Emerging Drugs for Irritability in Autism Spectrum Disorder

AHMAD SHAMABADI AND SHAHIN AKHONDZADEH

Roozbeh Psychiatric Hospital, Tehran University Of Medical Sciences

June 7, 2025

Autism Spectrum Disorder (ASD)

- **What is ASD?**

Early-onset neurodevelopmental disorder affecting social communication and behavior.

- **Prevalence of ASD**

Approximately 1% of children worldwide are affected.

- **Impact on Daily Life**

Significant impact on daily functioning, substantial DALYs.

- **Key Characteristics**

Challenges in social interaction, repetitive behaviors, and atypical behaviors like irritability.

- **Economic Burden**

High lifetime costs associated with education, healthcare, and support services.

Irritability: A Key Target for Intervention

Irritability in ASD
Irritability is frequently observed in individuals with ASD.

Manifestations of Irritability
Includes aggression, self-injury, tantrums, and difficulties in emotional regulation.

Impact of Irritability
Significantly impacts well-being, family life, and social engagement.

Current Treatments
Risperidone and aripiprazole are approved, but long-term use has side effects.

The Need for Novel Therapies
More effective and tolerable treatments are urgently needed.

Risperidone and aripiprazole

- **No drug is effective in treating the core behavioral manifestations of ASD**

But drugs may be effective in treating associated behavioral problems and comorbid disorders.

- **Beneficial effects of risperidone and aripiprazole on challenging and repetitive behaviors**
- **Approved by the US Food and Drug Administration for irritability associated with ASD**
- **Significant benefits of risperidone for ages 5-17 years and aripiprazole for ages 6-17 years**
- **Short-term and long-term administration is beneficial**

But some side effects (e.g., weight gain, anxiety, and sexual dysfunction) may limit use in the long-term.

- **70% of children with ASD receive medications**

But only limited evidence exists that the beneficial effects outweigh the adverse effects.

Neuropathophysiology of Irritability

- **Glutamatergic System**

Hyperactivity can lead to excitotoxicity and neuronal dysfunction.

- **GABAergic System**

Imbalance between inhibitory and excitatory pathways.

Reduced GABA receptor density in key brain regions.

- **Inflammation**

Significant impact on daily functioning, substantial DALYs.

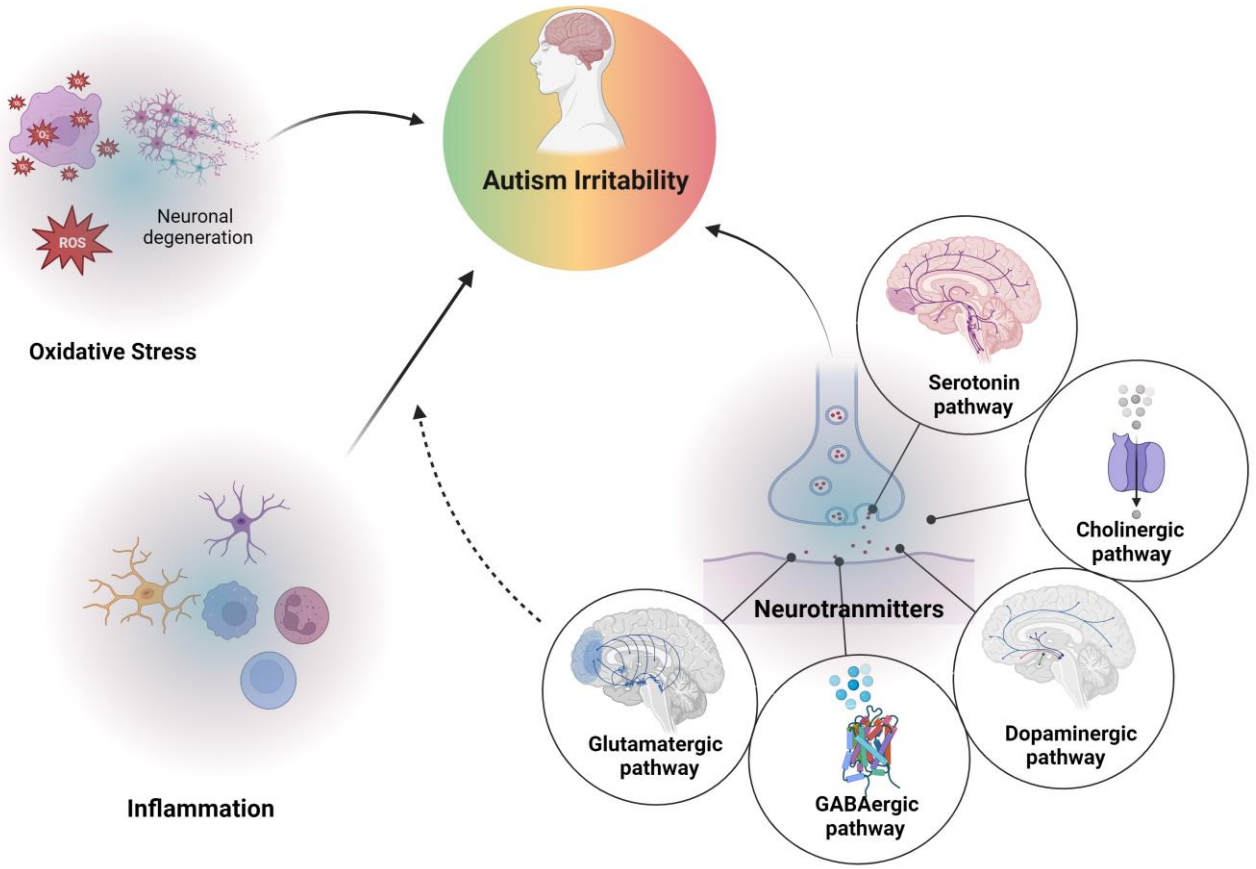
- **Oxidative Stress**

Accumulation of reactive oxygen species (ROS).

Reduced antioxidant capacity.

- **Other Neurotransmitters**

Serotonin, dopamine, and acetylcholine pathway dysregulation.



Emerging Pharmacological Interventions

- **Diverse Agents Under Investigation**

A wide range of pharmacological agents have been evaluated in recent clinical trials, focusing primarily on medications with anti-inflammatory, antioxidant, or neurotransmitter-modulating effects. Key drug classes under study include glutamatergic antagonists (e.g., memantine, amantadine), anti-inflammatory drugs (e.g., celecoxib, simvastatin), antioxidants (e.g., N-acetylcysteine, sulforaphane), cholinergic agents (e.g., galantamine), and immunomodulators.

Memantine: A Promising Glutamate Modulator

Memantine as adjunctive treatment to risperidone in children with autistic disorder: a randomized, double-blind, placebo-controlled trial

Ali Ghaleiha [1], Mahtab Asadabadi, Mohammad-Reza Mohammadi, Maryam Shahei, Mina Tabrizi, Reza Hajiaghaee, Elmira Hassanzadeh, Shahin Akhondzadeh

- **Clinical Evidence**
- Ghaleiha *et al.* (2013): Improved irritability in children with ASD as an adjunct to risperidone.
- Nikvarz *et al.* (2017): Comparable effects to risperidone on irritability.

- **Mechanism of Action**

Uncompetitive NMDA receptor antagonist.

- **Safety and Tolerability**

Generally safe and well-tolerated in studies.

Sulforaphane: Anti-inflammatory and Antioxidant

Mechanism of Action

Enhances cytoprotective enzyme activity, detoxification, and free radical elimination.

Clinical Evidence

- Singh *et al.* (2014): Sulforaphane significantly better than placebo in reducing irritability in ASD patients aged 13-30.
- Momtazmanesh *et al.* (2020): Significant improvements in irritability with adjunctive sulforaphane in patients aged 4-12 years.
- Zimmerman *et al.* (2021): No improvements in irritability with broccoli seed extract.

Safety and Tolerability

No serious adverse events reported, but weight gain, insomnia, irritability, and intolerance of taste and smell were noted.

Sulforaphane as an adjunctive treatment for irritability in children with autism spectrum disorder: A randomized, double-blind, placebo-controlled clinical trial

Sara Momtazmanesh [1], Zeinab Amirimoghaddam-Yazdi [1], Hossein Sanjari Moghaddam [1], Mohammad Reza Mohammadi [1], Shahin Akhondzadeh [1]

N-acetylcysteine: Glutathione Precursor and Antioxidant

- **Mechanism of Action**

Restores GSH levels, scavenges oxidants, and has anti-glutamatergic properties.

- **Clinical Evidence**
- Hardan *et al.* (2012): Improvement in irritability in children with ASD.
- Ghanizadeh *et al.* (2013): Lower ABC-I subscale score in the NAC group.
- Nikoo *et al.* (2015): Greater reduction in irritability scores with risperidone plus NAC.
- Dean *et al.* (2017): No superiority of NAC over placebo in improving the Developmental Behaviour Checklist's irritable item.

- **Safety and Tolerability**

Safe and acceptable side effect profile, with mild events such as gastrointestinal symptoms reported.

N-acetylcysteine as an adjunctive therapy to risperidone for treatment of irritability in autism: a randomized, double-blind, placebo-controlled clinical trial of efficacy and safety

Mohammadali Nikoo [1], Hanieh Radnia, Mehdi Farokhnia, Mohammad-Reza Mohammadi, Shahin Akhondzadeh

Galantamine: Acetylcholinesterase Inhibitor

- **Mechanism of Action**

Cholinergic stimulating effects through acetylcholinesterase inhibition and nAChRs ligand potentiation.

- **Clinical Evidence**

Ghaleiha *et al.* (2014): Galantamine adjunct to risperidone confirmed effect on irritability.

- **Safety and Tolerability**

Generally regarded as safe and well-tolerated, with side effects including macular rash, headache, and increased appetite.

Galantamine efficacy and tolerability as an augmentative therapy in autistic children: A randomized, double-blind, placebo-controlled trial

Ali Ghaleiha [1], Mohammad Ghyasvand [2], Mohammad-Reza Mohammadi [2], Mehdi Farokhnia [2], Noorollah Yadegari [2], Mina Tabrizi [3], Reza Hajiaghaee [4], Habibeh Yekehtaz [2], Shahin Akhondzadeh [5]

Celecoxib: Selective COX-2 Inhibitor

- **Mechanism of Action**

Diminishes cytokine-induced COX-2 production and inhibits the NF-kB pathway.

- **Clinical Evidence**

Asadabadi *et al.* (2013): Celecoxib better than placebo in improving irritability.

- **Safety and Tolerability**

Safe and tolerable, with minor adverse events such as abdominal pain, decreased appetite, and nausea noted.

Celecoxib as adjunctive treatment to risperidone in children with autistic disorder: a randomized, double-blind, placebo-controlled trial

Mahtab Asadabadi [1], Mohammad-Reza Mohammadi, Ahmad Ghanizadeh, Amirhossein Modabbernia, Mandana Ashrafi, Elmira Hassanzadeh, Saeedeh Forghani, Shahin Akhondzadeh

Palmitoylethanolamide: Endocannabinoid Family

- **Mechanism of Action**

Binds to cannabinoid receptors, protects neural cells from glutamate toxicity, and has anti-inflammatory properties.

- **Clinical Evidence**

Khalaj *et al.* (2018): Significant difference between groups in terms of irritability over time with adjunctive PEA.

- **Safety and Tolerability**

Reported to be safe and tolerable in ASD patients.

Palmitoylethanolamide as adjunctive therapy for autism: Efficacy and safety results from a randomized controlled trial

Mona Khalaj [1], Amene Saghazadeh [2], Elham Shirazi [1], Mohammad-Reza Shalbafan [1], Kaveh Alavi [1], Mitera Hakim Shooshtari [1], Fatemeh Yousefi Laksari [1], Maryamalsadat Hosseini [1], Mohammad-Reza Mohammadi [2], Shahin Akhondzadeh [3]

Pentoxifylline: Methylxanthine Derivative

- **Mechanism of Action**

Inhibits TNF synthesis and production of cytokines, facilitates the release of 5-HT, and has inhibitory effects on 5-HT uptake.

- **Clinical Evidence**

Akhondzadeh *et al.* (2010): Greater reduction in ABC-I subscale scores in the risperidone + pentoxifylline group.

- **Safety and Tolerability**

Differences in adverse events between the groups were not significant.

Double-blind placebo-controlled trial of pentoxifylline added to risperidone: effects on aberrant behavior in children with autism

Shahin Akhondzadeh [1], Jalil Fallah, Mohammad-Reza Mohammadi, Reza Imani, Mohammad Mohammadi, Bahman Salehi, Ahmad Ghanizadeh, Maedeh Raznahan, Soodeh Mohebbi-Rasa, Shams-Ali Rezazadeh, Saeedeh Forghani

Simvastatin: Statin

- **Mechanism of Action**

Inhibitory effects on cholesterol synthesis, lowers ROS production, lipid peroxidation, and proinflammatory cytokines.

- **Clinical Evidence**

Moazen-Zadeh *et al.* (2018): Significant differences in terms of irritability between the simvastatin group and the placebo group.

- **Safety and Tolerability**

No serious adverse events, but myalgia and increased appetite were reported.

Simvastatin as an Adjunctive Therapy to Risperidone in Treatment of Autism: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial

Ehsan Moazen-Zadeh [1], Fatemeh Shirzad [1], Mohammad-Ali Karkhaneh-Yousefi [1], Rasoul Khezri [1], Mohammad-Reza Mohammadi [1], Shahin Akhondzadeh [1]

Amantadine: NMDA Receptor Antagonist

- **Mechanism of Action**

Anti-inflammatory and neuroprotective properties.

inhibits microglial activation.

- **Clinical Evidence**
- King *et al.* (2001): Administration does not significantly alter irritability in patients, compared with placebo.
- Mohammadi *et al.* (2013): Significant improvement of irritability with amantadine adjunct to risperidone.

- **Safety and Tolerability**

No serious adverse events, but myalgia and increased appetite were reported.

Double-blind, placebo-controlled trial of risperidone plus amantadine in children with autism: a 10-week randomized study

Mohammad-Reza Mohammadi [1], Nourrollah Yadegari, Elmira Hassanzadeh, Mehdi Farokhnia, Habibeh Yekehtaz, Omid Mirshafiee, Shahin Akhondzadeh

Minocycline: Antibiotic with Neuroprotective Properties

- **Mechanism of Action**

Microglia-deactivating, anti-apoptotic, anti-inflammatory, and antioxidant properties.

- **Clinical Evidence**

Ghaleiha *et al.* (2016): Administration of minocycline adjunct to risperidone better than adjunctive placebo regarding the improvement of irritability.

- **Safety and Tolerability**

Safe and well-tolerated, but some adverse events, including diarrhea, headache, and nausea, were reported.

Minocycline as Adjunctive Treatment to Risperidone in Children with Autistic Disorder: A Randomized, Double-Blind Placebo-Controlled Trial

Ali Ghaleiha [1], Rosa Alikhani [2], Mohammad-Reza Kazemi [3], Mohammad-Reza Mohammadi [2], Payam Mohammadinejad [2], Atefeh Zeinoddini [2], Mehdi Hamedi [2], Mona Shahriari [2], Zahra Keshavarzi [1], Shahin Akhondzadeh [1]

Other Emerging Medications

- **Pregnenolone**, **prednisolone**, **riluzole**, **propentofylline**, **pioglitazone**, and **topiramate** (all as adjuncts to risperidone) have shown some evidence of benefit and safety.
- **Clonidine** and **methylphenidate** (used for ADHD) have also been reported to be significantly better than placebo.

Limitations of the clinical evidence

1. • **Small Sample Sizes**
   • Many studies are limited by small participant groups, potentially affecting the generalizability of findings.
2. • **Add-on Therapy Focus**
   • The efficacy of interventions is often tested as an adjunct, not as a primary treatment.
3. • **Short Follow-up Periods**
   • Studies often lack long-term data, hindering assessment of sustained treatment effects.
4. • **Parent-Reported Measures**
   • Reliance on subjective parent reports can introduce bias. Example: ABC-I.
5. • **Statistical vs. Clinical Significance**
   • Emphasis on statistical significance may overshadow practical improvements for patients.

Moving Forward: Hope for Improved Outcomes

- **New Medication Avenues**

Emerging medications show promise in treating irritability associated with ASD.

- **Deeper Neuropathophysiology Insight**

Understanding the neuropathophysiology of ASD is key for targeted therapies.

- **Repositioning Existing Drugs**

Repurposing and combining existing drugs can speed up therapeutic advancements.

- **Continued Research Essential**

Ongoing research is vital to ensure the effectiveness and safety of new treatments.

Charting the Course for Future Research

- **Controlled Trials**

  Large-scale randomized controlled trials are needed to validate findings and establish robust evidence.

- **Monotherapy Efficacy**

  Evaluating monotherapy approaches can simplify treatment regimens and reduce potential side effects.

- **Objective Outcome Measures**

  Employing objective measures alongside parent reports enhances the reliability and validity of outcomes.

- **Meaningful Outcomes**

  Focusing on outcomes and effect sizes ensures clinical relevance and practical significance.

- **Personalized Medicine**

  Tailoring treatments to individual patient profiles may optimize therapeutic benefits and minimize adverse effects.

- **Dual-Action Drugs**

  Prioritizing drugs with dual effects may offer synergistic benefits by targeting multiple pathological mechanisms.

Reference

Expert Opinion on Emerging Drugs ›
Volume 29, 2024 - Issue 1

Mini-review

Emerging drugs for the treatment of irritability associated with autism spectrum disorder

Ahmad Shamabadi, Hanie Karimi, Razman Arabzadeh Bahri, Mohsen Motavaselian & **Shahin Akhondzadeh**

Pages 45-56 | Received 01 Nov 2023, Accepted 30 Jan 2024, Published online: 04 Feb 2024

Cite this article https://doi.org/10.1080/14728214.2024.2313650