptoms: A systematic review
Glenn Nielsen a*, Jon Stone b, Mark J Edwards c

- Metanlysis of PT for functional motor symptoms
- 29 studies with 373 patients (21 studies had <10 patients)
- Improvement in 60-70%
Physiotherapy for functional motor disorders: a consensus recommendation

Glenn Nielsen,1,2 Jon Stone,3 Audrey Matthews,4 Melanie Brown,4 Chris Sparkes,5 Ross Farmer,6 Lindsay Masterton,7 Linsey Duncan,7 Alisa Winters,3 Laura Danielli,3 Carrie Lumsden,7 Alan Carson,8 Anthony S David,9,10 Mark Edwards1

Box 1 General treatment principles for physiotherapy for functional motor disorder (FMD)

- Build trust before challenging/pushing the patient.
- Project confidence making it clear that the physiotherapist knows about FMD.
- Create an expectation of improvement.
- Open and consistent communication between the multidisciplinary team and patient.
- Involve family and carers in treatment.
- Limited ‘hands-on’ treatment. When handling the patient, facilitate rather than support.
- Encourage early weight bearing. ‘On the bed strength’ will not usually correlate with ability to stand in functional weakness.
- Foster independence and self-management.
- Goal directed rehabilitation focusing on function and automatic movement (eg. walking) rather than the impairment (eg. weakness) and controlled (‘attention-full’) movement (eg. strengthening exercises).
- Minimise reinforcement of maladaptive movement patterns and postures.
- Avoid use of adaptive equipment and mobility aids (though these are not always contra-indicated).
- Avoid use of splints and devices that immobilise joints.
- Recognise and challenge unhelpful thoughts and behaviours.
- Develop a self-management and relapse prevention plan.

Table 3 Examples of techniques for specific symptoms to normalise movement

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Movement Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leg weakness</td>
<td>Early weight bearing with progressively less upper limb support, eg. ‘linger-up’ support, preventing the patient from taking weight through walking aids/supporting surfaces.</td>
</tr>
<tr>
<td></td>
<td>Standing in a safe environment with side to side weight shift.</td>
</tr>
<tr>
<td></td>
<td>Crawling in 4 point then 2 point kneeling.</td>
</tr>
<tr>
<td></td>
<td>Increase walking speed.</td>
</tr>
<tr>
<td></td>
<td>Treadmill walking (with or without a body weight support harness and feedback from a mirror).</td>
</tr>
<tr>
<td>Ankle weakness</td>
<td>Elicit ankle dorsiflexion activity by asking the patient to walk backwards, with anterior/posterior weight shift while standing or by asking the patient to walk by sliding their feet, keeping the plantar surface of each foot in contact with the floor.</td>
</tr>
<tr>
<td>Upper limb weakness</td>
<td>Elicit upper limb muscle activity by asking the patient to bear weight through their hands (eg. 4 point kneeling or standing with hands resting on a table) weight bearing with weight shift or crawling.</td>
</tr>
<tr>
<td></td>
<td>Minimise habitual non-use by using the weak upper limb functionally to stabilise objects during tasks, for example, stabilise paper when writing, a plate when eating.</td>
</tr>
<tr>
<td></td>
<td>Practice tasks that are very familiar or important to the individual, that may not be associated with symptoms eg. use of mobile phone, computer and tablet.</td>
</tr>
<tr>
<td></td>
<td>Stimulate automatic upper limb postural response by sitting on an unstable surface such as a therapy ball, resting upper limbs on a supporting surface.</td>
</tr>
<tr>
<td>Gait disturbance</td>
<td>Speed up walking (in some cases, this may worsen the walking pattern)</td>
</tr>
<tr>
<td></td>
<td>Slow down walking speed.</td>
</tr>
<tr>
<td></td>
<td>Walk by sliding feet forward, keeping plantar surface of foot in contact with the ground (i.e., like wearing ski). Progress towards normal walking in guided steps.</td>
</tr>
<tr>
<td></td>
<td>Build up a normal gait pattern from simple achievable components that progressively approximate normal walking. For example—side to side weight shift, continue weight shift allowing feet to ‘automatically’ advance forward by small amounts; progressively increase this step length with the focus on maintaining rhythmic weight shift rather than the action of stepping.</td>
</tr>
<tr>
<td></td>
<td>Walk carrying small weight-distribution in each hand.</td>
</tr>
<tr>
<td></td>
<td>Walking backwards or sideways.</td>
</tr>
<tr>
<td></td>
<td>Walk to a set rhythm (eg. in time to music, counting 1, 2, 1, 2, 1).</td>
</tr>
<tr>
<td></td>
<td>Exaggerated movement (eg. walking with high steps).</td>
</tr>
<tr>
<td></td>
<td>Hauling up or down the stairs (this is often easier that walking on flat ground.</td>
</tr>
<tr>
<td>Upper limb tremor</td>
<td>Make the movement ‘voluntary’ by actively doing the tremor, change the movement to a larger amplitude and slower frequency, then slow the movement to stillness.</td>
</tr>
<tr>
<td></td>
<td>Teach the patient how to relax their muscles by actively contracting their muscles for a few seconds, then releasing.</td>
</tr>
<tr>
<td></td>
<td>Changing habitual postures relevant to symptom production. For example, reduce footfall weight bearing.</td>
</tr>
<tr>
<td></td>
<td>Perform a competing movement, for example, clapping to a rhythm or a large flowing movement of the symptomatic arm as if conducting an orchestra.</td>
</tr>
<tr>
<td></td>
<td>Focus on another body part, for example, tapping the other hand or foot.</td>
</tr>
<tr>
<td></td>
<td>Muscle relaxation exercise, for example, progressive muscle relaxation techniques, EMG biofeedback from upper trapezius muscle or using mirror feedback.</td>
</tr>
<tr>
<td>Lower limb tremor</td>
<td>Side to side or anterior-posterior weight shift. When the tremor has reduced show weight, shift to stillness.</td>
</tr>
<tr>
<td></td>
<td>Competing movements such as toe-tapping.</td>
</tr>
<tr>
<td></td>
<td>Ensure even weight distribution when standing. This can be helped by using weighing scales and/or a mirror for feedback.</td>
</tr>
<tr>
<td>Fixed dystonia</td>
<td>Change habitual sitting and standing postures to prevent prolonged periods in end of range joint positions and promote postures with good alignment.</td>
</tr>
<tr>
<td></td>
<td>Normalise movement patterns (eg. sit to stand, transfers, walking) with an external or altered focus of attention (ie, not the dystonic limb).</td>
</tr>
<tr>
<td></td>
<td>Encourage unhelpful protective avoidance behaviors and encourage normal sensory experiences (eg., wearing shoes and socks, weight bearing as tolerated, not having the arm in a ‘protected’ position).</td>
</tr>
<tr>
<td></td>
<td>Recognise symptoms prior to a jerky movement and be prepared to deal with these.</td>
</tr>
<tr>
<td></td>
<td>Strategies to treat overactive muscles off the sitting and lying leg, by allowing the supporting surface to take the weight of a limb. Cushions or folded towels may be needed to bring the supporting surface up to the limb where contractures are present.</td>
</tr>
<tr>
<td></td>
<td>The patient may need to be taught to be aware of maladaptive postures and overactive muscles in order to use strategies.</td>
</tr>
<tr>
<td></td>
<td>Consider examination under sedation, especially if completely fixed or concerned about contractures.</td>
</tr>
<tr>
<td></td>
<td>Consider a trial of electrical muscle stimulation or functional electrical stimulation to normalise limb posture and movement.</td>
</tr>
<tr>
<td>Functional jerks</td>
<td>Movement retarding may be less useful for intermittent or sudden jerky movements. Instead, look for self-focused attention or premonitory symptoms prior to a jerk that can be addressed with distraction or redirected attention.</td>
</tr>
<tr>
<td>Myoclonus</td>
<td>When present, address pain, muscle over-activity or altered patterns of movement that may precede a jerk.</td>
</tr>
</tbody>
</table>

EMG, electromyography.
Clinical Pearls to Management

• Physical therapy &/or speech therapy for functional movement disorders

• Cognitive behavioral therapy for behavioral spells (non-epileptic behavioral events) or episodic disorders

• Management of psychological comorbidities, multiple somatizations, chronic pain
How to use this website ...

Most people with functional or dissociative neurological symptoms have a combination of symptoms like "weakness, numbness and fatigue" or "blackouts and sleep problems".

Click on a symptom on the right or use the menu above to explore the symptoms that are relevant to you.

Click on "Causes" to discover what is known about....

- what is going wrong in the body when they do happen (Mechanisms) and
- why people become vulnerable to these symptoms (Causes)

Click on "Misdiagnosis" to find out how likely it is that your diagnosis is wrong.

Click on "In the mind?" for some answers to this question.

Click on "Treatment" for discussion of what treatments may help.

Click on "Stories" for some real patient stories.

Downloads and Links ...

Click on "Links and Downloads tab" on the menu above to access a wide range of leaflets, booklets and internet links.
Case 21

- A 27-year old woman is admitted to your acute inpatient unit with subacute agitation, delusions, and hallucinations
- PMH is significant only from untreated ADHD and smoking. No history of mood or thought disorders.
- 4 days ago she stopped sleeping
- 3 days ago she became anxious and emotionally labile. Speech was pressured. She was convinced of being pregnant despite 4 negative pregnancy tests. She began seeing jewels and gold coins on the walls.
Case 21

- She was admitted from the ED to acute psychiatry, requiring haloperidol and lorazepam for agitation and combativeness. Violent outbursts required restraints.

- During hospital days 1-2, she alternates between periods of agitation, lucidity, and unresponsiveness

- At times she has waxy catatonia

- Then she develops periods of tachycardia and hyperthermia, then non-convulsive status epilepticus requiring Neuro ICU transfer
You doubted a primary psychiatric cause all along and suspect a neurologic one. Which tumor is the most likely cause?

A. Meningioma
B. Teratoma
C. Oligodendroglioma
D. Glioblastoma
E. Small cell carcinoma
12 women
14-44 years
Psychiatric symptoms
Amnesia
Seizures
Dyskinesias
Autonomic dysfunction
Hypoventilation
Teratoma removal +/- immunotherapy brought about recovery
Anti-NMDA Receptor Encephalitis

- Anti-NMDAR encephalitis is the most common antibody-mediated autoimmune encephalitis (4% of encephalitis)
- Most commonly affects young women (9F:1M) and kids
- May have prodrome resembling viral illness
- Severe subacute psychiatric symptoms, memory loss, seizures, abnormal movements, autonomic instability
  - Psychosis symptoms often predominate
  - 77% are first evaluated by a psychiatrist
  - Median age 21 similar to schizophrenia, bipolar
Anti-NDMAR Encephalitis: Characteristic features

- Prodromal headache, fever, viral-like illness
- Prominent psychiatric manifestations
  - Anxiety, agitation, bizarre behavior, hallucinations, delusions, disorganized thinking
- Insomnia
- Memory deficits
- Seizures
- Decreased level of consciousness, stupor with catatonic features
- Frequent dyskinesias
  - Orofacial, choreoathetoid movements, dystonia, rigidity, opisthotonic postures
- Autonomic instability
  - Hyperthermia, fluctuations of blood pressure, tachycardia, bradycardia, cardiac pauses, and sometimes hypoventilation requiring mechanical ventilation
- Language dysfunction
  - Diminished output, mutism, echolalia
Anti-NDMAR Encephalitis: Differential diagnosis

- Delirium from toxic/metabolic encephalopathy
- Primary psychiatric disorders
  - Acute psychosis, schizophrenia
  - Mania
- Malignant catatonia
- Neuroleptic malignant syndrome
- Viral encephalitis
- Creutzfeldt-Jacob disease
- Non-convulsive status epilepticus
- Other autoimmune encephalitis
  - LGI1, Caspr2, AMPA, GABA-A, GABA-B antibodies
Anti-NMDAR antibodies & teratomas

- Ovarian teratoma in 55% of women over 18
  - Greatest in Asian, African Am.
  - 15% in girls <14 yrs
  - Our patient’s pelvic CT and ultrasound showed inconclusive 2 cm cyst, but pelvic MRI suggested a teratoma, which was resected

- Brain MRI is abnormal in <50%

- CSF abnormal in 90%: Lymphocytic pleocytosis, OCBs

- Anti-NMDAR Abs in serum or CSF
  - CSF higher sensitivity and specificity
Psychiatric Autoimmunity: N-Methyl-d-Aspartate Receptor IgG and Beyond

Jennifer L. Kruse, M.D., Maria I. Lapid, M.D., Vanda A. Lennon, M.D., Ph.D., Christopher J. Klein, M.D., Orna O’Toole, M.D., Sean J. Pittock, M.D., Edythe A. Strand, Ph.D., Mark A. Frye, M.D., Andrew McKeon, M.D.

Original Research Reports

Psychosis and/or mood disturbance

Has the patient had similar past episodes that responded to routine psychiatric treatments?

Yes

Further autoimmune evaluation unlikely to be informative

No

Evaluate for the following features:

1. **Psychiatric**
   - Atypical age of onset
   - Abrupt onset of severe symptoms, especially behavioral disorganization or catatonia, in absence of prodrome, past psychiatric history or inciting cause

2. **Speech & Language**
   - New speech or language abnormality less commonly encountered in psychiatric illness (e.g. echolalia, neologisms, mutism, aphasia, perseverative/repetitive speech)

3. **Cognitive & Neurologic**
   - New onset delirium, encephalopathy, seizures or movement disorders without toxic or metabolic cause evident

Consider head MRI, EEG, serum autoantibody profile & lumbar puncture (test for CSF glucose, protein, cell counts, oligoclonal bands, and autoantibody profile), particularly if personal or family history of cancer or autoimmunity.
Anti-NMDAR encephalitis treatment

• Prompt diagnosis and treatment associated with good prognosis
  • 75% fully recover or have mild sequela
  • Better with teratoma, if promptly removed
  • IV steroids, IVIG, plasma exchange, cyclophosphamide, rituximab, seizure control, supportive care

• Challenging: prolonged ICU, difficult placement
  • Refractory seizures, autonomic instability
  • Behavioral dyscontrol

• Slow recovery. Average 3 month hospitalization

• Relapse in 25%, mainly those without tumor

Titulaer, Lancet Neurology 2013
Clinical Pearls

• Consider anti-NMDAR encephalitis in a young woman without psychiatric history who presents with a subacute neuropsychiatric symptoms

• Search for antibodies in serum/CSF and teratoma especially in women >18 yrs old
Case 22

- A 70-year old man is brought to clinic by his wife because he has been having violent behavior at night.
- From sleep he may start talking, yelling, punching, and thrashing around. Often later in the night. May recall a dream of being attacked or chased.
- He has struck his wife and also fallen out of bed and hit head on nightstand. Though going on for 5 years, she was too embarrassed to bring it up before.
Which medication could be used to prevent this injurious behavior?

A. Quetiapine
B. Mirtazapine
C. Venlafaxine
D. Clonazepam
E. Carbidopa/levodopa
REM Sleep Behavior Disorder

• Loss of normal muscle atonia during REM sleep
• Dream enactment: patients “act out” dreams (being chased/attacked): vocalize, complex movements
• Punch, kick, thrash, fall out of bed, knock over nightstand, scream, shout, swear
• Injure self (60%) or bed partner (20%)
REM Sleep Without Atonia
REM Sleep Behavior Disorder (RBD)

- Prevalence 0.5%; typical onset age 40-70; 7% in age 70-89; greater in men
- Collateral history from bed partner is critical, though patients may recall dreams for days

Which condition are patients with RBD at greatest risk of developing?

A. Obstructive sleep apnea
B. Major depressive disorder
C. Narcolepsy
D. Parkinson disease
E. Restless leg syndrome
RBD Causes

- **Antidepressants:** TCA, MAOI, SSRI, SNRI
  - Precipitates/exacerbates in up to 6%
  - Most common cause of RBD in patients < 40y
- **Withdrawal of barbiturates, caffeine, alcohol**
- **Narcolepsy with cataplexy:** orexin failure of REM sleep/wake boundary control
- **Pontine lesions:** vascular, MS, neoplasm
- **Alpha-synuclein neurodegeneration**
  - REM sleep-related neurons an early target
  - Most with “idiopathic” RBD eventually develop a neurodegenerative condition (months to decades, 50% convert every 10 years)
  - Parkinson disease, Lewy body dementia, MSA
  - Early Sx: anosmia, constipation, MCI, subtle parkinsonism
  - Depression a harbinger for early neurodegeneration?

References:
Distinguish from Nocturnal Frontal Lobe Epilepsy and Non-REM Parasonmias

TYPICAL FEATURES DISTINGUISHING NOCTURNAL PAROXYSMAL EPISODES

REM
- RBD
  - Often in neurodegenerative disorders
  - Usually late onset
  - No family history
  - Last third of the night
  - Memory of dream mentation

- NIGHTMARE
  - Tend to disappear throughout life
  - Last third of the night
  - Mild autonomic activation
  - Memory of dream mentation

NREM
- DISORDERS OF AROUSAL
  - Tend to disappear throughout life
  - Triggering factors
  - First third of the night
  - Usual amnesia

Nocturnal frontal lobe epilepsy

Nocturnal Frontal Lobe Seizure Semiology

Figure 1 Photograms taken from the video recording of a frontal epileptic seizure in six patients. The pictures show an almost typical motor pattern characterized by raising and abduction of the legs, frightened expression and screaming. This pattern is seldom observed during parasomnias.
Distinguish from Restless Leg Syndrome and Periodic Limb Movements

- Restless legs syndrome (RLS)/Willis-Ekbom disease (WED) is a clinical syndrome diagnosed by the presence of the following 5 features:
  1. An urge to move the legs related to uncomfortable/unpleasant sensations in the legs
  2. Worse during periods of rest or inactivity, such as lying down or sitting
  3. Partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues
  4. Only occurs or is worse in the evening or night than during the day
  5. Not solely accounted for as symptoms primary to another medical or a behavioral condition (eg, myalgia, venous stasis, leg edema, arthritis, leg cramps, positional discomfort, habitual foot tapping)
Distinguish from Restless Leg Syndrome and Periodic Limb Movements

• Secondary symptoms may include the following:
  • Resultant insomnia
  • Periodic limb movements of sleep
    • Sudden brief “triple flexion response” leg movements in NREM sleep
    • Occur in >80% of patients with RLS/WED but
    • Also seen in other sleep disorders like untreated obstructive sleep apnea
    • Can trigger arousal parasomnias in children
RBD Evaluation

- Sleep-wake history
  - Timing of vocalizations/behaviors to differentiate from confusional arousals, sleep walking, sleep terrors
- Neurologic history/exam
  - Anosmia, constipation, orthostasis, bradykinesia, cognitive
- Medications: antidepressants
- Possibly MRI, EEG, neuropsychometrics
- Polysomnography (OSA, PLM, seizure)
RBD Management

- Education
- Make the bedroom safe
- Eliminate offending meds if possible
- Neurological evaluation?
- Clonazepam 0.25-2.0mg
- Melatonin 3-15mg qhs

McCarter et al. Sleep Med 2013
Clinical Pearls

• REM Sleep Behavior Disorder represents dream enactment behavior with loss of normal REM atonia and carries increased risk of developing a neurodegenerative disorder

• Treatment with clonazepam is generally effective, but melatonin may be better tolerated
Treatment tip from a patient
Case 23

• A 62-year-old man is referred for depression and hallucinations

• For 6-12 months, family reports he has lost interest in things, “looks depressed”, may be hard to arouse from long naps, stares off a lot, but also has periods of confusion, has gotten lost driving, and moves slower

• He is convinced his wife of 40 years is having an affair

• He admits to sometimes seeing and talking to his deceased parents on the couch or seeing a giraffe out the window

• No past psychiatric history or medications
Case 23

- Exam: slow stooped shuffling gait; facial masking; psychomotor retardation; slight symmetric rest tremor
- MMSE: 26/30. Slow responses. Impaired attention (serial 7s) and figure copying. Learning, recall, language intact.
- Denies feeling down, depressed, hopeless, suicidal
- Recognizes hallucinations “aren’t real”
- Believes his neighbor is stealing tools from his basement
- No other thought disorder
What is the most likely diagnosis?

A. Major depressive disorder
B. Schizophreniform disorder
C. Parkinson disease
D. Parkinson disease with dementia
E. Dementia with Lewy bodies
Dementia with Lewy bodies (DLB or LBD)

- Second most common neurodegenerative dementia after Alzheimer’s disease
- Up to 26% of dementia
- Lewy bodies: intraneuronal inclusions staining for alpha-synuclein
  - Affecting cortical regions (vs. PD)
  - Often co-existing AD pathology
McKeith Criteria

- Third report of the DLB consortium
- Neurology 2005

<table>
<thead>
<tr>
<th>Clinical and radiologic features of dementia with Lewy bodies (DLB)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Central feature (essential for the diagnosis)</strong></td>
</tr>
<tr>
<td>Progressive cognitive decline, dementia</td>
</tr>
<tr>
<td><strong>Core features (two features essential for diagnosis of probable DLB, one for possible DLB)</strong></td>
</tr>
<tr>
<td>Fluctuating cognition</td>
</tr>
<tr>
<td>Recurrent well-formed, detailed visual hallucinations</td>
</tr>
<tr>
<td>Spontaneous features of parkinsonism</td>
</tr>
<tr>
<td><strong>Suggestive features (one suggestive feature with one core feature may diagnose probable DLB, one or more suggestive features may diagnose possible DLB)</strong></td>
</tr>
<tr>
<td>REM sleep disorder</td>
</tr>
<tr>
<td>Severe neuroleptic sensitivity</td>
</tr>
<tr>
<td>Low dopamine transporter uptake in basal ganglia on SPECT or PET</td>
</tr>
<tr>
<td><strong>Supportive features (common features with undetermined diagnostic specificity)</strong></td>
</tr>
<tr>
<td>Repeated falls</td>
</tr>
<tr>
<td>Syncope or transient loss of consciousness</td>
</tr>
<tr>
<td>Severe autonomic dysfunction</td>
</tr>
<tr>
<td>Hallucinations in other modalities</td>
</tr>
<tr>
<td>Systematized delusions</td>
</tr>
<tr>
<td>Depression</td>
</tr>
<tr>
<td>Relative preservation of medial temporal lobe on MRI or CT</td>
</tr>
<tr>
<td>Generalized low uptake on SPECT or PET perfusion imaging with reduced occipital activity</td>
</tr>
<tr>
<td>Abnormal (low uptake) MIBG myocardial scintigraphy</td>
</tr>
<tr>
<td>Prominent slow wave activity and temporal lobe transient sharp waves on EEG</td>
</tr>
<tr>
<td><strong>Conflicting features (features which make DLB less likely)</strong></td>
</tr>
<tr>
<td>Cerebrovascular disease evidenced by focal neurologic signs or neuroimaging</td>
</tr>
<tr>
<td>Other physical illness or brain disorder which is consistent with some or all of clinical features</td>
</tr>
<tr>
<td>First appearance of parkinsonism at late stage (severe) dementia</td>
</tr>
<tr>
<td><strong>Temporal sequence (feature which distinguishes DLB from Parkinson disease dementia)</strong></td>
</tr>
<tr>
<td>Dementia should occur before or concurrently with onset of parkinsonism</td>
</tr>
</tbody>
</table>
DLB Clinical Features

• Dementia
  • Early impairment of attention, psychomotor speed, executive and visuospatial function. Memory loss late.

• Fluctuations
  • Variably severe fluctuations in cognition/confusion and alertness/somnolence lasting seconds to days
  • Episodes of daytime drowsiness, long naps, staring spells, disorganized speech

• Visual hallucinations
  • Early symptom affecting 2/3. Often well-formed, people/animals. Distinguishes from AD. Underreported.
DLB Clinical Features

• REM sleep behavior disorder
  • In up to 85% of DLB patients. Associated with synucleinopathies. May precede other Sx by decades.

• Other hallucinations
  • Variably formed auditory, olfactory, tactile

• Systematized delusions
  • In up to 75%
  • Capgras, spousal infidelity, other paranoia
Management of Dementia

- **Cholinesterase inhibitors**: first line treatment
  - Randomized control trials with rivastigmine\(^1\) and donepezil\(^2\) and several open-label trials
  - More efficacious than in Alzheimer’s
    - Co-existing AD markers (hippocampal atrophy, amyloid-\(\beta\) load) predict poorer med response\(^3\)
    - Benefiting cognition, fluctuations, anxiety, delusions, hallucinations, caregiver burden

- **Memantine**: mixed or minimal benefit
  - Worsening delusions/hallucinations\(^4\) by binding the PCP site of NMDAR

\(^1\)McKeith et al. Lancet 2000
\(^2\)Mori et al. Ann Neurol 2012
\(^3\)Graff-Radford et al. Brain 2012
\(^4\)Ridha et al. Neurol 2005
Management of Depression

• Common in DLB

• Distinguish from parkinsonian signs
  • Facial masking, bradykinesia, bradyphrenia, apathy, anorexia, sleep difficulty

• Distinguish from pseudobulbar affect
  • Educate; low dose TCA, SSRI
  • Dextromethorphan/quinidine (Nuedexta)

• Treat depression; harness alerting/sedating FX
  • SSRIs, venlafaxine, buproprion, mirtazapine
  • Avoid TCAs with anticholinergic side effects
Management of Psychosis

• Education, sleep hygiene, redirection, r/o infections
• Remove/reduce offending meds
  • Dopamine agonists, anticholinergics, benzos
• Cholinesterase inhibitors
• Neuroleptic sensitivity
  • D2 receptor blockers: acute/severe parkinsonism or impaired consciousness in about 50%
  • Quetiapine preferred: start 12.5-25mg qhs, up to 200mg
  • Clozapine: limited to psychiatrists
  • Black box warning for dementia-related psychosis
  • Pimavanserin: 2nd gen antipsychotic newly approved for PD-associated hallucinations & delusions (not for dementia-related psychosis)
Case 24

• A 67-year old librarian is referred to you due to her daughter’s concerns about behavioral changes. She has a remote history of post-partum depression. Her insomnia from restless legs syndrome has finally improved with treatment changes 2 months ago.

• However, she has subsequently started spending much of her savings on online shopping, began gambling at the local casino, and has gained weight with compulsive eating.
What is the most likely cause of her behavioral changes?

A. Late onset bipolar disorder
B. Frontotemporal dementia
C. Dopamine agonist-induced impulse control disorder
D. Paraneoplastic limbic encephalitis
E. Lewy body disease
Why not…?

• **Bipolar:** Rarely onset in 60s. Absence of reduced need for sleep, grandiosity.

• **Frontotemporal dementia:** Possible. Can cause apathy or impulsivity/disinhibition, but rare & insidious.

• **Paraneoplastic limbic encephalitis:** Expect global encephalopathy, seizures, other findings.

• **Lewy body disease:** Neurodegenerative cause of subcortical dementia & parkinsonism, not disinhibition.
RLS Treatment

- Dopamine agonists (pramipexole, ropinirole) have become first line treatment for moderately severe or daily restless leg syndrome
- Mesolimbic dopamine system mediates reward functions and modulates impulse control
At-risk for pathological gambling: imaging neural reward processing under chronic dopamine agonists

Birgit Abler, Roman Hahlbrock, Alexander Unrath, Georg Grön and Jan Kassubek
Impulse Control Disorders

• Pathologic gambling
• Hypersexuality
• Excessive spending
• Binge eating
• Punding—complex, stereotyped, purposeless, repetitive actions
• Hobbyism

• May develop many months after initiation or dose escalation
<table>
<thead>
<tr>
<th>Disorders intrinsic to Parkinson disease</th>
<th>Disorders associated with dopaminergic therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>Delirium</td>
</tr>
<tr>
<td>Anxiety disorders</td>
<td>Hallucinations</td>
</tr>
<tr>
<td>Apathy</td>
<td>Paranoia and delusions (psychosis)</td>
</tr>
<tr>
<td>Anhedonia</td>
<td>Impulse control disorders</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Compulsive behaviors</td>
</tr>
<tr>
<td>Akathisia</td>
<td></td>
</tr>
<tr>
<td>Impaired executive function</td>
<td></td>
</tr>
<tr>
<td>Dementia</td>
<td></td>
</tr>
<tr>
<td>REM sleep behavior disorder</td>
<td></td>
</tr>
</tbody>
</table>
Clinical Pearl

- Dopamine receptor agonists should be a suspected cause of new impulse control disorders in Parkinson disease or RLS patients taking such medications.
- Dose reduction or discontinuation is generally curative.
Learning Objectives

• Functional neurological disorders
  • Gain insight into possible pathophysiology of functional movement and other conversion disorders and updates on their diagnosis and management

• Cognitive/behavioral disorders
  • Recognize features of autoimmune and degenerative neurological disorders that can present with predominantly psychiatric symptoms

• Sleep disorders
  • Review diagnosis and management of selected sleep disorders that may be associated with neurologic or psychiatric symptoms or disease
Thank you
Bonus material
Case 1

- 46 year old female multiple visits to ED and two hospitalizations this year for depression and suicide attempt
- Chronic migraines for two years
- Concern about overuse of analgesics
- Significant anxiety symptoms, fatigue, no longer working now and has financial stressors
Migraine Epidemiology

• Migraine prevalence: 17% of women, 6% of men

• Increased risk of psychiatric comorbidity in migraine and other headache disorders
  • Depression: 2-4 times higher, bidirectional
  • Anxiety Disorders: 3-10 times higher (panic>OCD or GAD)
  • Bipolar disorder: 3-7 times higher (higher if aura)

• Higher levels of anxiety & depression in chronic migraine than episodic migraine

Lipton et al. Neurol 2007
Hamelsky, Lipton. Headache 2006
Baskin et al. Headache 2006
Basis of Comorbidity: Migraine, Anxiety & Depression

- Genetic correlation: twins studies
  - Migraine more heritable when no depression
  - Bidirectional causality: one causes the other
  - Syndromic association: spectrum disorder
- Common biologic neurotransmitter substrate
  - Low serotonin levels
  - Abnormal tyrosine metabolism on DA/NE synth
- Imbalanced glutamatergic & GABAergic activity?
Establishing the Headache Type (via ICHD-3 beta)

• “Headache attributed to psychiatric disorder”
  • Somatization or psychotic (delusional) disorder
  • Rare situations (with limited evidence) where headache is purely a psychiatric cause
    • e.g. headache from delusion that metal plate surreptitiously inserted into head, delusion of brain tumor despite normal imaging, or part of somatization disorder

• Vast majority of headaches with psychiatric disorders represent comorbidity and warrant diagnosis of both a primary headache diagnosis and the comorbid psychiatric diagnosis
Primary Headache Disorders

- Migraine
  - >5 HA, 4-72h; N/V or photo/phonophobia;
  - 2 of: unilateral, pulsatile, mod-severe, motion ↑

- Tension-type headache
  - Bilateral, non-pulsating, mild-mod, no N/V

- Chronic daily headache: > 15 days/month
  - Migraine, tension, or medication overuse
Challenges of Comorbid Patients

- Poorer prognosis
  - Greater disability, activity restriction; worse QOL
  - More refractory to treatment?

- Reduced adherence to medication regimen
  - Greater analgesic medication overuse

- Drug side effects & interactions
  - Worsening depression or headache

- Therapeutic opportunities
  - Treating headaches & depression/anxiety leads to better headache treatment outcome
  - Dual efficacy medications vs. 2 best medications

1 Jette et al. Headache 2007
2 Radat et al. Headache 1999
Headache & Depression

• Dual-action antidepressants: 5-HT, NE reuptake
  • Amitriptyline, nortriptyline
    • 25-50mg/d for headache, 150mg/d for depression
    • Sedation, urinary retention, wt gain, blurred vision
    • Overdose of 3-5 times daily dose can be fatal
  • Venlafaxine
    • 75-150mg/d for migraine, tension headache
    • Well tolerated. Nausea, sexual, insomnia, dreams, HTN
  • Mirtazapine—complex action
    • Second line after amitriptyline for tension headache

• SSRIs? Poor efficacy for headache

• Beta blockers probably OK
  • No evidence of increasing depression

1 AAN Practice Parameter 2000
3 Ozyalcin et al. Headache 2005
4 Bendtsen et al. Neurol 2004
5 Ko et al. JAMA 2002
6 Van Melle et al. JACC 2006
Headache & Anxiety Disorders

• Generalized anxiety disorder
  • Venlafaxine: initial GAD and migraine treatment\(^1,2\)
  • Gabapentin: migraine, adjunct for GAD
  • Pregabalin: GAD, +/- migraine\(^3\)
  • Buspirone: GAD, +/- migraine\(^4\)

\(^1\) Bulut et al. Clin Neurol NSurg 2004
\(^2\) Ozyalcin et al. Headache 2005
\(^3\) Calandre et al. Clin Neuropharm 2010
\(^4\) Lee et al. Headache 2005
Case 2

• 26 year old female with bipolar disorder
• Hospitalized in graduate school with first manic episode and now has returned to her home
• Episodic severe throbbing headaches with nausea, photophobia, and phonophobia
• Currently on Lithium
• Not using birth control
If her goal were monotherapy, which medication is the LEAST IDEAL choice for management of both bipolar disorder and prophylaxis of migraine without aura?

A. Divalproex sodium
B. Topiramate
C. Lamotrigine
D. Carbamazepine
Headache & Bipolar Disorder

• Anticonvulsant mood stabilizers for migraine
  • Valproate (Level A)
  • Topiramate (A)
  • Carbamazepine: bipolar, possibly migraine (C)
• Not dual efficacy
  • Gabapentin: maybe migraine (U), not bipolar
  • Lamotrigine: bipolar, not migraine (aura?)
• Avoid antidepressants for headache without mood stabilizer → precipitate mania
Medication-related Issues

- Chronic headache & medication overuse
  - Concern in patients with psychiatric comorbidity
  - Narcotics, alcohol, other CNS-acting medications

- Antiepileptics and suicide event risk\(^1\)
  - FDA 2008 metaanalysis: 1.8 fold increased risk among 11 AEDs in patients with epilepsy, pain, or psychiatric disorders
  - 0.24\% in placebo to 0.43\% in AED (1.9 more per 1000)
  - Subsequent studies: ↑ risk except in epilepsy

- Serotonin syndrome with triptans + SSRIs/SNRIs\(^2\)
  - FDA 2006 warning based on n=10 (none met Hunter criteria).
  - AHS 2010: “insufficient class IV data to limit use; be vigilant”; 700,000 taking both in U.S.

\(^1\)Arana et al. NEJM 2010
\(^2\)Evans et al. Headache 2010
Rational Approach

• Be vigilant for psychiatric and headache comorbidity

• Adequate dose and duration of migraine prophylactic trials

• Look for dual action therapeutic opportunities

• Incorporate non-pharmacologic therapies
  • Migraine diet, lifestyle modification, relaxation, biofeedback, cognitive behavioral therapy
Case 3

• A 52-year old man with schizophrenia presents with insidious development of abnormal movements. He has a long history of first-generation antipsychotic exposure but is currently on a stable dose of risperidone.

• Exam shows mild-moderate choreiform dyskinesias of the limbs, axial dystonia, as well as oral, lingual, and facial dyskinesias such as tongue protrusion and lip smacking
Which treatment strategy for tardive dyskinesia has the best evidence?

A. Withdrawal of dopamine receptor blocking agents
B. Switching from typical to atypical antipsychotics
C. Clonazepam
D. Tetrabenazine
E. Botulinum toxin A
Tardive Dyskinesia

• Definition
  • Hyperkinetic movement disorder that appears with delayed onset after prolonged use of dopamine receptor blocking agents (neuroleptics and metoclopramide)

• Movements
  • Choreoathetosis, dystonia, akathisia, stereotyped behaviors (tics, facial grimacing)

• Temporal profile
  • Transient (upon initiation), withdrawal-emergent (kids), or persistent
TD Clinical Course

- Insidious, affects up to 30% with long-term antipsychotics
- May occur as early as 1 to 6 months after drug initiation
- May appear after dose reduction or discontinuation (“unmasked” by removal of hypokinetic effects of the dopamine blocker)
  - Withdrawal dyskinesias often resolve in weeks but may be precursor to persistent TD
- Often reversible, especially in younger patients (50-90%)
TD Differential Diagnosis

- Neurologic disorders with psychiatric symptoms—Huntington’s, Wilson’s, lupus, antiphospholipid antibody syndrome
- Akathisia—feeling of motor restlessness
- Acute dyskinesia—upon drug initiation
- Tremor—rare as a tardive syndrome (seen with rigidity as drug-induced Parkinson’s, improves with withdrawal)
- Spontaneous orofacial dyskinesias in the elderly
- Other causes of dystonia
- Stereotypies and psychotic mannerisms in schizophrenia
- Tourette’s
## Selected adverse effects of antipsychotic medications for schizophrenia

<table>
<thead>
<tr>
<th>First generation agents</th>
<th>Weight gain/diabetes mellitus</th>
<th>Hypercholesterolemia</th>
<th>EPS/TD</th>
<th>Prolactin elevation</th>
<th>Sedation</th>
<th>Anti-cholinergic side effects</th>
<th>Orthostatic hypotension</th>
<th>QTc prolongation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpromazine</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+/ND</td>
<td>+</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>-</td>
<td>-/ND</td>
<td>ND</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>-</td>
<td>-/ND</td>
<td>+</td>
</tr>
<tr>
<td>Loxapine</td>
<td>++</td>
<td>ND</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+/ND</td>
<td>+</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>++</td>
<td>ND</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>-</td>
<td>-/ND</td>
<td>ND</td>
</tr>
<tr>
<td>Pimozide</td>
<td>+</td>
<td>ND</td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+/ND</td>
<td>+</td>
</tr>
<tr>
<td>Thioridazine*</td>
<td>++</td>
<td>ND</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++/ND</td>
<td>+++</td>
</tr>
<tr>
<td>Thiothixene</td>
<td>++</td>
<td>ND</td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>-</td>
<td>+/ND</td>
<td>+</td>
</tr>
<tr>
<td>Trifluoperazine</td>
<td>++</td>
<td>ND</td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>-</td>
<td>+/ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Second generation agents[1]</th>
<th>Weight gain/diabetes mellitus</th>
<th>Hypercholesterolemia</th>
<th>EPS/TD</th>
<th>Prolactin elevation</th>
<th>Sedation</th>
<th>Anti-cholinergic side effects</th>
<th>Orthostatic hypotension</th>
<th>QTc prolongation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-/ND</td>
<td>-</td>
</tr>
<tr>
<td>Asonapine</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>-</td>
<td>+/ND</td>
<td>-</td>
</tr>
<tr>
<td>Clozapine*</td>
<td>+++</td>
<td>+++</td>
<td>-</td>
<td>-</td>
<td>+++</td>
<td>+++</td>
<td>+++/ND</td>
<td>+</td>
</tr>
<tr>
<td>Iloperidone</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+++</td>
<td>++/ND</td>
<td>++</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-/ND</td>
<td>-</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>-</td>
<td>++</td>
<td>+</td>
<td>++/ND</td>
<td>+</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+++</td>
<td>+</td>
<td>-</td>
<td>++/ND</td>
<td>++</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>++</td>
<td>+++</td>
<td>-</td>
<td>-</td>
<td>++</td>
<td>+</td>
<td>++/ND</td>
<td>++</td>
</tr>
<tr>
<td>Nisopride</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>+++</td>
<td>+</td>
<td>-</td>
<td>++/ND</td>
<td>+</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+/ND</td>
<td>++</td>
</tr>
</tbody>
</table>

Adverse effects may be dose dependent.
EPS: extrapyramidal symptoms; TD: tardive dyskinesia; ND: no data.
* Thoridazine is also associated with dose-dependent retinopathy pigmentosa. Refer to text.
* Clozapine also causes granulocytopenia or agranulocytosis in approximately 1 percent of patients requiring regular blood cell count monitoring.

Adapted from:
1. Treatment Guidelines from The Medical Letter; August 2010; Vol. 8 (96): 61. [www.medicalletter.org](http://www.medicalletter.org)
TD Management

- **Prevention?** Avoid/minimize long-term metoclopramide and first-generation antipsychotics. Lowest dose for proper indications.
  - Chronic prophylactic anticholinergics not indicated (only for acute dystonic reaction)

- **Withdrawal of dopamine blockers?** Only a few Class III/IV studies (insufficient data, Level U). May worsen dyskinesias in first few weeks. APA recommends withdrawal only in patients whose psychosis can tolerate it.

- **Switch from typical to atypical drug?** Class IV studies give conflicting results (Level U) though it is considered “prudent” to switch if possible.

- **Pharmacologic treatment?** Limited data
  - **Clonazepam** probably effective (1 Class I 12-week study, Level B), but benefit waned by 5-8 months
  - **Ginkgo biloba** extract probably effective (1 Class I 12-week study on schizophrenia inpatients, Level B)
  - Risperidone might help but not recommended as causes parkinsonism
  - **Level U:** acetazolamide, bromocriptine, thiamine, baclofen, vitamins E/B6, selegiline, clozapine, olanzapine, melatonin, nifedipine, haloperidol, levetiracetam, quetiapine, ziprasidone, buspirone, reserpine, methylxldopa…

- **Interventions?** Botulinum toxin A, ECT, deep brain stimulation all Level U
Clinical Pearl

• Evidence-based data are limited, but clonazepam and ginkgo biloba have strongest evidence for treatment of tardive dyskinesias

• Prevention is key