Disclosure: Dr. Jacobson

With respect to the following presentation, there has been no relevant (direct or indirect) financial relationship between the party listed above (and/or spouse/partner) and any for-profit company which could be considered a conflict of interest.
• Review necessary assessment and considerations
• Review evidence base for pharmacologic management of acute aggression management
• Review evidence base for pharmacologic management of chronic aggression, irritability and self injurious behavior
You are consulted on a patient with ASD who arrived at the ED agitated:

- He is on Seroquel and guanfacine at home
- Directed by outpatient psychiatrist to take extra Seroquel yesterday, caregiver repeated this dosing instruction earlier today
- He received Zyprexa (zydis) when he arrived at the ED per agitation protocol; when that was not effective Ativan was given
- Currently he is yelling, covering his ears, pacing around the room, lying down and curling up in a ball, jumping when approached
- Caregiver has visible bruises on arms
• You inquire about PE findings and presentation
  – ED not yet able to draw blood
  – ‘PE not concerning’
  – HEENT and oral exam limited when specific inquiries made due to agitation

• You arrive and are told by ED staff ‘what that kid needs is some Haldol’
Specific considerations

- Psychiatric considerations
- Increased dopaminergic load over 24H
  - Double dose of quetiapine, added olanzapine
- Covering ears: ? AH
- Limited sleep overnight
- New environment = stress response
- Benzodiazepines may have disinhibited

- Physical considerations
- Covering ears: ? Otitis media
- Not eating: ? Oral sores or dental concerns
- Constipation
- Several doses of QT prolonging agents
Patient Specific History

- History of aggression
- History of self injurious behavior
- Historical triggers for aggression
- Signs of distress for this patient
- Soothing strategies effective for this patient

Considerations

- Medical reason for admission
- Educational level/setting
- Ability to perform ADLs
- Comorbid diagnoses
  - Both medical and psychiatric
- Prior response to medications
- Medications patient may be taking

Pharmacologic strategies

• Manage comorbid psychiatric illness

• Proactively reduce risk for disruptive behaviors

• Acute management of agitation

Robyn P. Thom, Christopher J. McDougle, Eric P. Hazen. Challenges in the Medical Care of Patients With Autism Spectrum Disorder: The Role of the Consultation-Liaison Psychiatrist, Psychosomatics, 2019
Pharmacologic strategies

• Manage comorbid psychiatric illness
  – Psychiatric symptoms assessment
  – Verify home psychotropic regimen
  – Inquire about prior response to psychotropic medication
  – Coordinate with outpatient clinicians
    • Proactively increasing home dosing regimen
    • Consider PRN use prior to an encounter anticipated to be challenging
MANAGEMENT OF EMERGENT AGITATION
Emergent agitation

- Behaviors communicate symptoms
  - Pain
  - Fear
  - Sensory overload
  - Baseline behaviors may also be present

- Goal to prevent harm to patient or staff
Emergency agitation strategies

• Proactively reduce risk for disruptive behaviors
  – Recognize early warning
  – Implement behavioral strategies

• Danger for harm of self or others
  – Emergent medication necessary
  – When calm enough reattempt behavioral intervention

Beta Agitation Guidelines

• Discourage use of medication as a restraint; diagnose cause and target medication to disease process
• Nonpharmacologic approaches used first when possible
• Medication to calm, not induce sleep
• Involve patient/parent in medication selection process as possible
• Oral medication preferred over IM when possible

Agitation guidelines

• For psychosis driven agitation antipsychotic should be used
  – Risperidone: most evidence to support use (if oral medication accepted)
  – Small RCT quetiapine more effective than FGAs
  – IM formulations necessary at times

• Benzodiazepines
  – For agitation due to withdrawal or not related to psychiatric illness

Current ED practice

• Retrospective description of ED management of agitation 128 visits (120 pts)
  – 70% received lorazepam, 20% received chlorpromazine

• Patients with ASD (& Aspergers) more likely to receive AP (75% vs 28%)
  – Unable to assess effectiveness
  – Standardized agitation assessment not in place
Current ED practice

- Overall medication for acute agitation/aggression safe and well tolerated
  - Single agent (82%)
  - Within recommended dose range

• Quetiapine similar or greater efficacy compared to first generation antipsychotics
  – Quetiapine 53% efficacy
  – FGA efficacy ranged from 30-50%
    • Haloperidol: 36%
    • Loxapine: 30%
    • Chlorpromazine: 50%
  – FGAs with greater EPS
• Studies lacking on acute agitation management in ASD

• Mild-Mod agitation/Cooperative patient
  – Oral antipsychotic
  – Alpha-2 agonists
    • Wt <45 kg: Clonidine 0.05 mg dose; max 0.2 - 0.3 mg/D in divided doses
    • Wt >45 kg: Clonidine 0.1 mg; max 0.3 - 0.4 mg/D in divided doses

• Benzodiazepines and Anticholinergic agents may disinhibit

  – Avoid as initial management
  – If necessary cautious trial with careful dose progression may be warranted
• Benzodiazepines:
  – commonly used in medical settings
  – familiar for medical team and nursing

• Anticholinergic agents:
  – helpful (in particular with medical comorbidities)

• Monitor for paradoxical reactions
Pharmacologic target symptoms for autism spectrum disorder

- Irritability and aggression
- Hyperactivity and inattention
- Aberrant social behavior
- Repetitive behaviors
- Cognitive disorders
- Insomnia

Psychotropics to address pharmacologic target symptoms

- Irritability and aggression
  - Antipsychotics
- Hyperactivity and inattention
  - CNS stimulants
- Aberrant social behavior
  - Antipsychotics
- Repetitive behaviors
  - SSRIs
- Cognitive disorders
  - NMDA receptor antagonists
- Insomnia
  - Melatonin
FDA APPROVED ANTIPSYCHOTICS
You are consulted for a patient with ASD admitted for video EEG

Patient is on Abilify 5 mg QD at home

Prior trial of Risperdal 3 BID at home ‘didn’t work’ per caregiver; family stopped it and Abilify was tried

Parents asking for IVIG or CBD for agitation

Neurology would like assistance with ‘treatment planning’
• **Risperidone**
  – FDA approved in 2006 to target autism related irritability
  – defined as tantrums, aggression, self-injury
  – ages 5 years and older

• **Aripiprazole**
  – FDA approved in 2009 to target autism related irritability
  – ages 6 - 17 years
Evidence for Risperidone

• 2002: risperidone reduced serious behavioral problems
  – N = 101 children with autism
  – 56.9% vs 14.1% reduction in irritability

• 2005: high recurrence of irritability when risperidone was replaced with placebo
  – after 6 mo of treatment

• 2004: Shea et al. found risperidone helped with irritability in children with autism and other PDDs
Evidence for Risperidone

- Low doses used in children as young as 2 years old
- Improves adaptive functioning
- Can lead to improved behavior
- Commonly used internationally for children (and adults) with autism

Evidence for Risperidone

- Lower relapse rates of aggression
- Increased length of time to relapse
  – after 6 months of treatment
- Persistent efficacy
- Good tolerability


Evidence for Aripiprazole

• Effective for severe irritability
  – 25 children with pervasive developmental disorder, open label study, 14 weeks
  – 98 children, double blind, randomized, placebo controlled, 8 weeks
    • Safe and well tolerated

• 2016 Cochrane review
  – moderate evidence in literature to support benefit
  – notable SE
  – re-evaluate use after stabilization of irritability

Adverse Side Effects

• Risperidone
  – Somnolence
  – Increased appetite, weight gain
  – Increased serum prolactin

• Aripiprazole
  – Significantly more weight gain than placebo but less than risperidone
  – Treatment emergent EPS
  – Vomiting
OFF-LABEL ANTIPSYCHOTICS
• Clozapine
  – *May be useful for severe aggression and self-injury not responsive to other medications*

• Lurasidone
  – *Not significantly superior to placebo in reducing moderate to severe irritability*

• **Olanzapine**
  – Mixed response from variety of studies
  – Additional administration routes may be helpful
  – Substantial weight gain

• **Paliperidone**
  – Significant improvement in irritability

Stigler, K., Mullett, J., Erickson, C., Posey, D., & McDougle, C. Paliperidone for irritability in adolescents and young adults with autistic disorder. *Psychopharmacology* 2012
• Quetiapine
  – Open label trials - poorly tolerated, serious ASE; minimal efficacy
  – 1 study described benefit for sleep and aggression, related to sedation

• Ziprasidone
  – Open label trial, 75% were treatment responder
  – Increased QTc interval (needs EKG monitoring), initial sedation, acute dystonic reactions common ASE

OFF-LABEL MOOD STABILIZERS
Mood Stabilizers

• Divalproex sodium
  – Most extensively studied AED
  – Some early case reports showed improvement in maladaptive behaviors
  – Substantial improvement in retrospectively assigned CGI scores
  – 2 RCTs with small sample sizes had mixed results
  – Well tolerated
  – Requirements for blood work may limit feasibility

Mood Stabilizers

- Lamotrigine
  - No difference from placebo
  - Subset of children with autism and comorbid seizure disorder may have behavioral improvement

- Levetiracetam
  - 2 small samples with conflicting results

- Oxcarbazepine
  - No controlled trial of efficacy for irritability and risk of ASE (hyponatremia, seizures, allergy, worsened irritability)


• No medication addresses core symptoms of ASD

• May improve associated symptoms
  – AP: aggression and aberrant social behaviors
  – SSRI: repetitions/compulsions
  – Stimulants: inattention, hyperactivity

• Dosing may be much higher or lower than commonly used
In the pharmacologic management of aggression in patients with autism:

a) Risperidone has the most evidence supporting its use

b) A typical antipsychotic combined with a benzodiazepine is the preferred initial treatment

c) Benzodiazepines or anticholinergic medications should be used first

d) Atypical antipsychotics can be used interchangeably
References


References

• Bober et al. Risperidone in a very young child with PDD. J. AM. ACAD. CHILD ADOLESC. PSYCHIATRY, 2005, 44(8): 725-726


