Management of side effects of antipsychotics

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My spouse/partner and I have the following relevant financial relationship with a commercial interest to disclose:

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- Janssen – Consultant (Advisory Board)
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- UpToDate – Royalties, honoraria (content developer and editor)
Outline

• Antipsychotic side effect summary
• Critical side effect management
  – NMS
  – Cardiac side effects
  – Clozapine black box warnings
• Routine side effect management
  – Metabolic side effects
  – Motor side effects
  – Prolactin elevation
• The man-in-the-arena algorithm
Receptor profile and side effects

• **Alpha1**
  - Hypotension: slow titration

• **Dopamine2**
  - Dystonia: prophylactic anticholinergic
  - Akathisia, parkinsonism, tardive dyskinesia
  - Hyperprolactinemia

• **Histamine1**
  - Sedation
  - Weight gain

• **Muscarinic1-5**
  - Anticholinergic side effects including cognition
# Summary of antipsychotic side effects

<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>Weight gain</th>
<th>Somnolence</th>
<th>Akathisia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Brexpiprazole</td>
<td>+++</td>
<td>++</td>
<td>0</td>
</tr>
<tr>
<td>Cariprazine</td>
<td>++</td>
<td>0 (NNH 100)</td>
<td>+++</td>
</tr>
<tr>
<td>Risperidone</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>+++ (NNH 6)</td>
<td>+++ (NNH 7)</td>
<td>+++</td>
</tr>
<tr>
<td>Quetiapine ER</td>
<td>+++</td>
<td>+++ (NNH 7)</td>
<td>0</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>+</td>
<td>++</td>
<td>0</td>
</tr>
<tr>
<td>Asenapine</td>
<td>++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Iloperidone</td>
<td>+++</td>
<td>+++</td>
<td>0</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>+ (NNH 67)</td>
<td>+++</td>
<td>+++ (NNH 10)</td>
</tr>
</tbody>
</table>

**Anticholinergic:** olanzapine, quetiapine (could be adrenergic)

**Orthostatic hypotension:** risperidone/paliparidone, iloperidone

NNH = Number Needed to Harm

CRITICAL SIDE EFFECT MANAGEMENT
Neuroleptic malignant syndrome (NMS)

- Onset within 2 weeks of starting antipsychotic
- Tetrad
  - Fever
  - R rigidity: lead pipe rigidity, tremor, other
  - Mental status changes*: agitation, confusion
  - Autonomic instability: tachycardia; diaphoresis
- Elevated serum CK: >1000 IU/L
  - Leukocytosis, low iron (sensitive, not specific), myoglobinuria
- Differential diagnosis
  - Related disorders with fever/rigidity/dysautonomia
    - Serotonin syndrome
    - Malignant hyperthermia
    - Malignant catatonia
  - Other
    - CNS infection, systemic infection, seizures, drug intoxication (PCP), catatonia

Always consider forme fruste!

http://www.nmsis.org/
(Neuroleptic Malignant Syndrome Information Service)
Cardiac side effects – QTc prolongation

• QTc prolongation
  – Risk factor model: low potassium; long QTc syndrome
• Mechanism
  – hERG (human Ether-à-go-go-Related Gene)
    • Regulates potassium ion channel repolarization current
  – QTc prolongation increases risk for torsades de pointes
• Increased risk
  – Thioridazine: black box warning; 2D6; brand withdrawn
  – Pimozide: calcium channel blocker; 3A4 and 2D6; citalopram/escitalopram contraindicated
  – IV haloperidol
  – Ziprasidone
  – Iloperidone: similar to ziprasidone

Ziprasidone and QTc

• Modest effect
  – ZODIAC\textsuperscript{1} and pre-and post-approval studies\textsuperscript{2}
    • Average increase of QTc of 6 msec for each 100 ng/mL increase in ziprasidone blood levels
    • No signal for an increased risk of ziprasidone-associated cardiac death

• Clinical dilemma
  – Antipsychotics as component cause for development of torsades de pointes

\textsuperscript{2}Camm AJ et al. CNS Drugs. 2012;26:351.
Clozapine: 5 black box warnings

1. Agranulocytosis
2. Seizures
3. Myocarditis
4. Orthostatic hypotension (with syncope or cardiorespiratory arrest)
5. Increased mortality in elderly patients with dementia-related psychosis (class warning for all antipsychotics)
Agranulocytosis

- Highest risk: first 6 months
  - Monitoring prevents deaths from agranulocytosis
- Mandated registry-based prescribing
  - “No blood, no drug”
  - Weekly ANC for 6 months, then every other for 6 months, then monthly thereafter
  - Cut-offs
    - ANC at least 1,500/microL to start
    - Discontinue if moderate or severe neutropenia
    - Different cut-offs for BEN population
- Interrupt clozapine if fever and check ANC
- Rechallenge only if benefit outweighs risk

https://www.clozapinerems.com/
Seizures

• Dose-related seizure risk
  – High cumulative seizure risk: 10% (!)

• Most are tonic-clonic

• Prevention
  • Titration!
  • Therapeutic drug monitoring!
  • Pay attention to clinical comorbidities that increase seizure risk
  • Note red flags: myoclonus

• Treatment
  – Depakote is good choice
  – Carbamazepine is poor choice

Myocarditis

• Clinical features
  – Non-specific!

• Highest risk period is four weeks

• Management
  – High index of suspicion
  – No agreed-upon monitoring scheme
    • Consider adding inflammatory markers for 4 weeks
  – Consultation with cardiology

• Rechallenge discouraged in clear cases

Orthostatic hypotension

• Clozapine needs to be titrated
  – New patient
    • Establish sensitivity with test dose of 12.5 mg
    • No one titration scheme set in stone
      – Inpatient: increase 25 to 50 mg/d until you reach 300 to 440 mg per day (divided doses)
      – Take into account the patient when choosing a titration schedule
      – Consider TDM after reaching 100 mg/d
  – Established patient (!) after two missed doses
    • Start with 12.5 mg bid, then adjust more quickly
ROUTINE SIDE EFFECT MANAGEMENT
The day the music died
# CATIE – baseline cardiovascular risk factors

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th></th>
<th>Females</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CATIE</td>
<td>NHANES</td>
<td>P</td>
<td>CATIE</td>
</tr>
<tr>
<td></td>
<td>N = 509</td>
<td>N = 509</td>
<td></td>
<td>N = 180</td>
</tr>
<tr>
<td>Metabolic Syndrome Prevalence*</td>
<td>36.0%</td>
<td>19.7%</td>
<td>.0001</td>
<td>51.6%</td>
</tr>
<tr>
<td>Waist Circumference Criterion</td>
<td>35.5%</td>
<td>24.8%</td>
<td>.0001</td>
<td>76.3%</td>
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<tr>
<td>Triglyceride Criterion</td>
<td>50.7%</td>
<td>32.1%</td>
<td>.0001</td>
<td>42.3%</td>
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<tr>
<td>HDL Criterion</td>
<td>48.9%</td>
<td>31.9%</td>
<td>.0001</td>
<td>63.3%</td>
</tr>
<tr>
<td>BP Criterion</td>
<td>47.2%</td>
<td>31.1%</td>
<td>.0001</td>
<td>49.6%</td>
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<tr>
<td>Glucose Criterion</td>
<td>14.1%</td>
<td>14.2%</td>
<td>.9635</td>
<td>21.7%</td>
</tr>
</tbody>
</table>

*National Cholesterol Education Program (NCEP) criteria
NHANES = National Health and Nutrition Examination Survey III
NCEP ATP III Metabolic Syndrome

NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel III

<table>
<thead>
<tr>
<th>≥3 Risk Factors Required for Diagnosis</th>
<th>Defining Level</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risk Factor</strong></td>
<td><strong>Defining Level</strong></td>
</tr>
<tr>
<td>Abdominal obesity</td>
<td>Waist circumference</td>
</tr>
<tr>
<td>Men</td>
<td>&gt;40 in (&gt;102 cm) (IDF-94 cm)</td>
</tr>
<tr>
<td>Women</td>
<td>&gt;35 in (&gt;88 cm) (IDF-80 cm)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>&gt;150 mg/dL (1.7 mmol/L)</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>&lt; 40 mg/dL (1.03 mmoI/L)</td>
</tr>
<tr>
<td>Men</td>
<td>&lt;50 mg/dL (1.29 mmoI/L)</td>
</tr>
<tr>
<td>Women</td>
<td></td>
</tr>
<tr>
<td>Blood pressure</td>
<td>≥130/85 mm Hg</td>
</tr>
<tr>
<td>Fasting blood glucose</td>
<td>&gt;100 mg/dL (5.6 mmoI/L)</td>
</tr>
</tbody>
</table>

HDL = high-density lipoprotein

IDF = International Diabetes Federation
Metabolic syndrome controversies

• Competing definitions
  • WHO, NECP ATP-III, American Association of Clinical Endocrinologists (AACE), European Group for Study of Insulin Resistance (EGIR), International Diabetes Federation (IDF)

• Lack of consensus
  • Essential features
  • Cut-offs for different ethnic groups
  • Cut-offs for pediatric metabolic syndrome

• Definitions often highly technical and not practical

• Is MS really a syndrome?
  • POSSIBLE SOLUTION: look at each risk factor individually

Antipsychotic-induced weight gain I

- Most robust predictor: H1 receptor affinity; 5HT2C polymorphisms
- Melanocortin 4 receptor (MC4R) gene in obesity (GWAS)$^1$
- Common variants near MC4R gene associated with severe antipsychotic-induced weight gain$^2$
- Muscarinic 3 receptor key role in insulin secretion$^3$
- Dopamine, striatum, reward systems$^4$

$^3$Nurjono M et al. Schizophr Res. 2014; 157: 244.
Almost all antipsychotics show weight gain after extended use

- Weight gain more pronounced in antipsychotic naïve patients
- Not clearly dose-dependent

Meta-analysis in first-episode patient

- Short-term (3 months or less) weight gain: 3.22 kg
- Long-term (over 3 months) weight gain: 5.3 kg
- More weight gain in Western samples
- Only antipsychotic that did not cause weight gain: ziprasidone

Metabolic prevention

A. Choose wisely, if you can - prevent
B. Screen and monitor - detect
C. Prevent/blunt weight gain - mitigate
   • Switch
   • Add behavioral management
   • Add weight loss medications
Choose wisely, if you can

• Relative risk (Schizophrenia PORT 2009)¹
  Clozapine=olanzapine
  low-potency FGAs
  risperidone=paliperidone=quetiapine
  medium-potency FGAs
  high-potency antipsychotics=molindone*=aripiprazole=ziprasidone

• Lurasidone best among new antipsychotics (?)²,³
  – Pooled analysis from 6 clinical trials³
  – Mean weight change at month 12
    • -0.4 kg with lurasidone
    • +2.6 kg with risperidone
    • +1.2 kg with quetiapine XR.

PORT = Patient Outcomes Research Team
²de Hert et al. CNS Drugs. 2012 Sep 1;26(9):733-59

*discontinued
Possible BENCHMARK

80% glucose monitoring (40% lipid monitoring)

Switching to aripiprazole (CAMP)

CAMP study = comparison of antipsychotics for metabolic problems
Behavioral interventions for SMI

- Evidence-based practice
  - ACHIEVE\textsuperscript{1}
  - STRIDE\textsuperscript{2}
  - In SHAPE\textsuperscript{3}

- STRIDE core interventions
  - Increasing awareness through monitoring
  - Creating personalized diet and exercise
  - Reducing calories
  - Improving diet
  - Increasing physical activity
  - Graphing progress

Weight loss is possible for patients with SMI\textsuperscript{4}

Long-term support might be needed

Role of individual lifestyle intervention?

\textsuperscript{3}Bartels SJ et al. Psychiatr Serv 2013;64:729.
\textsuperscript{4}Bartels SJ. Am J Psychiatry 2015;172:9. (editorial)
FDA-approved weight loss medications

• Withdrawn 1997: fen-phen
• Withdrawn 2010: sibutramine (Meridia)
• Orlistat (Xenical, OTC Alli)
• Lorcaserin (Belviq) - CIV
• *Phentermine plus topiramate (Qsymia) – CIV
• Bupropion plus naltrexone (Contrave)
• *Liraglutide (Saxenda; lower-dose: Victoza)

Weight loss medications and schizophrenia

- Metformin$^{1,2,3}$
- Topiramate$^4$
- Amantadine$^5$
- Liraglutide$^6$

Metformin in schizophrenia

- **First-episode (Wang trial)**\(^1\)
  - N=72; early course
  - 500 mg bid
    - Weight loss
    - Improved insulin sensitivity

- **Chronic (Jarskog trial)**\(^2\)
  - N=148; chronic patients
  - 1000 mg bid
    - −2.0 kg (95% CI=−3.4 to −0.6; \(p=0.007\))
    - 17.3% lost > 5% (vs. 9.8% placebo)

- **Systematic review**\(^3\)
  - Mean weight loss 3.17 kg
  - Other drugs also show benefit

- **Safety analysis**\(^4\)
  - Mostly GI side effects
  - N/V 14%, diarrhea 7%

Is it time to extend the early intervention paradigm for treating first-episode psychosis to encompass the body as well as the mind?


Metformin

- Mechanism of action\(^1\)
  - Does not cause hypoglycemia by itself
- Safety
  - Renally excreted
  - Metformin toxicity\(^2\)
  - Careful if active alcoholism (lactic acidosis)
  - Vitamin B12 deficiency\(^3\)
  - Safe for cognition\(^4\)
- Dosing
  - Target dose 2000 mg TDD (with food)

Bariatric surgery

• Treatment of choice for class III obesity
  – Sustained weight loss
  – Improved blood sugar control
• Many barriers for patients with serious mental illness
  – Often excluded by bariatric centers
  – Unclear efficacy if antipsychotics continued
  – Excess of suicides after surgery

Need for med-psych integration ("reverse integration")

“All organizations are perfectly designed to get the results they get!”

- Don Berwick, MD (and others)
Drug-induced extrapyramidal symptoms (EPS)

• **By time course**
  - Peracute: Acute dystonic reaction (ADR)
  - Acute: Akathisia, NMS
  - Subacute: Parkinsonism
  - Chronic: Tardive dyskinesia (TD)

• **Other syndromes**
  - Pisa syndrome
  - Rabbit syndrome
  - See also: supersensitivity psychosis*

Antipsychotic-induced motor side effects

Akathisia - treatment

• Recognize
  – Differential diagnosis: psychotic agitation
• Change antipsychotic drug regimen
  – Reduce dose
  – Switch to low-risk antipsychotic
    • Iloperidone\(^1\), quetiapine, clozapine
• If not possible add anti-akathisia medication
  – Benzodiazepines
  – Propranolol 40 to 80 mg per day
  – Serotonin 2A receptor antagonists\(^2\)
    • Mirtazapine 15 mg per day
  – Anticholinergics ineffective (add only if Parkinsonism)

Poyurovski M. Br J Psychiatry. 2010;196(2):89-91. [REVIEW]
\(^1\)Weiden PJ et al. CNS Drugs. 2016 Aug;30(8):735-47.
Parkinsonism - treatment

• Anticholinergics
  – Avoid because of cognitive side effects
  – If used prophylactically, stop after one month

• Amantadine
  – Good alternative to anticholinergics
  – Dose: 100 mg twice daily
  – Possible benefit: weight loss

Tardive dyskinesia (TD)

- **Incidence**
  - FGA: 5% per year
  - SGA: 3.9% per year

- **Risk factors**
  - FGA > SGA > clozapine
  - Age (over age 45): 26% year 1; 52% year 2; 60% year 3
  - Dose and duration of treatment (cumulative dose)
  - Sensitivity to EPS (acute EPS)
  - Other:
    - Alcohol and drug use; females; mood disorders; diabetes

TD is iatrogenic!

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TD – clinical features

• Delayed onset (“tardive”)
• Repetitive, involuntary, purposeless movements (“choreiform”)
• Grimacing, tongue protrusion, lip smacking, puckering and pursing, and rapid eye blinking; rapid movements of the arms, legs, and trunk; involuntary movements of the fingers

http://www.ninds.nih.gov
TD - differential diagnosis

- Spontaneous movements in schizophrenia
- Old age (edentulous; orobuccal dyskinesias)
- Drug-induced dyskinesias
  - “Crack dance”
  - L-DOPA
- Choreas
  - Huntington’s disease
  - Sydenham’s chorea
  - Chorea gravidarum
- Blepharospasm and Meige syndrome
- Tourette’s and other tic disorders
- Tumors or strokes
- Systemic lupus erythematosus

Freudenreich O. Psychotic disorders. LWW 2008
Management of TD

**PREVENT**
- Clear indication for antipsychotic
- Short term treatment, if possible
- Lowest-risk choice and lowest dose

**MONITOR**
- Baseline motor exam
- Longitudinal follow-up
- At least annual AIMS

**TREAT**
- Slowly taper antipsychotic, if possible
- Switch to quetiapine or clozapine, if possible
- Treat TD symptomatically
How to use (any) rating scale

1. Clinical examination
2. Diagnosis
3. Rating of severity*

*Pick the correct rating scale for your purpose
Abnormal involuntary movement scale (AIMS)

Severity scores
Total score (sum of 1 to 7)
Global severity score
Incapacitation
Insight into movements
Tips on using the AIMS

• A score on a the AIMS is not a diagnosis
  – There is no mention of TD in the AIMS

• Assessment
  – Look at 7 body areas
  – Severity for each
  – Functional relevance and insight

• Score what you see
  – Do not count tremor
  – Do not count gum chewing (!)

• Repeat every 6 months or more frequently if high risk

Tardive dyskinesia - treatment

First-line
- Dopamine-depleting agents
  - Reserpine
  - Tetrabenazine
  - Deutetrabenazine
  - Valbenazine

Second-line
- Amantadine
- Benzodiazepines
- Beta-blockers
- Branched-chain amino acids
- Levetiracetam
- Vitamin B6 – but toxicity?
- Vitamin E – perhaps as prophylaxis
- Botox injections – for focal TD; orofacial TD
- Deep brain stimulation – for tardive dystonia

VMAT 2 inhibitors


Waln O and Jankovic J. Tremor Other Hyperkin Mov 2013;3.
Vesicular monoamine transporter (VMAT)

- Transport protein of synaptic vesicles
- Presynaptic neuron
- 2 types
  - VMAT2 for monoamine neurons
- Inhibition increases cytosolic neurotransmitter → vulnerable to MAO degradation → depletion
- 2 binding sites
  - Reserpine*
  - Tetrabenazine

*Also used in veterinary medicine as long-acting horse tranquilizer
Tetrabenazine

• Indications
  – FDA-approved (2008) for Huntington’s disease
  – Off-label for tic disorders and treatment of choice for TD

• Mechanism of action
  – VMAT2 inhibitor

• Side effects
  – Significant: poor tolerability
    • Somnolence, insomnia, akathisia, depression
    • Parkinsonism
  – Short half-life: frequent dosing (TID)
  – DDI: 2D6
  – QTc prolongation

• Expensive

Valbenazine

- VMAT2 inhibitor
- FDA-approved April 11, 2017 for adults with tardive dyskinesia
- Longer half-life (20 hours): QD dosing
- Clinical trials
  - Phase II: KINECT 1, KINECT 2
  - Phase III: KINECT 3, KINECT 4 (one-year safety/tolerability study)
- **KINECT 3** (6 week trial)*
  - N=234
  - Blinded, central raters**
  - Aims score improvements
    - 80 mg: 3.2 points (d=0.90)
    - 40 mg: 1.9 points (d= 0.52)
    - Placebo: 0.1 points
  - Side effects: akathisia, arthalgia, dry mouth, vomiting, dyskinesia

Tetrabenazine and valbenzine metabolism

Tetrabenazine (TBZ) racemic mixture

(-)-TBZ enantiomer

(+)–TBZ enantiomer

(-)–α-HTBZ

(-)–β-HTBZ

VMAT-2
- Low affinity
Off-target effects
- Dopamine receptors
- Serotonin Receptors
- Adrenergic receptors

(+)–α-HTBZ

(+)–β-HTBZ

VMAT-2
- Potent inhibition
Off-target effects
- None or minimal

Valbenazine

Non-P450 hydrolysis

Mono-Oxidation

Metabolite

TBZ = Tetrabenazine
HTBZ = Dihydrotetrabenazine

Freudenreich O and Remington G. Clin Schizophr Rel Psychoses. 2017;11(2):113-9
Deutetrabenazine

• Deuterated tetrabenazine
• FDA-approval April 2017 for Huntington’s disease (brand name Austedo)
  – Start 6 mg per day, increase by 6 mg weekly
  – Twice daily dosing
  – Up to 24 mg twice daily (48 mg TDD)
• Clinical phase II/III trials ongoing
  – Huntington Study Group
  – AIM-TD*, RIM-TD (open-label, one-year safety study)

Hyperprolactinemia

• Tubero-infundibular pathway
  – Dopamine is PIF (prolactin-inhibiting factor)
• Gender-specific problems\textsuperscript{1}
  – Females have higher prolactin elevations
  – Female side effects
    • (Secondary) amenorrhoea and infertility
    • Gynecomastia and galactorrhea
    • Loss of libido
  – Male side effects
    • Loss of libido, erectile dysfunction
    • Gynecomastia and galactorrhea
• Long-term effects
  – (Secondary) hyopogonadism $\rightarrow$ osteoporosis $\rightarrow$ fracture risk\textsuperscript{2}
  – Increased breast cancer risk?\textsuperscript{3}
  – No increased endometrial cancer risk\textsuperscript{4}
• Metformin for antipsychotic-induced hyperprolactinemia\textsuperscript{5}

"Prolactin-sparing" antipsychotics

Hyperprolactenemia

- Paliperidone
- Risperidone, first-generation AP
- Olanzapine*
- Lurasidone, asenapine
- Ziprasidone
- Iloperidone, quetiapine, clozapine
- Aripiprazole** and partial agonists

*Usually transient
**Can lower prolactin levels

Antipsychotics and pregnancy

• Nationwide Medicaid database
  – First trimester exposure to antipsychotics
    • N=9258 exposures to atypical antipsychotics
    • N=733 exposures to typical antipsychotics

• Results
  – Congenital malformations
    • Not exposed: atypical:typical = 3.3% vs. 4.5% vs. 3.8%
  – Relative risks (after confounding adjustment)
    • Atypical RR, 1.05; (95% CI, 0.96-1.16)
    • Typical RR, 0.9; (95% CI, 0.62-1.31)
    • Risperidone RR, 1.26; (95% CI, 1.02-1.56)

• Systematic review
  – High relapse risk if abrupt discontinuation
  – Highest risk: maternal morbidity and untreated illness*

Iatrogenic toxicity

Questioning the ‘neuroprotective’ hypothesis: does drug treatment prevent brain damage in early psychosis or schizophrenia?

Joanna Moncrieff

British Journal of Psychiatry February 2011

Antipsychotic Medications and Brain Volume

Do We Have Cause for Concern?

David Lewis. Archives of General Psychiatry February 2011

“It suggests the disquieting conclusion that the benefits of active neuroleptics in reducing relapse may exact a price in occupational terms.”

-Timothy Crow (1980s)
“Little evidence was found to support a negative long-term effect of initial or maintenance antipsychotic treatment on outcomes, compared with withholding treatment.”

Citizenship in a republic

It is not the critic who counts; not the man who points out how the strong man stumbles, or where the doer of deeds could have done them better. The credit belongs to the man who is actually in the arena, whose face is marred by dust and sweat and blood; who strives valiantly; who errs, who comes short again and again, because there is no effort without error and shortcoming; but who does actually strive to do the deeds; who knows great entusiasms, the great devotions; who spends himself in a worthy cause; who at the best knows in the end the triumph of high achievement, and who at the worst, if he fails, at least fails while daring greatly, so that his place shall never be with those cold and timid souls who neither know victory nor defeat.
Sequential antipsychotic trials

You need to be “The man in the arena.”

- **Select**
  - Lowest-risk choice
  - Patient preference
  - Early ancillary medical prevention
    - Behavioral interventions
    - Adjunctive metformin

- **Monitor**
  - Follow antipsychotic monitoring guidelines

- **Step-up**
  - Switch antipsychotics
  - Add behavioral interventions
  - Treat medical morbidities
THANK YOU!

John Umstead Hospital, Butner, NC, ca. 1995