Risperidone for ‘Irritability’

- Pivotal DBPC-PG trials\(^1,2\)
  - 101 & 79 children, 5-17y & 5-12y, respectively
  - 8-wk treatment with drug or placebo
  - flexible doses, M = 1.8 & 1.5 mg/d, respectively
- Results
  - Irritability ↓, Hyperactivity ↓, Stereotypy ↓ (ABC)
  - responders (drug vs placebo, CGI-I): 69% vs 12% & 54% vs 18%, respectively
  - AEs more frequent after drug than placebo: appetite increase/weight gain, somnolence, fatigue, tremor

Aripiprazole for ‘Irritability’

- Pivotal DBPC-PG trials: flexible\(^3\) & fixed dose\(^4\)
  - 98 & 218 children, 6-17y
  - 8-wk treatment with drug or placebo
  - flexible doses: 2 mg/d (5%), 5 mg/d (33%) 10 mg/d (41%) 15 mg/d (21%)
  - fixed doses: 5, 10, 15 mg/d
- Results
  - Irritability ↓, Hyperactivity ↓, Stereotypy ↓ (ABC)
  - responders: flexible - 67% (drug) vs 16% (placebo) fixed - ~ 50% (drug, every dose) vs 35% (placebo)
  - AEs: profile similar to risperidone’s with less weight gain and somnolence but more tremor and other EPS
Lingering Questions About Antipsychotic Drugs and Autism

- Pharmacological Rationale?
- Long-term side effects?
  - tardive dyskinesia, dystonia, akathisia
  - hyperprolactinemia (risperidone)
- Effects on learning?
- Same effects in adults as children?
- Safer, more tolerable alternatives?

Tip: Metformin Attenuates Weight Gain Attributable to Antipsychotic Use

- Meta-analysis of 6 DBPC trials with children, adolescents and adults (n = 336) who had gained weight during treatment with antipsychotics
- Metformin vs placebo (M difference after 3-4 mo)
  - weight: -3.16 kg, p = .0002
  - BMI: -1.21 kg/m^2, p = .0001
  - waist circumference: -1.99 cm, p = .005
  - insulin resistance (HOMA-IR): -1.71, p = .004

Psychostimulants for Hyperactivity

- Amphetamines
  - seldom beneficial, poorly tolerated in early studies
  - not subsequently studied for the last 37 years
- Methylphenidate (MPH)
  - 4-wk DBPC-CO trial; 72 children, ages 5-14y
  - mean doses: 0.0, .125, .25, .50 mg/kg/dose, tid
  - MPH superior to placebo; small-medium effect sizes, depending on dose and rater
  - responders: 49% to MPH - any dose, 20% to placebo
  - drop-outs from intolerable drug effects: 18%

Nonstimulant Drugs for Hyperactivity

- Atomoxetine
  - small (n = 16, 5-15y) DBPC-CO, flexible dosing trial
  - final mean dose after 6 wk = 44.2 mg/d, divided bid.
  - drug superior to placebo, medium effect size
  - serious AE: violence leading to hospitalization
- Guanfacine (immediate release)
  - prospective open trial involving 25 (5-14y) non-responders to methylphenidate
  - final doses after 8 wk = 1-3 mg/d, divided bid or tid
  - 48% responders (CGI-I), large effect size
  - drop-outs from intolerable drug effects: 12%
Tip: Cyproheptadine for Managing Hyperactivity in Very Young Children

- Cyproheptadine is approved for treating hypersensitivity reactions & migraine prophylaxis in children ≥ 2y.
- Drug has multiple mechanisms of action, most important being histamine H₁ & serotonin 5-HT₂A/2C receptor antagonism (or inverse agonism).
- Cyproheptadine, 0.2 mg/kg/d + haloperidol, 0.05 mg/kg/d was superior (p < .003) to placebo + haloperidol for reducing aberrant behavior (ABC) in an 8-wk DBPC-PG trial involving 40 children, aged 3-11y.¹⁰

Valproate (divalproex) for Irritability

- ¹ˢᵗ DBPC-PG trial: 30 non-epileptics (6-20y) treated with valproate or placebo for 8 wk¹¹
  - final mean serum concentration: 77.7 mcg/dl
  - no significant difference between groups
  - weight gain: valproate > placebo (1.98 vs 1.10 kg)
- ²ⁿᵈ DBPC-PG trial: 27 non-epileptics (5-17y) treated with valproate or placebo for 12 wk¹²
  - final mean serum concentration: 80.2 mcg/dl
  - valproate superior to placebo, 62.5% vs 9.1% response rates (CGI-I), moderate effect size
  - weight gain: valproate ≅ placebo (1.37 vs 1.34 kg)

Other Mood Stabilizers

- Lamotrigine¹³
  - DBPC-PG; n = 28, 3-11y; dose titrated (8-wk) to 5.0 mg/kg/d (4 wk); no significant clinical benefits.
- Levetiracetam¹⁴
  - DBPC-PG; n = 20, 5-17y; dose titrated (4 wk) to 20-30 mg/kg/d (6 wk); no significant clinical benefits.
- Topiramate (adjunctive to risperidone 2-3 mg/d)¹⁵
  - DBPC-PG; n = 40, 4-12y; topiramate, titrated to 100 or 200 mg/d, significantly improved risperidone effects on irritability, hyperactivity and stereotypy (ABC)

SSRIs for Repetitive Behavior: Adults

- Fluvoxamine¹⁶
  - DBPC-PG; n = 30, 18-53y; ~ 3-wk dose titration to M = 276.7 mg/d for additional 9 wk
  - global responders: 53% drug vs 0 placebo (CGI-I)
  - M↓ repetitive behavior: 36% drug vs 0 placebo (Y-BOCS), large effect size
- Fluoxetine¹⁷
  - DBPC-PG; n = 34, 18-60y; ~ 3 wk dose titration to M = 64.8 mg/d for additional 9 wk
  - global responders: 35% drug vs 0 placebo (CGI-I)
  - M↓ repetitive behavior: 16% drug vs 6% placebo (Y-BOCS, actual data), medium effect size
SSRIs for Repetitive Behavior: Children

• Fluvoxamine\textsuperscript{18}
  - DBPC-PG; \(n = 34\), 5-18y; started at 25 mg q2d, increased by 25 mg every 3-7d to mean 106.9 mg/d
  - 14/18 (78\%) of drug group dropped out due to AEs
  - DBPC-CO; \(n = 39\), 5-16y; 8-wk treatments separated by 4-wk washout; slow (4-wk) dose titration to mean final dose 0.36 mg/kg/d (9.9 mg/d)
  - Improvement in CY-BOCS significantly greater with fluoxetine than placebo; medium effect size
  - No difference in AEs but 16\% required dose reduction while on fluoxetine due to emerging agitation

• Fluoxetine\textsuperscript{19}
  - DBPC-CO; \(n = 39\), 5-16y; 8-wk treatments separated by 4-wk washout; slow (4-wk) dose titration to mean final dose 0.36 mg/kg/d (9.9 mg/d)
  - Improvement in CY-BOCS significantly greater with fluoxetine than placebo; medium effect size
  - No difference in AEs but 16\% required dose reduction while on fluoxetine due to emerging agitation

• Citalopram\textsuperscript{20}
  - DBPC-PG, 12 wk; \(n = 149\), 5-17y
  - dose/d: starting, 2.5 mg; \(<\ 40\) kg, biweekly titration by +2.5 mg (6 wk), thereafter biweekly titration by +5mg; \(\geq\ 40\) mg, weekly titration by +2.5 mg (5 wk) thereafter biweekly titration by +5 mg – maximum 20 mg/d
  - No significant drug-placebo difference in response rates (CGI-I) or mean CY-BOCS ratings
  - Significantly more AEs after drug: increased energy, decreased concentration, hyperactivity, stereotypy, diarrhea, insomnia, nightmares, prolonged seizure (1)

Buspirone for Anxiety

• Few studies of pharmacotherapy for anxiety
• Prospective 6-8 wk open trial with buspirone\textsuperscript{21}
  - \(n = 22\), 6-17y; starting dose = 15 mg/d; final dose = 15-45 mg/d, divided bid or tid.
  - “much improved” 41\% and “moderately improved” 32\% (CGI-I: anxiety)
  - no serious side effects (none at all, 73\%)
  - improvement sustained in 2-12 mo follow-up
  - one case of reversible dyskinesia after 10 mo

Melatonin for Sleep Onset Insomnia

• Evidence for pineal hypofunction in children with autism that resolves with puberty\textsuperscript{22} Deficit in melatonin secretion correlates with symptom severity: \(r = .45\)
• Three PCDB-CO studies\textsuperscript{23-25} including 79 children (2-18y) treated with melatonin 3-15 mg for up to 3 mo have shown drug significantly…
  - Shortens M latency to sleep onset by 28-47 min
  - Lengthens M total sleep duration by 21-52 min
  - But does not significantly affect awakenings; i.e., does not manage sleep maintenance insomnia.
Naltrexone for SIB?

- Reviews of drug’s effects on SIB in mental retardation in general and autism in particular
  - Positive results from many case studies and open trials, probably reflecting publication bias
  - Conflicting results from controlled trials, probably reflecting methodological differences & deficiencies
  - Conclusion: drug probably effective in a minority
- Best evidence: 5-y retrospective survey of all institutionalized adult DD patients in Texas
  - 56 cases, 19 (34%) with autism; M dose = 97 mg/d
  - Responders: 57% (clinical staff) & 25% (blind review)
  - Course of improvement: continuous for 30 mo

Oxidative Stress and Neuroinflammation in Autism Spectrum Disorders
Emerging Concepts and Pharmacotherapy

Pathophysiology

Oxidative Stress ↔ Neuroinflammation

**Oxidative Stress**
- Causes
  - Toxicant exposure?
  - Mitochondrial defect?
  - Deficient defense?
- Effects
  - Reactive O₂ species ↑
  - Lipid peroxidation
  - Purkinje cell apoptosis?
  - Axonal degeneration?

**Neuroinflammation**
- Cause
  - Dysregulated innate immune response?
- Effects
  - Glial activation & proliferation (gliosis)
  - Inflammatory cytokines ↑ & Matrix metalloproteinases ↑
  - Edema/hypoperfusion?

Antioxidants

- L-Carnosine
  - Design: 8-week, DBPC-PG; n = 31, 3-12y
  - Dose: 400 mg bid
  - Results: Global behavior ↑, receptive language ↑ on carnosine but not placebo. No serious AEs.
- N-Acetylcysteine (NAC)
  - Design: 12-week, DBPC-PG; n = 28, 3-12y
  - Dose: 900 q.d → bid → tid, each for 4 weeks
  - Results: NAC vs placebo - irritability (ABC) ↓, repetitive behavior ↓, sociability ↑. No serious AEs.
Anti-inflammatory Microglia Stabilizers

- Pioglitazone (PPAR_γ inhibitor - antidiabetic)\textsuperscript{32}
  - design: 4-mo prospective open trial; \( n = 25, 3-17y \)
  - dose: 30 mg/d (3-5y) or 60 mg/d (6-17y)
  - results: irritability ↓, lethargy ↓, stereotypy ↓, hyperactivity ↓ (ABC), Δ inversely age-related (\( r = -0.43-.52 \))
- Pentoxifylline (PDE inhibitor - hemorrheologic)\textsuperscript{33}
  - design: 10-wk, DBPC-PG, adjunctive to risperidone (2-3 mg/d); \( n = 40, 4-12y \)
  - doses: 200 → 400 & 300 → 600 mg/d (≤ 40 & > 40kg)
  - results: add-on effect - irritability ↓, lethargy ↓, stereotypy ↓, hyperactivity ↓, inappropriate speech ↓ (ABC)

Also Minocycline – see Appendix C

Appendices

- A. Abbreviations
- B. Down Syndrome – New Developments
- C. Fragile X Syndrome – New Developments
- D. References

Conclusions

- Presently approved antipsychotics: effective for controlling irritability but can cause serious side effects.
- Psychostimulants: limited efficacy, can exacerbate hyperactivity, (guanfacine better?).
- Mood stabilizers: not consistently beneficial.
- SSRIs: high probability of AEs before puberty, effective after puberty for controlling repetitive behavior.
- Buspirone: less than ideal but may reduce anxiety in some patients with ASDs.
- Melatonin: safe hypnotic with limited efficacy.
- Antioxidants & anti-inflammatory drugs: await further developments but do not be surprised by a breakthrough

Appendix A: Abbreviations Not Defined in Text or Commonly Used

- Aβ: amyloid beta (peptide)
- ABC: Aberrant Behavior Checklist
- AE: adverse event
- BMI: Body Mass Index
- CGI-I: Clinical Global Impression - Improvement
- CY-BOCS: Children’s Yale-Brown Obsession-Compulsion Scale
- DBPC-CO: double-blind, placebo-controlled-crossover
- DBPC-PG: double-blind, placebo-controlled-parallel group
- DD: developmentally disabled
Appendix A (cont.)

- EPS: extrapyramidal (motor) symptoms
- fmr1 KO: fragile x mental retardation-1 gene - Knockout
- HOMA-IR: Homeostatic-insulin resistance (model)
- M: mean
- mGluR: metabotropic glutamate receptor
- PDE: phosphodiesterase
- PPAR\(\gamma\): paroxisome proliferator activated receptor gamma
- SIB: self-injurious behavior
- Y-BOCS: (adult) Yale-Brown Obsession-Compulsion Scale

Appendix B: Down Syndrome (DS)

- DS: Cholinergic Hypothesis\(^{34}\)
  - triplication of gene for amyloid precursor protein
  - excessive production of A\(\beta_{1-42}\) peptide from birth
  - binding of soluble peptide at \(\alpha_7\) nicotinic acetylcholine receptor during childhood & adolescence
  - eventual formation of insoluble A\(\beta\) plaques with neurofibrillary tangles between neurons in 4th decade
  - early onset of Alzheimer's Disease in 5th-6th decade
  - initial interference with cholinergic transmission may be countered with acetylcholinesterase inhibitors; e.g. donepezil

Appendix B (cont.)

- Several open trials showed a positive effect of donepezil on cognitive functions in children, adolescents and young adults with DS
- Sharply contrasting results from more recent, methodologically divergent DBPC-PG trials\(^{35-37}\)
  - children, \(n = 129\), 10-17y, 10 wk with 2.5-10 mg/d or placebo: no drug effect
  - young adults: \(n = 123\), 18-35y, 12 wk with 5-10 mg/d or placebo: equivocally positive drug effect
  - severely impaired older adults: \(n = 21\), 32-58y, 24 wk with 3mg/d or placebo: strongly positive drug effect

Appendix C: Fragile X Syndrome (FXS)

- ‘mGluR Theory’ of pathophysiology in FXS\(^{38}\)
- Mouse model (fmr1-KO) of FXS confirms theory
- Drug screening based on theory and model
- Minocycline identified as one agent (among others) that reverses FXS pathophysiology\(^{39}\)
  - drug: tetracycline antimicrobial that strongly inhibits microglial activation by an unknown mechanism.
  - immediate effect: reduction in microglial release of inflammatory cytokines and expression of matrix metalloproteinase-9
  - ultimate effect: normalization of abnormal synapses
Appendix C (cont.)

• Retrospective parent reports of beneficial minocycline effects in 50 children with FXS\textsuperscript{40}
• Prospective 8-wk open study of 20 adolescents & adults with FXS (13-32y), randomly assigned doses of 100 & 200 mg/d, divided b.i.d.\textsuperscript{41}
  • responders: 18/19 (CGI-I)
  • Improvement (ABC): irritability ↓, stereotypy ↓, hyperactivity ↓, inappropriate speech ↓ (all, p < .002)
• DBPC-CO trial (3 mo/condition) involving 50 children with FXS, 3 ½ -16y, nearing completion at MIND Institute (UC Davis)\textsuperscript{42}

Appendix D (cont.)


Appendix D: References


Appendix D (cont.)

### Appendix D (cont.)


### Appendix D (cont.)


Appendix D (cont.)

42. www.ClinicalTrials.gov: Identifier NCT0153156