“One pill makes you larger, one pill makes you small, but…”

The ones your doctor gives you….

A Guide for Detecting Adverse Drug Events in Patients with Intellectual and Developmental Disabilities (ID and ASD)

Lauren Charlot, PhD
Angela Hasiotis, MD
Stephen Ruedrich, MD

- Overview of proposed guide, special concerns for people with IDD/ASD
  - Dr. Charlot
- Antipsychotic Medications
  - Dr. Hasiotis
- Mood Stabilizing Medications
- Summary and Discussion
  - Dr. Ruedrich
A Guide Specific to Needs of Our Patients

- NOT a repeat of existing guidelines
- What is needed for people with IDD/ASD?
  - What symptoms require self-report?
  - How can we change assessment to catch these problems?
- Also, addressing current over reliance on medications to control behavior
  - How do we make more accurate diagnoses?
  - Promote multidisciplinary assessment and care?
  - Promote more coordinated care?
  - Increase attention to promoting wellness?

DEFINING TERMS

- SIDE EFFECTS: Any undesired actions or effects of a drug or treatment. Negative or adverse effects may include headache, nausea, hair loss, skin irritation, or other physical problems.
  - “The international pharmacovigilance community has recognized that the term side effect tends to minimize the injury from drugs and has recommended that this term no longer be used”

DEFINING TERMS


- Adverse Drug Event (ADE)
  - “an injury resulting from medical intervention related to a drug” The Institute of Medicine
  - Adverse Drug Reaction (ADR)
  - An adverse drug reaction occurs at usual doses and is caused by the action of the drug. Onset may be sudden or develop over time
"Physicians … commonly classify gastrointestinal adverse drug reactions as ‘side effects’ and believe them to be common and unavoidable consequences of medical care, not clinically significant manifestations of disease."

"……However, even though only a small percentage of these events are serious, these “side effects” are so common that serious manifestations…are not rare.

**Side Effects**

**TRENDS in PSYCHOPHARMACOLOGIC TREATMENT of Individuals with IDD**

- People with ID:
  - Treated with PSYCH MEDS at HIGH rates
  - Often treated for off label indications
    - More likely for reduction of non-specific signs of agitation (aggression, SIB, tantrums, etc)
  - Treated with high rates of multi-drug regimens
  - Debate as to whether or not current practice is really evidence based
    - Particular concerns about extensive use of AP drugs
    - Experts who carefully review data conclude evidence is POOR for practice
  - Multi-drug regimens are now the NORM
    - NO EVIDENCE BASE exists for this


**Psychoactive Medication Rates**

- Cross sectional- Reviewed Medicaid claims
- > 60,000 children with ASDs
- All US states and Washington DC
- Study period: 2001 to 2005,
- 56% had used at least 1 psychotropic med
- 20% >>>> 3 medications.
Psychoactive Medication Use

- Children - 0 to 2 yrs >>> 18% taking psych med
- Children - 3 to 5 yrs >>> 32%, taking psych med
- Neuroleptic drugs >>>> most commonly prescribed drug class (31%);
- Antidepressants (25%)
- Stimulants (22%)

Several moderators associated with greater likelihood of psychoactive medication use:
- being male, older, and white; being in foster care or designation in the Medicaid disability category; having comorbid psychiatric diagnoses; and receiving additional specialized autism spectrum disorder services.


- Multicenter US based investigation
- Prescription trends for adolescents and adults with ASDs
- Longitudinal ---- 4.5 years
- Study start:
  - 70% of sample - at least ONE psychoactive med
  - 87% receiving > 1.
  - ONCE initiated, treatment most often continued with increasing numbers of the cohort being started on psychoactive meds over the study period.
  - Concluded that individuals with ASDs are “an increasingly medicated population.” (p.10).

BACKGROUND

- Side effects may have direct or indirect effects
  - i.e. direct – toxicity from elevated blood levels
  - cause pain or distress with impact on mood and behavior
- Frequently missed in patients with ID and ASD
- At times, the only sign =
  - alterations in mood and behavior
- Looks the same as psychiatric symptoms
Physical Illness and Challenging Behavior

- Physical illness has been directly linked to problem behaviors in people with IDD
  - Most people with IDD are referred for psychiatric care due to problem behaviors i.e. aggression, SIB, disruptive behaviors


PAIN and BEHAVIOR

- Pain or physical discomfort may act as a "setting event" lowering the threshold for challenging behaviors
- People with IDD have few ways to express distress and are poor at reporting their internal states


Why do health problems get missed?

- Patients with ID often have a limited capacity to self-report medical problems, side effects and medical history
- At times, may evidence a high tolerance for pain
Often We Rely on Informant Reports

- Informants
  - Over – report externalizing problems
  - Under - report internalizing symptoms
  - Give you THEIR diagnosis v what they actually saw

Non-psychiatric health problems among psychiatric inpatients with Intellectual Disabilities.

RESULTS (n = 198 inpts)

- Inpatients with more medical diagnoses had longer lengths of stay – ($r^* .32, p < 0.0001$).
- Inpatients taking more psychoactive medications had more medical problems – (Spearman $r^* .32, p < 0.0001$)
RESULTS (n = 198 inpts)

- For 40%, medical problem(s) or medication side effect(s) were the primary causes of the altered mental status, mood and behavior leading to an acute psychiatric stay
- Most common:
  - Constipation
  - GERD
  - EPS (Extra-pyramidal Symptoms)

Lauren Charlot, PhD (1)
Susan Abend, MD (2)
Paula Ravin, MD (1)
Kimberly Mastis, MD (1)
Len Doehfler, PhD

(1) Department of Psychiatry, University of Mass Medical School (UMMS), Worcester MA
(2) The Healthcare Quality Management Group (Framingham, MA)
(3) Eunice Kennedy Shriver Center UMMS (Waltham MA)

Acknowledgements: This work was funded by the Commonwealth Medicine UMass Medical School Internal Grants Initiative

ADVERSE DRUG EVENTS

- Examined rates of ADEs in a sub group of the larger initial sample
- Close inspection of 72 charts
- Identified elements that could be detected in chart reviews that would suggest the presence of the ADE
Data Elements

- Constipation
- BMI > 25 30
- Falls
- Gait problems
- Sedation
- Akathisia
- Dystonia
- Parkinsonian symptoms (EPS)
- Abnormal Labs

Mean Number of Psychoactive Medications per Person for 198 Psychiatric Inpatients with ID

<table>
<thead>
<tr>
<th>Group</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASD</td>
<td>3.34</td>
</tr>
<tr>
<td>DS</td>
<td>2.2</td>
</tr>
<tr>
<td>OTHER</td>
<td>3.2</td>
</tr>
<tr>
<td>ALL</td>
<td>2.9</td>
</tr>
</tbody>
</table>

Psychoactive Medications

- Antipsychotic: 48%
- Anticonvulsants: 30%
- Antidepressant: 48%
- Benzodiazepine: 46%
- SSRIs: 37%
- Anti-Parkinsonian: 25%
Aggression = Fever

- Not diagnostically specific
  - MANY OF OUR PATIENTS HAVE A "LIMITED BEHAVIORAL REPERTOIRE"
    - When tired...
    - When upset about changes in routine....
    - When unhappy about an interaction with a peer....
    - When ill....

  THE SAME SET OF symptoms of ALTERED MOOD AND BEHAVIOR MAY BE manifested for a different reason each time

RESULTS

- The 72 psychiatric inpatients averaged 2.5 ADEs per person

Patients with multiple recent medication changes had more ADEs
Switching and Drug Changes

- Valdovinos et al. 2005
- High rates of health problems and side effects
- > side effects with > recent medication changes

SEDATION, GAIT PROBLEMS & FALLS

- Patients taking AP drugs were more likely to be identified with this combined set of problems
  - $p < 0.01$

RISK for missing ADEs in Patients with ASD/ID

- Lack of data on occurrence in this population
- Differential Diagnosis of Psychiatric Disorders is more challenging
  - Symptom checklist approach leads to over-identification of drug responsive d/os
  - These may seem “treatment resistant” requiring complex multi-drug regimens
- Often, the only surface manifestation is agitation
  - It looks like something psychiatric
Multidrug Treatment

- Use of complex multidrug regimens may cause a cascade of troubles in patients with ID who have a fragile neurological and physical substrate.
Multiple Versus Single Antipsychotic Agents for Hospitalized Psychiatric Patients: Case-Control Study of Risks vs Benefits (2009)

- Inpatients treated with monotherapy or polytherapy
- 70 matched pairs
- Chlorpromazine-equivalent daily dose
- A number of outcome measures
- Concluded: “Short-term treatment with multiple antipsychotics was associated with major increases in drug exposure, adverse events, and time in the hospital but with no apparent gain in clinical benefit.”

Patient-Related Risk of Side Effects or ADEs

- Age/Gender
  - Non ID >>> females > risk of AP drug SEs
- Genetic variations impacting metabolic pathways
  - Polymorphisms – rapid and slow metabolizers
- Level of global brain impairment
  - Decreased redundancy in neural circuits
  - Most studies suggest brain impairment, cognitive impairment > risk
- Specific risk related to site/type of affected brain circuits...e.g.,
  - Neuroleptic-induced movement problems in patients with cerebral palsy, cerebellar hypoplasia, basal ganglia abnormalities
  - Trigging of tics in some patients treated with anti-ADHD drugs
  - Effects of DA blockade on attention and concentration in the setting of specific frontal impairment
  - Drugs lowering seizure threshold in patients with epilepsy

Not Better, Just Different...

- Newer research suggests the FGAs are not better than older medications in terms of neurological side effects and that the studies finding this used haloperidol in higher doses as a comparison drug
- Most critical >> individual profile of each drug’s impact on various neurotransmitter systems and the individual’s risk issues
Age adds risk: Mean # Medical Problems X Age Group  n = 65 Consultation Referrals

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Medical Problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>age 15-25</td>
<td>3.72</td>
</tr>
<tr>
<td>age 26-45</td>
<td>4.95</td>
</tr>
<tr>
<td>age 46 or &gt;</td>
<td>8.17</td>
</tr>
</tbody>
</table>

Special Risk Issues for People with IDD/ASD

- People with IDD have baseline neuromotor abnormalities
- Medications may worsen existing problems
- Our patients have high rates of polypharmacy
- Drug induced motor problems may be missed in our patients

Review of Movement Disorders and AP Drugs

Adverse effects of antipsychotics as outcome measures
Samantha Hamer and Peter M. Haddad. BJP 2007, 191:s64-s70.
Access the most recent version at DOI: 10.1192/bjp.191.50.s64

• Studies of psychoactive medications focus on efficacy with limited attention given to side effects or Adverse Drug Events
  – When addressed, ADE rates are high but often described as well “tolerated”
  – EFFICACY often = ONLY the reduction of a negative symptom or behavior

What do we know about TOLERABILITY?

• NOT MUCH…
• How do we assess TOLERABILITY of side effects in patients who cannot or do not reliably self-report symptoms?
• Studies report drugs are “well tolerated” because patients choose to continue
• Patients with IDD don’t make this choice
• Tolerability – patients decide to continue or stop taking the medicine
  – CATIE study –Real World investigation of AP drugs in patients with schizophrenia
  – Key outcome = Pt stops taking the drug @ 70 % across all arms

The Idea That AP Drug Treatment Broadly Applied is a First Line Approach May Be Flawed….

• “The majority of RCTs are of short duration, with treatment periods of 6–12 weeks. Three RCTs of 6 months duration in children with autism and disruptive behavioral disorders have demonstrated significant weight gain and a higher risk of extrapyramidal side effects in children treated long term (Luby et al. 2006; Nagaraj et al. 2006; Reyes et al. 2006).”
Gastrointestinal Symptoms in a Sample of Children with PDDs

- 172 children entering 1 of 2 trials
- 39 (22.7%) pos for GI problems
  - primarily constipation and diarrhea.
- Ss with GI problems - more severe symptoms
  - irritability, anxiety, and social withdrawal.
- And were < responsive to medication treatments
  - MPH and RSPD

30 Years Ago... When I was 12...

- Worries re use of psychoactive meds (ie AP Drugs - Mellaril, Thorazine & Haldol) to suppress aggressive behavior
- Many individuals with ID or ASD
  - treated with large doses
  - “control” mainly related to sedation vs treating specific disorders
- Focus on outcomes of reduced negative behavior vs promoting “wellness” or more adaptive functioning

Methods used to detect side effects

“Remember how you never found me when we played hide-and-seek?”
“Did you know that I never looked?”
Side Effect Assessment Scales

- Kalachnik (1999) reviewed side effect assessment scales in the population
  - In: Eds Norman A. Wieseler and Ronald H. Hanson, AAMR, Challenging Behavior of Persons with Mental Health Disorders and Severe Developmental Disabilities, pp 151-204.
- Types of side effect assessment scales
  - medication specific scales
  - general purpose scales (MEDS, MOSES)
  - side effect specific scales (AIMS, BARS DISCUS for TD)

MEDS-Matson Evaluation of Drug Side-effects

The Matson Evaluation of Drug Side-effects (MEDS) is a 93 item scale designed to assess side effects common to psychotropic medication use. Parents/caretakers familiar with the individual rates each item. Nine domains comprise the

1) Cardiovascular/Hematologic
2) Gastrointestinal
3) Endocrine/Genitourinary
4) Eye/Ear/Nose/Throat
5) Skin/Allergies/Temperature
6) CNS-General
7) CNS-Dystonia
8) CNS-Parkinsonism/Dyskinesia
9) CNS-Akathasia.

Individuals with ASD/IDD suffer from different ADEs or Unusual Presentations

- Physical structural factors seen in ASD/IDD might add risk so that rare or infrequent ADEs may occur at higher rates
- UMASS experience showed some unusual reactions:
  - waxing and waning presentations of NMS spectrum
  - unexpectedly long periods of persistence of neuromotor ADEs and encephalopathies
  - Stress increases existing neuromotor symptoms giving appearance of control (he can walk when he wants to...)
PROPOSED GUIDE

• NADD supporting development of Guide to Increase Side Effects Detection for people with IDD/ASD
• The goal is not simply to repeat existing guidelines but to emphasize the risks of missed ADEs related to unique characteristics of our patients, and to provide suggestions for increasing accurate and reliable detection

CORE GOALS for a GUIDE

• Even when prescribers use guidelines --- no comprehensive guides highlight which monitoring practices are likely insufficient when applied to special populations---
  – What ADEs are more likely to be missed when the only source of reporting is through informants?
  – How exactly should surveillance differ for patients with ID and ASDs?

The BIG QUESTIONS for us....
Among the Most Commonly Prescribed Psychoactive Medications:

• Which ADEs usually detected via patient self-report?
• Which ADEs likely to manifest only via altered mood, mental status or behavior?
• Based on above, what changes to usual surveillance are needed to increase detection rates?
• Autonomic/Cardiac
  – Dizziness – orthostatic hypotension
  – BP drops when you stand up
  – Tachycardia (Rapid Pulse Rate)
• Cognitive effects
  – Encephalopathy/Delirium (“Brain Fog”)
  – Memory problems, confusion
  – Difficulty concentrating, focusing attention

• Mood
  – Irritability
  – Anxiety

• GI/Appetitive
  – Constipation
  – Diarrhea
  – Nausea
  – Increased or decreased appetite
  – Weight gain or loss
  – Increased thirst

• Neuromotor/Motor
  – Muscle stiffness and/or Muscle weakness
  – Changes in gait and Falls
  – Unsteadiness, ataxia
  – Akathisia/Motor restlessness
• Other
  – Headaches
  – Urinary retention
  – Fatigue, sedation
  – Sleep disruption or disturbance
Recognize that AGGRESSION is a FINAL COMMON PATHWAY for Distress –like a fever....

- Given the extreme numbers of people with ID/ASD taking psychoactive medications
  - In the event of changes in mood, behavior and mental status:
    - ADEs should be considered as a potentially significant source
    - Other medical issues
  - Our patients are poor at self-report, and the same alterations in mood, beh etc. may be due to varied sources

Recognize CLUES that a behavior change is really about physical distress or side effects

- Are there also changes in “biologic” functions?
  - Differentiate confusion from psychiatric decomp
- Know the common side effects
  - Use MEDS – excellent tool BUT, clarify each symptom
    - Check for validity and reliability at the symptom level
- Think/Remind PCP – How is this generally revealed? Does pt self-report play a key role?
- If the patient is unlikely to tell us, we need to “cast a wide net”
Know the AP Drug-Induced Movement Disorders

**Extrapyramidal symptoms**

- **Tardive Dyskinesia**
  - Orofacial dyskinesia – darting, writhing tongue and lip movements often caused by medication

- **Dystonia**
  - Sustained or writhing postures of the trunk, limbs or head and neck, often one sided or 'hemi'

- **Akathisia**
  - Inner sense of restless, need to move, with anxiety and distress

- **Parkinsonism**
  - Walking leaning forward, shuffling, tremors, drooling, rigidity at the shoulders, neck and trunk
  - Walking problems, changes in gait

Don’t Confuse Phenomenology & Etiology

- Symptoms look the same, but come from very different origins
  - Mania, hypomania vs. Endogenous bipolar disorder
  - Psychosis vs. Acute psychosis or acute exacerbation

- **Psychiatric Diagnostic Overshadowing**
  - Once a psych dx is given it is seen as the cause of all subsequent fluctuations in mood and behavior
  - Recent case referred for ECT for bipolar disorder had NMS

- Same symptom is provoked by medication (is a side effect) vs acute psychiatric condition
  - Irritability, motor restlessness
  - DSMIV criteria for ADEs may be very significant

- New medical symptoms never evaluated to identify source
  - Patient develops urinary incontinence
  - DKA/P related
  - Eventually found to have significant retention
  - Further assessment points to treatment with benztropine

ADEs –Phenomenology & Etiology

**ADEs secondary to drug tapers or discontinuation may be seen as evidence of relapse**

- Antipsychotic or SSRI initiated to treat:
  - Irritability
  - Affective lability
  - Motor restlessness/ agitation
  - Sleep disturbance
  - Associated aggression

- Antipsychotic or SSRI rapid taper or dc:
  - Irritability
  - Affective lability
  - Motor restlessness/ agitation
  - Sleep disturbance
  - Associated aggression
Round-Up the Usual Suspects

- Headaches
- Constipation
- GERD
- Sedation
- Akathisia
- EPS
  - Tremors
  - Gait changes
  - OGC
  - Dysphagia
- Urinary Retention
- Orthostasis

The Guide: Symptoms >> Drug >> Side Effect

- Tracking back from symptoms to side effects:
  - Urinary incontinence
  - Constipation
  - Gait changes, falls
  - Swallowing problems
  - Fatigue
  - Refusals of programs previously easy and fun
  - Sit down strikes
  - Atypical seizures

Using behavioral descriptions of symptoms....
USE BEHAVIORAL ANCHORS to ASSESS/MONITOR

<table>
<thead>
<tr>
<th>AE</th>
<th>Possible Observed Behavior</th>
<th>Surveillance Suggestions</th>
</tr>
</thead>
</table>
| Fatigue | 1. Complains of feeling tired
2. Looks tired (dark circles under eyes)
3. < level of activity from baseline
4. Less able to perform usual tasks and routines
5. Onset or > agitation re task demands
6. Unsteady gait | At initiation of Rx:
Rate possible observable behaviors on Likert scale to establish baseline and following titration of the drug. Risk-Benefit analysis considering down-stream impact on quality of life vs. safety, and potential for remote negative outcomes. |

Medication History

- Obtain the history of ADVERSE DRUG REACTIONS
- Patients often get put back on drugs that made them ill because they do not self-report reliably
  - Medication Histories include details re the effects of medication changes and co-occurring life events, other treatments etc.

Recognize the impact of stress: Sometimes we underestimate the impact

- Stress may worsen underlying illness
- Infections may worsen existing problems like EPS, neuromotor symptoms
- Waxing and waning, comes and goes does not = "behavioral"
What Can Prescribers Do?

- Use multiple informants
- Use various data sources
- Insist informants tell you what they observe and not just what they feel might be wrong
- Resist pressure to prescribe when people who make referral have not done THEIR homework
- Insist on a “team” approach—don’t bare all of the burden
- Advocate for “Medical Home”

CAREGIVERS

- If you ask for help when there is a behavior problem or change...
- Who do we ask first?
  - Should it always be a psychiatrist?
- Always remember that our clients/loved ones with ID/ASD may not be able to tell us really what is bothering them...

Intentional Vomiting, Fluid-Seeking, Incontinence etc. etc.

- In 90% of referrals to the UMASS Team, individuals seen as faking illness, displaying symptoms to gain attention—after a more “aggressive” work-up— a REAL physical or health cause was identified
BCBAs/BEHAVIORISTS, DSPS

• If you perform Functional Assessment of a new or worsening behavior….
  – Attend to the key influence of context
    • Context is BOTH external & internal
    • Some CBs are “state-dependent”
  – The best treatment of severe Challenging Behavior (CB) is to understand its roots and design prevention, teach skills

Charlot, 2014

Lets Not Get Carried Away

• In many instances, psychoactive medications are helpful and necessary
• Clearly, risk-benefit assessment needed
• For a number of individuals, risk without treatment can also be great

Charlot, 2014

Evidence Base: What Works for Challenging Behaviors?
Heyvaert, Maes and Onghena (2010)

• Identified 30 investigations meeting inclusion criteria
  Randomized Clinical Trials (RCTs)
• Looked at biological, psychotherapeutic, behavioral and other modalities
• All calculated effect sizes were positive
• NO one modality superior to any other
  – Urge further study to “elucidate mechanisms of effects, to increase understanding of why such varied interventions would all result in significant positive results”
  – More considered risk analyses of selected treatments
Be a critical consumer of the research and our EVIDENCE BASE - déjà vu all over again......

- Thioridazine (Mellaril) a psycho-sedative virtually free of side-effects. LJ Le Vann - Alberta Medical Bulletin, 1961

Always listen to what the doctors tell you.

But...don't give up...if you know patient has not had a thorough work-up
• “Begin at the beginning,” the King said, very gravely, “and go on till you come to the end: then stop.”
  – Lewis Carroll