



USC University of
Southern California

MANAGEMENT OF AGGRESSION IN AUTISTIC PATIENTS

Julienne Jacobson MD

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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’

- 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

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

- 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

- Manage comorbid psychiatric illness
- Proactively reduce risk for disruptive behaviors
- Acute management of agitation

- 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

- Behaviors communicate symptoms
 - Pain
 - Fear
 - Sensory overload
 - Baseline behaviors may also be present
- Goal to prevent harm to patient or staff

- 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

- 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

- 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

- 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

- 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***

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

- 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

- 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

McCracken et al. Risperidone in children with autism and serious behavioral problems. *NEJM*. 2002

Research Units on Pediatric Psychopharmacology Autism Network. Risperidone treatment of autistic disorder: longer-term benefits and blinded discontinuation after 6 months. *Am J Psychiatry*. 2005

- 2004: Shea et al. found risperidone helped with irritability in children with autism and other PDDs

Shea et al. Risperidone in the treatment of disruptive behavioral symptoms in children with autistic and other pervasive developmental disorders. *Pediatrics*. 2004.

- 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

Luby et al. Risperidone in Preschool Children with Autistic Spectrum Disorders: An investigation of Safety and Efficacy. *Journal of Child and Adolescent Psychopharmacology*, 2006

Masi et al. Open trial of risperidone in 24 young children with pervasive developmental disorders. *J. Am. Acad. Child Adolesc. Psychiatry*, 2001

Bober et al. Risperidone in a very young child with PDD. *J. Am. Acad. Child Adolesc. Psychiatry*, 2005

Williams et al. Risperidone and adaptive behavior in children with autism. *J Am Acad. Child Adolesc. Psychiatry*, 2006

Hsia et al. Psychopharmacological prescriptions for people with autism spectrum disorder (ASD): a multinational study. *Psychopharmacology*, 2014

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

Troost et al. Long term effects of risperidone in children with autism spectrum disorders: a placebo discontinuation study. *J. Am. Acad. Child Adolesc. Psychiatry*, 2005

McCracken J et al. Risperidone Treatment of Autistic Disorder: Longer-Term Benefits and Blinded Discontinuation After 6 Months. *Am J Psychiatry*, 2005

- 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

Hirsch LE, Pringsheim T. Aripiprazole for autism spectrum disorders (ASD). *Cochrane Database Syst Rev.* 2016.

Stigler KA, Diener JT, Kohn AE, Li L, Erickson CA, Posey DJ, McDougle CJ. - Aripiprazole in Pervasive Developmental Disorder Not Otherwise Specified and Asperger's Disorder: A 14-Week, Prospective, Open-label Study. *J Child Adolesc Psychopharmacology* 2009

Owen R, Sikich L, Marcus RN, Corey-Lisle P, Manos G, McQuade RD, Carson WH, Findling RL. Aripiprazole in the Treatment of Irritability in Children and Adolescents with Autistic Disorder. *Pediatrics* 2009.

- **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

Chen, N., Bedair, H., McKay, B., Bowers, M., Mazure, C., & Chen, N. Clozapine in the treatment of aggression in an adolescent with autistic disorder. *The Journal of Clinical Psychiatry*. 2001

Clinical effects of clozapine on autistic disorder. *American Journal of Psychiatry*. 1996

Lambrey, S., Falissard, B., Martin-Barrero, M., Bonnefoy, C., Quilici, G., Rosier, A., ... Lambrey, S. Effectiveness of clozapine for the treatment of aggression in an adolescent with autistic disorder. *Journal of Child and Adolescent Psychopharmacology*. 2010

Loebel, A., Brams, M., Goldman, R., Silva, R., Hernandez, D., Deng, L., ... Findling, R. Lurasidone for the Treatment of Irritability Associated with Autistic Disorder. *Journal of Autism and Developmental Disorders*. 2016

- Olanzapine
 - Mixed response from variety of studies
 - Additional administration routes may be helpful
 - Substantial weight gain
- Paliperidone
 - Significant improvement in irritability

Potenza, M., Holmes, J., Kaner, S., & McDougle, C. Olanzapine Treatment of Children, Adolescents, and Adults with Pervasive Developmental Disorders: An Open-Label Pilot Study. *Journal of Clinical Psychopharmacology* 1999

Malone, R., Cater, J., Sheikh, R., Choudhury, M., & Delaney, M. Olanzapine Versus Haloperidol in Children With Autistic Disorder: An Open Pilot Study. *Journal of the American Academy of Child & Adolescent Psychiatry* 2001

Stigler, K., Erickson, C., Mullett, J., Posey, D., McDougle, C., & Stigler, K. Paliperidone for irritability in autistic disorder. *Journal of Child and Adolescent Psychopharmacology* 2010

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

Martin, A., Koenig, K., Scahill, L., Bregman, J., & Martin, A. Open-label quetiapine in the treatment of children and adolescents with autistic disorder. *Journal of Child and Adolescent Psychopharmacology* 1999

Findling, R., Mcnamara, N., Gracious, B., O'Riordan, M., Reed, M., Demeter, C., & Blumer, J. Quetiapine in Nine Youths with Autistic Disorder. *Journal of Child and Adolescent Psychopharmacology* 2004

Golubchik, P., Sever, J., & Weizman, A. Low-Dose Quetiapine for Adolescents With Autistic Spectrum Disorder and Aggressive Behavior: Open-Label Trial. *Clinical Neuropharmacology* 2011

Malone, R., Delaney, M., Hyman, S., & Cater, J. Ziprasidone in adolescents with autism: an open-label pilot study. *Journal of Child and Adolescent Psychopharmacology* 2007



OFF-LABEL 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

Hollander, E., Dolgoff-Kaspar, R., Cartwright, C., Rawitt, R., & Novotny, S. An open trial of divalproex sodium in autism spectrum disorders. *The Journal of Clinical Psychiatry*. 2001

Hellings, J., Weckbaugh, M., Nickel, E., Cain, S., Zarcone, J., Reese, R., ... Cook, E. Double-Blind, Placebo-Controlled Study of Valproate for Aggression in Youth with Pervasive Developmental Disorders. *Journal of Child and Adolescent Psychopharmacology* 2005

Eric Hollander, William Chaplin, Latha Soorya, Stacey Wasserman, Sherry Novotny, Jade Rusoff, ... Evdokia Anagnostou. Divalproex Sodium vs Placebo for the Treatment of Irritability in Children and Adolescents with Autism Spectrum Disorders. *Neuropsychopharmacology* 2009

- 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)

Belsito, K., Law, P., Kirk, K., Landa, R., & Zimmerman, A. Lamotrigine Therapy for Autistic Disorder: A Randomized, Double-Blind, Placebo-Controlled Trial. *Journal of Autism and Developmental Disorders* 2001

Wasserman, S., Iyengar, R., Chaplin, W., Warner, D., Waldoks, S., Anagnostou, E., ... Wasserman, S. Levetiracetam versus placebo in childhood and adolescent autism: a double-blind placebo-controlled study. *International Clinical Psychopharmacology* 2006

Rugino, A., & Samsok, C. Levetiracetam in Autistic Children: An Open-Label Study. *Journal of Developmental & Behavioral Pediatrics* 2002

- 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

- 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*, Volume 60, Issue 5, 2019, Pages 435-443.
- Wilson, Michael & Pepper, David & Currier, Glenn & Holloman, Garland & Feifel, David. (2012). The Psychopharmacology of Agitation: Consensus Statement of the American Association for Emergency Psychiatry Project BETA Psychopharmacology Workgroup. *The western journal of emergency medicine*. 13. 26-34.
- LeClerc S, Easley D. Pharmacological therapies for autism spectrum disorder: a review. *P T*. 2015 Jun;40(6):389-97. PMID: 26045648; PMCID: PMC4450669.
- Kendrick JG, Goldman RD, Carr RR. Pharmacologic Management of Agitation and Aggression in a Pediatric Emergency Department - A Retrospective Cohort Study. *J Pediatr Pharmacol Ther*. 2018;23(6):455-459. doi:10.5863/1551-6776-23.6.455
- Yip L, Aeng E, Elbe D. Management of Acute Agitation and Aggression in Children and Adolescents with Pro Re Nata Oral Immediate Release Antipsychotics in the Pediatric Emergency Department. *J Child Adolesc Psychopharmacol*. 2020 Nov;30(9):534-541. doi: 10.1089/cap.2019.0171. Epub 2020 Oct 9. PMID: 33035069.
- Hirsch LE, Pringsheim T. Aripiprazole for autism spectrum disorders (ASD). *Cochrane Database Syst Rev*. 2016 Jun 26;2016(6):CD009043. doi: 10.1002/14651858.CD009043.pub3. PMID: 27344135; PMCID: PMC7120220.
- Belsito, K., Law, P., Kirk, K., Landa, R., & Zimmerman, A. (2001). Lamotrigine Therapy for Autistic Disorder: A Randomized, Double-Blind, Placebo-Controlled Trial. *Journal of Autism and Developmental Disorders*, 31(2), 175-181.
- Wasserman, S., Iyengar, R., Chaplin, W., Warner, D., Waldoks, S., Anagnostou, E., ... Wasserman, S. (2006). Levetiracetam versus placebo in childhood and adolescent autism: a double-blind placebo-controlled study. *International Clinical Psychopharmacology*, 21(6), 363-367.
- Rugino, A., & Samscock, C. (2002). Levetiracetam in Autistic Children: An Open-Label Study. *Journal of Developmental & Behavioral Pediatrics*, 23(4), 225-230.
- Hollander, E., Dolgoff-Kaspar, R., Cartwright, C., Rawitt, R., & Novotny, S. (2001). An open trial of divalproex sodium in autism spectrum disorders. *The Journal of Clinical Psychiatry*, 62(7), 530-534.
- Hellings, J., Weckbaugh, M., Nickel, E., Cain, S., Zarcone, J., Reese, R., ... Cook, E. (2005). A Double-Blind, Placebo-Controlled Study of Valproate for Aggression in Youth with Pervasive Developmental Disorders. *Journal of Child and Adolescent Psychopharmacology*, 15(4), 682-692.
- Eric Hollander, William Chaplin, Latha Soorya, Stacey Wasserman, Sherry Novotny, Jade Rusoff, ... Evdokia Anagnostou. (2009). Divalproex Sodium vs Placebo for the Treatment of Irritability in Children and Adolescents with Autism Spectrum Disorders. *Neuropsychopharmacology*, 35(4), 990-998. 41

- Stigler, K., Erickson, C., Mullett, J., Posey, D., McDougale, C., & Stigler, K. (2010). Paliperidone for irritability in autistic disorder. *Journal of Child and Adolescent Psychopharmacology*, 20(1), 75-78.
- Stigler, K., Mullett, J., Erickson, C., Posey, D., & McDougale, C. (2012). Paliperidone for irritability in adolescents and young adults with autistic disorder. *Psychopharmacology*, 223(2), 237-245.
- Martin, A., Koenig, K., Scahill, L., Bregman, J., & Martin, A. (1999). Open-label quetiapine in the treatment of children and adolescents with autistic disorder. *Journal of Child and Adolescent Psychopharmacology*, 9(2), 99-107.
- Findling, R., Mcnamara, N., Gracious, B., O'Riordan, M., Reed, M., Demeter, C., & Blumer, J. (2004). Quetiapine in Nine Youths with Autistic Disorder. *Journal of Child and Adolescent Psychopharmacology*, 14(2), 287-294.
- Golubchik, P., Sever, J., & Weizman, A. (2011). Low-Dose Quetiapine for Adolescents With Autistic Spectrum Disorder and Aggressive Behavior: Open-Label Trial. *Clinical Neuropharmacology*, 34(6), 216-219
- Malone, R., Delaney, M., Hyman, S., & Cater, J. (2007). Ziprasidone in adolescents with autism: an open-label pilot study. *Journal of Child and Adolescent Psychopharmacology*, 17(6), 779-790.
- Chen, N., Bedair, H., McKay, B., Bowers, M., Mazure, C., & Chen, N. (2001). Clozapine in the treatment of aggression in an adolescent with autistic disorder. *The Journal of Clinical Psychiatry*, 62(6), 479-480.
- Clinical effects of clozapine on autistic disorder. (1996). *American Journal of Psychiatry*, 153(5), 738a-738.
- Lambrey, S., Falissard, B., Martin-Barrero, M., Bonnefoy, C., Quilici, G., Rosier, A., ... Lambrey, S. (2010). Effectiveness of clozapine for the treatment of aggression in an adolescent with autistic disorder. *Journal of Child and Adolescent Psychopharmacology*, 20(1), 79-80.
- Loebel, A., Brams, M., Goldman, R., Silva, R., Hernandez, D., Deng, L., ... Findling, R. (2016). Lurasidone for the Treatment of Irritability Associated with Autistic Disorder. *Journal of Autism and Developmental Disorders*, 46(4), 1153-1163.
- Luby et al. Risperidone in Preschool Children with Autistic Spectrum Disorders: An investigation of Safety and Efficacy. *Journal of Child and Adolescent Psychopharmacology*. 2006 (16):575-587
- Masi et al. Open trial of risperidone in 24 young children with pervasive developmental disorders. *J. Am. Acad. Child Adolesc. Psychiatry*, 2001, 40(10):1206-1214.

- Bober et al. Risperidone in a very young child with PDD. *J. AM. ACAD. CHILD ADOLESC. PSYCHIATRY*, 2005, 44(8): 725-726
- Williams et al. Risperidone and adaptive behavior in children with autism. *J Am Acad. Child Adolesc. Psychiatry*, 2006;45(4):431-439
- Hsia et al. Psychopharmacological prescriptions for people with autism spectrum disorder (ASD): a multinational study. *Psychopharmacology* (2014) 231:999-1009
- Troost et al. Long term effects of risperidone in children with autism spectrum disorders: a placebo discontinuation study. *J. Am. Acad. Child Adolesc. Psychiatry*, 2005;44(11):1137-1144.
- McCracken J et al. Risperidone Treatment of Autistic Disorder: Longer-Term Benefits and Blinded Discontinuation After 6 Months. *Am J Psychiatry* 2005; 162:1361-1369
- Stigler KA, Diener JT, Kohn AE, Li L, Erickson CA, Posey DJ, McDougale CJ. - Aripiprazole in Pervasive Developmental Disorder Not Otherwise Specified and Asperger's Disorder: A 14-Week, Prospective, Open-label Study. *J Child Adolesc Psychopharmacol.* 19:265-274, 2009
- Owen R, Sikich L, Marcus RN, Corey-Lisle P, Manos G, McQuade RD, Carson WH, Findling RL. Aripiprazole in the Treatment of Irritability in Children and Adolescents with Autistic Disorder. *Pediatrics* 2009;124:1533-1540
- Shea et al. Risperidone in the treatment of disruptive behavioral symptoms in children with autistic and other pervasive developmental disorders. *Pediatrics.* 2004. 114:634-41
- McCracken et al. Risperidone in children with autism and serious behavioral problems. *NEJM.* 2002. 347:314-21
- Research Units on Pediatric Psychopharmacology Autism Network. Risperidone treatment of autistic disorder: longer-term benefits and blinded discontinuation after 6 months. *Am J Psychiatry.* 2005;162(7):1361-1369. doi:10.1176/appi.ajp.162.7.1361
- Potenza, M., Holmes, J., Kanes, S., & McDougale, C. (1999). Olanzapine Treatment of Children, Adolescents, and Adults with Pervasive Developmental Disorders: An Open-Label Pilot Study. *Journal of Clinical Psychopharmacology*, 19(1), 37-44.
- Malone, R., Cater, J., Sheikh, R., Choudhury, M., & Delaney, M. (2001). Olanzapine Versus Haloperidol in Children With Autistic Disorder: An Open Pilot Study. *Journal of the American Academy of Child & Adolescent Psychiatry*, 40(8), 887-894.