Clinical Update on the Management of Schizophrenia

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Outline

• Psychosis prodrome
• Antipsychotic monotherapy
  • Comparative efficacy
  • Clozapine
• Negative symptom treatment
• Antipsychotic augmentation strategies
• Antipsychotic side-effect management
  • Tardive Dyskinesia
  • Weight gain

Omega-3 polyunsaturated fatty acid (PUFA) supplementation to prevent conversion to psychosis

• 81 people at ultra-high risk for psychosis were randomized to 12 wks of 1.2 g/day omega-3 PUFA or placebo

Amminger et al., Arch Gen Psychiatry 2010; 67: 146-154
Amminger et al., Nat Commun 2015; Aug 11; 6: 7934
Replication attempt of omega-3 PUFA for people at ultrahigh risk for psychosis

Transition rates:
- Omega-3: 6.7%
- Placebo: 5.1%

McGorry et al., JAMA Psychiatry 2017; 74: 19-27

Comparative Efficacy of APDs for Treatment of Schizophrenia

- Hierarchical efficacy comparison was performed using a multiple-treatments meta-analysis
- Blinded RCTs of patients with schizophrenia or related psychotic d/o were included
- To maximize participant homogeneity, trials were excluded that focused primarily on:
  - Clinically stable patients (e.g. relapse prevention studies)
  - Patients with predominant negative symptoms
  - Patients with concomitant medical illness
  - Treatment-resistant patients
- 212 RCTs with 43,049 participants were identified

Leucht et al., Lancet 2013; 382: 951-962
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Sunday, September 17, 2017

Efficacy of APDs Compared to Placebo

Leucht et al., Lancet 2013; 382: 951-962

Effect Sizes of APDs Compared to Placebo for EPS

Leucht et al., Lancet 2013; 382: 951-962
Effect Sizes of APDs Compared to Placebo for Weight Gain

Leucht et al., Lancet 2013; 382: 951-962

Clozapine Underutilization

- It is estimated that at least 30% of patients with schizophrenia have persistent positive symptoms and significant functional disability despite treatment with optimized doses of non-clozapine antipsychotics.
- These patients have treatment-resistant schizophrenia and are potential clozapine candidates

(Reviewed by Hasan et al., World J Biol Psychiatry 2012; 13: 318-378)
U.S. National Medicaid data 2001-2009 for people with treatment-resistant schizophrenia who started clozapine versus a standard antipsychotic

Stroup et al., Am J Psychiatry 2016; 173: 166-173
Comparative efficacy of APDs for Treatment-Resistant Schizophrenia (TRS)

- Integrate all RCT evidence of available APDs studied for TRS using a network meta-analysis
  - Allows comparison of relative effectiveness among all APDs that have been compared in at least 1 RCT, even if they have not been compared directly, as long as they are part of a connected network
- 40 blinded RCTs, N=5,172 people with TRS were included in the analysis
- Primary outcome: overall change in symptoms

Samara et al., JAMA Psychiatry; 2016; 73: 199-210

Efficacy of APDs in TRS: a Network Meta-analysis

Clozapine, olanzapine, risperidone showed a pattern of superiority with small effects

Clozapine did not demonstrate overall superiority

Role for Antidepressants in Schizophrenia Treatment?

- Depression and negative symptoms are prevalent in patients with schizophrenia and these contribute to significant functional impairment
- ~30% of patients with schizophrenia are prescribed antidepressant medication
- APA guidelines endorse management of depressive and negative symptoms with antidepressants
- However, the 2009 Schizophrenia Patient Outcomes Research Team (PORT) and the 2014 British NICE guidelines do not recommend their use, based on limited evidence (Buchanan et al., Schizophr Bull 2010; 36: 71-93; http://guidance.nice.org.uk/CG178)

Antidepressants for Depressive and Negative sx in Schizophrenia

<table>
<thead>
<tr>
<th>Trials</th>
<th>Participants</th>
<th>SMO (95% CI)</th>
<th>p-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depressive symptoms</td>
<td>42, 1949</td>
<td>-0.25 (-0.38, -0.12)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Negative symptoms</td>
<td>49, 1905</td>
<td>-0.30 (-0.44, -0.16)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Positive symptoms</td>
<td>42, 1656</td>
<td>-0.17 (-0.33, -0.01)</td>
<td>0.04</td>
</tr>
<tr>
<td>Overall symptoms</td>
<td>47, 1856</td>
<td>-0.24 (-0.39, -0.09)</td>
<td>0.002</td>
</tr>
<tr>
<td>Quality of life</td>
<td>2, 235</td>
<td>-0.32 (-0.57, -0.06)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Helfer et al., Am J Psychiatry 2016; 173: 876-886
Subgroup analysis for effects on depressive symptoms

Helfer et al., Am J Psychiatry 2016; 173: 876-886

Subgroup analysis for effects on negative symptoms

Helfer et al., Am J Psychiatry 2016; 173: 876-886
Cariprazine for Negative Symptoms of Schizophrenia

- Cariprazine (Vraylar™)
  - D2 and D3 partial agonist
  - 10-fold higher affinity at D3 compared to D2 receptors
  - 5-HT1A partial agonist
  - Phase 2 and Phase 3 studies showed efficacy of cariprazine in acute schizophrenia (Durgam et al., 2014 Schizophr Res; Durgam et al., 2015 J Clin Psychiatry)
  - Post hoc analyses suggested efficacy in people with predominant negative sxs and low positive sxs (Debelle et al., 2014 Eur Neuropsychopharm [abstr]; Debelle et al., 2015 Eur Psychiatry [abstr])
  - Led to design of 26 wk RCT comparing cariprazine vs risperidone in people with predominant negative sxs of schizophrenia
  - 461 subjects randomized, 77% completed study in each arm

Cariprazine vs Risperidone: Change in Negative Symptoms

![Graph showing the change in negative symptoms with cariprazine and risperidone over 26 weeks]

**Effect size=0.31**

*Figure 2: Mean change from baseline to week 26 in PANSS-factor score for negative symptoms.*

*p=0.0021 for the overall treatment effect of cariprazine versus risperidone. PANSS-PS=Negative and Positive Syndrome Scale factor score for negative symptoms. *p=0.0079; **p=0.0011; ***p=0.0016. **p=0.0022.

Nemeth et al., Lancet, 2017; 389: 1103-1113
Adjunctive Treatment to Antipsychotic Monotherapy in Schizophrenia

- Persistent symptoms despite optimized APD treatment has led to search for pharmacological combination treatments
- Meta-analyses have provided efficacy data on specific combination strategies, yet there has been no direct quantitative comparison across all individual combination strategies versus APD monotherapy.
- Systematic overview and quality appraisal of meta-analytic evidence was performed by Correll et al. (JAMA Psychiatry 2017; 74:675-684)
- 29 meta-analyses testing 42 combination treatments in 381 RCTs and N=19,833 participants were identified
Adjunctive Treatment to Antipsychotic Monotherapy in Schizophrenia

- AMSTAR – A Measurement Tool to Assess Systematic Reviews – (range 0-11) was used to rate the quality of the meta-analyses (Shea et al., J Clin Epidemiol 2009; 62: 1013-1020)
  - 89% of meta-analyses scored 8 or higher and 49% scored 11
- AMSTAR-Plus Content - assesses content quality of the meta-analyzed data (range 0-8) (developed by Correll et al (2017))
  - Mean AMSTAR-Plus Content score = 2.8 (!)
  - Only 1 meta-analysis had score over 4

Across 37 adjunctive treatments, 14 outperformed controls on total psychopathology, mostly with medium to large effect sizes. The recommendation to clinicians by the authors of each meta-analysis favoring use of the adjunctive tx was correlated with the effect size produced by each meta-analysis. However, when the quality of the meta-analyzed content was considered, the effect sizes were inversely correlated with study quality, reducing the confidence in these recommendations.

**CONCLUSION:** No pharmacological combination treatments had sufficient quality or consistent efficacy to support a recommendation over APD monotherapy.
Meta-analysis-Based Effect Sizes of Augmentation of any APD on Total Psychopathology

Tardive Dyskinesia (TD)

- Involuntary muscle movements associated with long term dopamine antagonist treatment
- Prevalence (Correll and Schenk, Curr Opin Psychiatry, 2008)
  - FGAs: 32.4%
  - SGAs: 13.1%
- General treatment approaches
  - Antipsychotic dose reduction
  - Switching from FGA to SGA or from SGA with higher D2 potency to lower D2 potency
- If TD symptoms are severe, consider clozapine
- Adjunctive treatments:
  - Presynaptic DA depletion via VMAT-2 inhibition: tetrabenazine (Xenazine)
  - Pyridoxine (Vit B6) 400 -1,200 mg/day (Lerner et al., 2001; Lerner et al., 2007)
  - Cholinesterase inhibitors (enhances post-synaptic cholinergic activity)
  - Benzodiazepines
Valbenazine: First FDA-approved treatment for Tardive Dyskinesia

- VMAT-2 inhibitor, structurally similar to tetrabenazine, shares 1 active metabolite with tetrabenazine
- $T_{1/2} = 20$ hrs
- Phase 3 trial, N=225 patients with TD
- 6 week, double-blind, RCT
- 3 arms: VBZ 40 mg vs VBZ 80 mg vs placebo
- Primary outcome:
  - Change in Abnormal Involuntary Movement Scale (AIMS) score from Baseline to Week 6 in 80 mg dose group

Hauser et al., Am J Psychiatry 2017; 174: 476-484
Valbenazine Tolerability

- Overall well tolerated, NNH=13
- Most commonly reported side effects:
  - Somnolence
  - Akathisia
  - Dry mouth
- Importantly, no increased risk of depression for VBZ given risk of depression associated with tetrabenazine.
- Can cause QT prolongation, use cautiously for:
  - Congenital long QT syndrome
  - Arrhythmias associated with prolonged QT interval
- No adjustment needed for mild to mod renal impairment
- Avoid use with MAOIs
Life Expectancy for People with Schizophrenia

<table>
<thead>
<tr>
<th>Population</th>
<th>Denmark Life expectancy</th>
<th>Finland Life expectancy</th>
<th>Sweden Life expectancy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Difference</td>
<td>Difference</td>
<td>Difference</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General population</td>
<td>75.7</td>
<td>75.7</td>
<td>78.2</td>
</tr>
<tr>
<td>Patients with schizophrenia</td>
<td>55.7</td>
<td>58.6</td>
<td>59.3</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General population</td>
<td>80.3</td>
<td>82.5</td>
<td>82.6</td>
</tr>
<tr>
<td>Patients with schizophrenia</td>
<td>63.8</td>
<td>66.9</td>
<td>65.7</td>
</tr>
</tbody>
</table>


Prevalence and Relative Risk of Modifiable Risk Factors for CVD in SCZ

- Cardiovascular disease associated with 50% of excess mortality in people with schizophrenia (Osby et al. 2000)

<table>
<thead>
<tr>
<th>Modifiable risk factors</th>
<th>Schizophrenia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prevalence (%)</td>
</tr>
<tr>
<td>Obesity</td>
<td>45-55</td>
</tr>
<tr>
<td>Smoking</td>
<td>50-80</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>10-15</td>
</tr>
<tr>
<td>Hypertension</td>
<td>19-58</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>25-69</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>37-63</td>
</tr>
</tbody>
</table>

De Hert et al., World Psychiatry 2011; 10: 52-77
Overweight and Obesity in Schizophrenia: Treatment Approaches

- Behavioral Interventions: diet and physical activity
  - Important for many aspects of healthy living, not just when trying to lose weight
  - May see limited participation in this population due to reduced motivation (negative sx), lack of insight/knowledge, low SES, limited access
- Switch to APD with less potential for weight gain
  - Risk for psychiatric decompensation – especially w/ clozapine
  - Potential for substituting side-effects
- Adjunctive therapy for weight loss
  - FDA and non-FDA approved treatments

Randomized Trial of Achieving Healthy Lifestyles in Psychiatric Rehabilitation (ACHIEVE STUDY)

Daumit et al., NEJM 2013; 368:1594-1602
Comparison of Antipsychotics for Metabolic Problems (CAMP) study

- 24 week study, 215 pts with schizophrenia taking OLZ, RIS or QUET, with BMI>27 and non-HDL cholesterol ≥130 mg/dL were randomized to STAY on current APD or SWITCH to aripiprazole.

Discontinuation of assigned drug: Switch N=47 (43.9%), Stay N=26 (24.5%)

Stroup et al., Am J Psychiatry 2011; 168: 947-956

Augmentation Strategies for Antipsychotic-Associated Weight Gain

- Metformin
  - Best-supported among studied agents with weight loss (~3 kg) across many RCTs and multiple recent meta-analyses (Mizuno et al., Schizophr Bull 2014; 40: 1385-1403; Fiedorowicz et al., Curr Psychiatry Rev 2012; 8: 25-36; Maayan et al., Neuropsychopharmacol 2010; 35:1520-1530)
  - Off-label use for weight loss

Metformin-mediated weight loss mechanisms

Malin et al., Curr Opin Endocrinol Diabetes Obes 2014; 21: 323-329
Metformin

- Side-effects (common – self limiting)
  - Nausea, vomiting, abdominal discomfort
  - Diarrhea
- Side-effects (rare, serious)
  - Hypoglycemia
  - Lactic acidosis (3 in 100,000 patient-years)
- Contraindications
  - Renal disease (eGFR < 45mL/min/1.73 m²)
  - Metabolic acidosis
- Precautions
  - Congestive heart failure
  - Alcohol Abuse
  - Hepatic disease
  - Dehydration

Metformin in the Treatment of Antipsychotic-induced Weight Gain in Schizophrenia (METS)

- 16 week RCT with 146 outpatients with SCZ or SczAff d/o with BMI ≥ 27 kg/m² on stable doses of 1 or 2 APDs
- Randomized to metformin or placebo
- Metformin titrated from 500 mg BID up to 1,000 mg BID, as tolerated

Jarskog et al., Am J Psychiatry 2013; 170: 1032-1040
Other adjunctive agents with meta-analytic evidence for APD-associated weight gain

**Topiramate** (Correll et al., J Clin Psychiatry 2016; 77: e746-e756)
- Off-label use for weight loss, approved for epilepsy and migraines
- 7 RCTs (N=327), dose range: 100–400 mg/day, duration: 8–24 wks
- Mean weight change: -3.14 kg
- Side effects often limit use
  - Fatigue
  - Cognitive slowing, memory impairment
  - Paresthesia

**Aripiprazole** (Mizuno et al., Schizophr Bull 2014; 40: 1385-1403)
- 3 RCTs (N=260), largest in patients taking clozapine (N=207)
- Dose range: 5 – 15 mg/day, duration: 8 – 16 wks
- Mean weight change: -2.13 kg
- Side effects associated with aripiprazole
  - Nausea, vomiting, anxiety, insomnia, EPS/akathisia

Liraglutide: GLP-1 agonist for weight loss and metabolic control in clozapine- or olanzapine-treated patients with SCZ

- Liraglutide approved for: 1) Type 2 diabetes 2) Obesity
- Glucagon-like peptide-1
  - incretin hormone secreted from L cells in gut in response to food
  - stimulates insulin secretion, inhibits glucagon secretion – lowers glucose levels
- 16 week study in 103 subjects who received liraglutide 1.8 mg/day or placebo sc

**Change from Baseline to Week 16**

<table>
<thead>
<tr>
<th></th>
<th>Liraglutide</th>
<th>Placebo</th>
<th>Est Treatment Difference (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>-4.7</td>
<td>0.5</td>
<td>-5.3 (-7.0 to -3.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>-0.2</td>
<td>0.06</td>
<td>-0.2 (-0.3 to -0.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cholesterol, total (mg/dL)</td>
<td>-19.3</td>
<td>3.5</td>
<td>-19.3 (-30.9 to -7.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>-15.4</td>
<td>-2.3</td>
<td>-15.4 (-23.2 to -7.7)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Larsen et al., JAMA Psychiatry 2017 74: 719-728
Key points

• Omega-3 PUFAs may not prevent conversion to psychosis in at-risk individuals
• Clozapine is underutilized and remains superior in many (but not all) studies and analyses
• Antidepressants have a role for treating depression and negative symptoms in SCZ
• No combination treatments to enhance antipsychotic efficacy beyond antipsychotic monotherapy can be clearly recommended at this time
• Valbenazine approved for TD
• Metformin represents most established adjunctive treatment for weight loss in overweight patients with SCZ

Thank you!