Clinical Update on the Management of Schizophrenia

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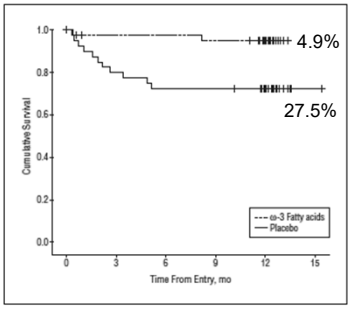
- Stock ownership: none

Outline

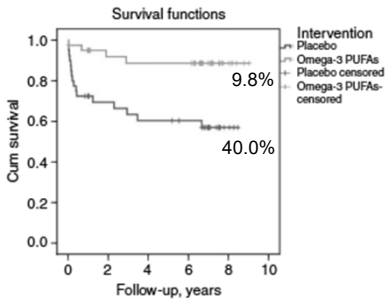
- Psychosis prodrome
- Antipsychotic monotherapy
  - Comparative efficacy
  - Clozapine
- Negative symptom treatment
- Antipsychotic augmentation strategies
- Antipsychotic side-effect management
  - Tardive Dyskinesia
  - Weight gain

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



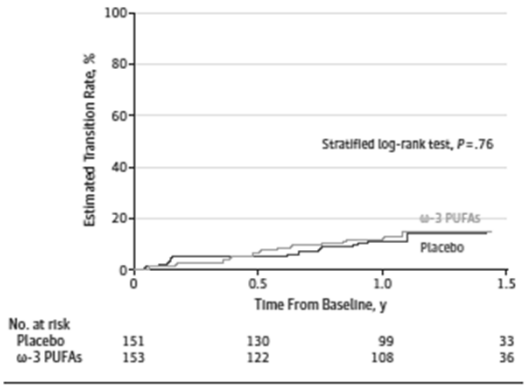
Amminger et al., Arch Gen Psychiatry 2010; 67: 146-154



Amminger et al., Nat Commun 2015; Aug 11; 6: 7934

Replication attempt of omega-3 PUFA for people at ultrahigh risk for psychosis

Figure 2. Survival Curves of the Rate of Transition to Psychosis in the ω-3 Polyunsaturated Fatty Acid (ω-3 PUFA) and Placebo Groups



Transition rates:

Omega-3: 6.7%

Placebo: 5.1%

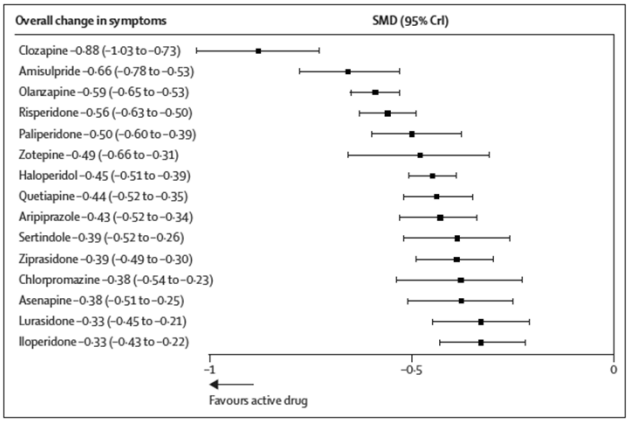
McGorry et al., JAMAPsychiatry 2017; 74: 19-27

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

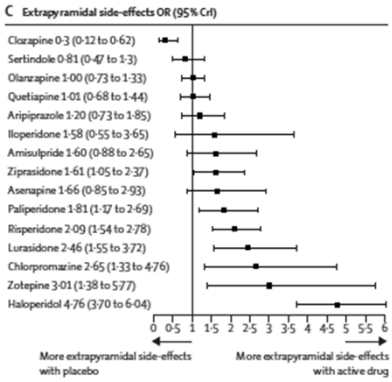
Leucht et al., Lancet 2013; 382: 951-962

Efficacy of APDs Compared to Placebo



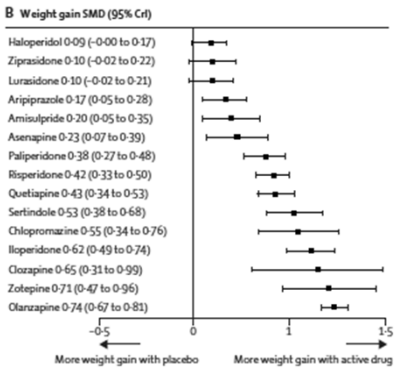
Leucht et al., Lancet 2013; 382: 951-962

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



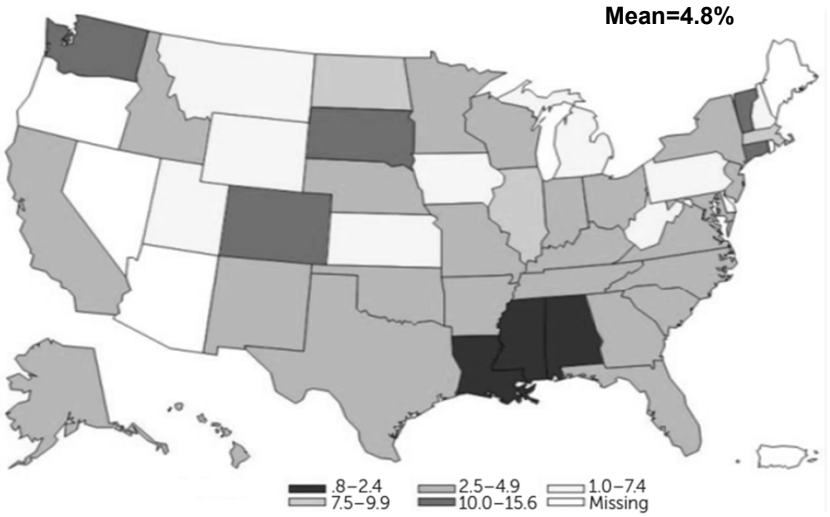
Leucht et al., Lancet 2013; 382: 951-962

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

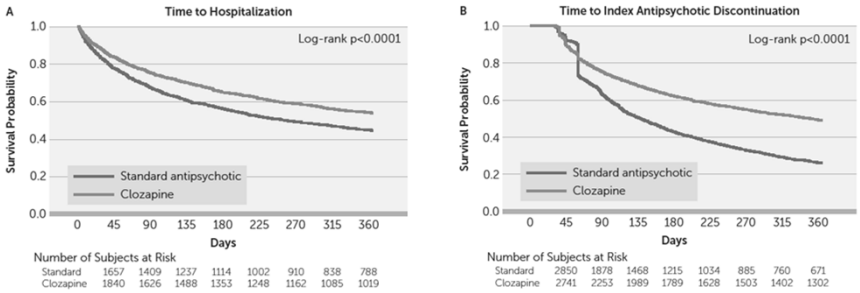
(reviewed by Hasan et al., World J Biol Psychiatry 2012; 13: 318-378)

FIGURE 1. Clozapine prescribing rates among Medicaid-insured adults with schizophrenia, 2006–2009



Olfson et al., Psychiatric Serv. 2016; 67:152

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)

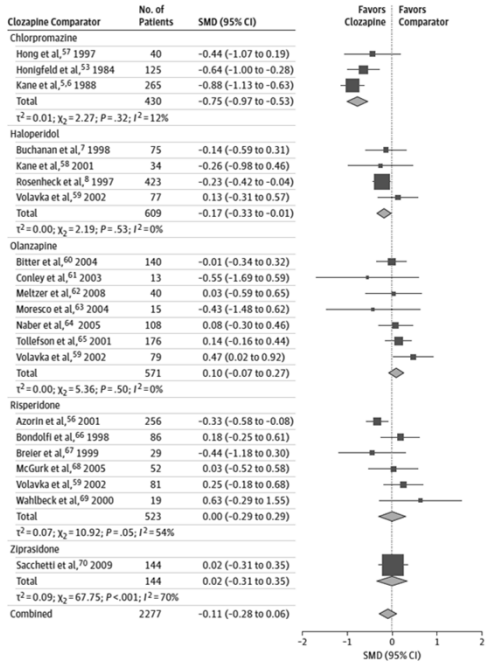
- Integrate all RCT evidence of available APDs studied for TRS using a network meta-analysis
  - Allows comparison of relative effectiveness among all APDs that have been compared in at least 1 RCT, even if they have not been compared directly, as long as they are part of a connected network
- 40 blinded 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

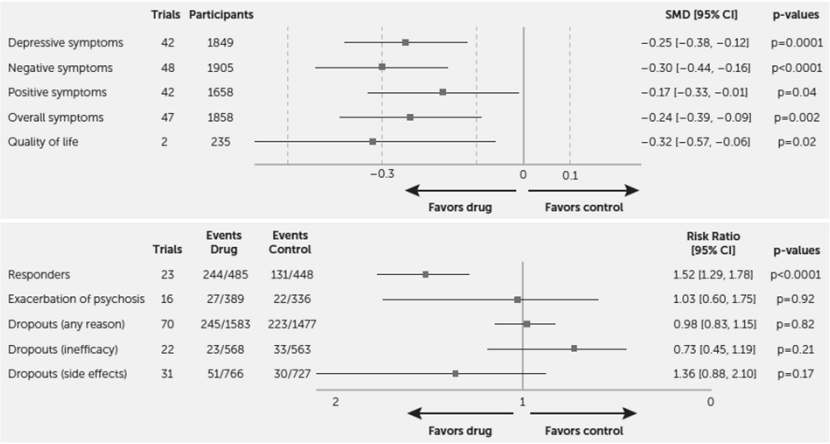


Samara et al., JAMA Psychiatry; 2016; 73: 199-210.

Role for Antidepressants in Schizophrenia Treatment ?

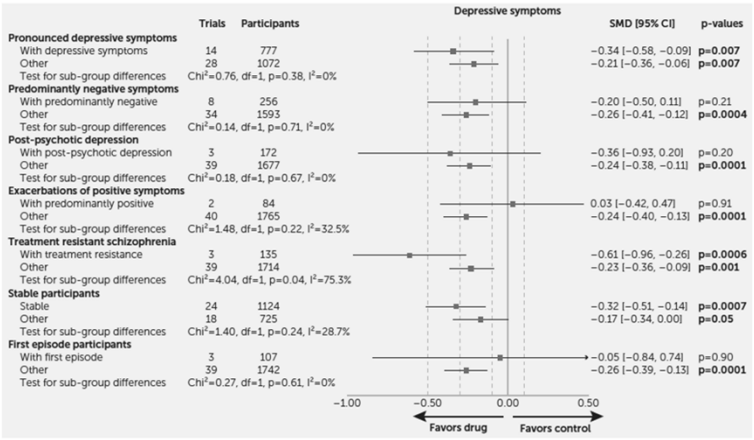
- Depression and negative symptoms are prevalent in patients with schizophrenia and these contribute to significant functional impairment
- ~30% of patients with schizophrenia are prescribed antidepressant medication
- APA guidelines endorse management of depressive and negative symptoms with antidepressants
- 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 sxs in Schizophrenia



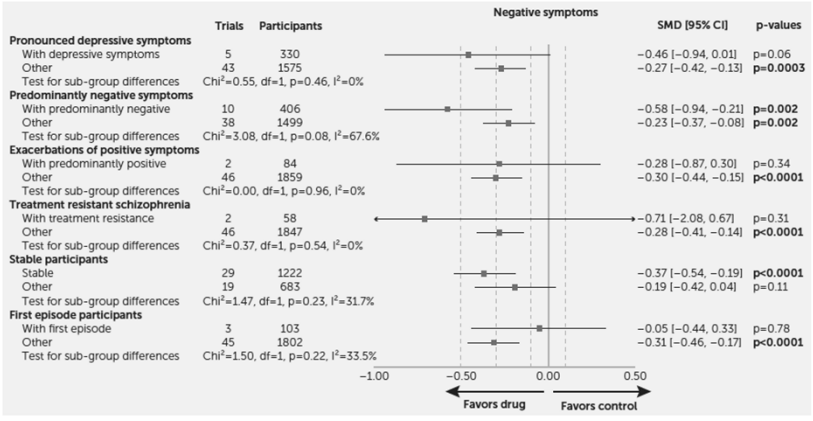
Helfer et al., Am J Psychiatry 2016; 173: 876-886

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

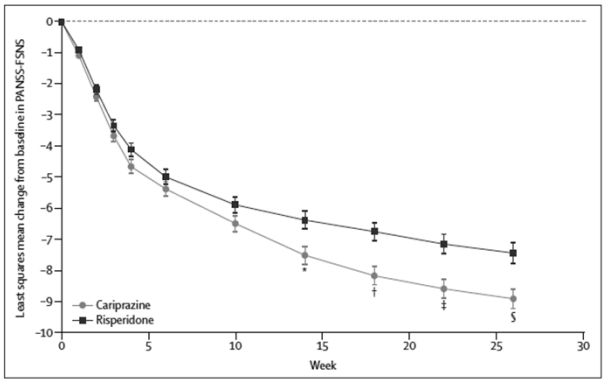
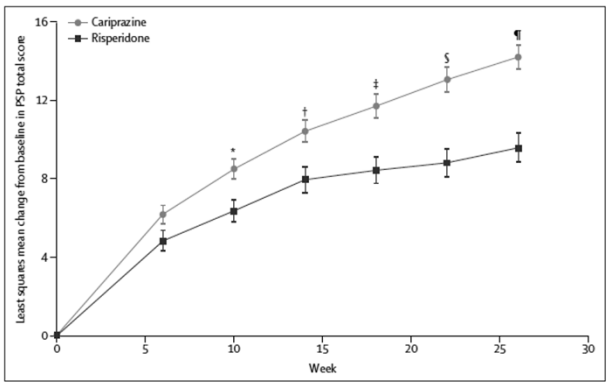


Figure 2: **Mean change from baseline to week 26 in PANSS-factor score for negative symptoms**
p=0·0092 for the overall treatment effect of cariprazine versus risperidone. PANSS-FSNS=Positive and Negative Syndrome Scale factor score for negative symptoms. *p=0·0079. †p=0·0011. ‡p=0·0016. §p=0·0022.

Effect size=0.31

Nemeth et al., Lancet, 2017; 389: 1103-1113

Cariprazine vs Risperidone: Change in Personal and Social Functioning



Effect size=0.48

Figure 3: **Mean change from baseline to week 26 in PSP total score**
p<0·0001 for the overall treatment effect of cariprazine versus risperidone. PSP=Personal and Social Performance Scale. *p=0·0053. †p=0·0046. ‡p=0·0004. §p<0·0001. ¶p<0·0001.

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

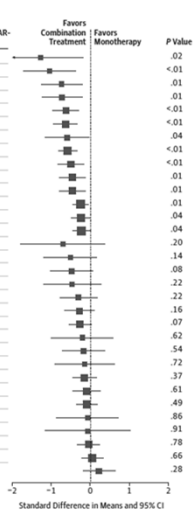
- AMSTAR – A Measurement Tool to Assess Systematic Reviews – (range 0-11) was used to rate the quality of the meta-analyses (Shea et al., J Clin Epidemiol 2009; 62: 1013-1020)
  - 89% of meta-analyses scored 8 or higher and 49% scored 11
- AMSTAR-Plus Content - assesses content quality of the meta-analyzed 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

Adjunctive Treatment to Antipsychotic Monotherapy in Schizophrenia

- 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

Drug Added to AP (Source)	Type of Agent	Statistics for Each Study: Standard Difference in Means	Lower Limit	Upper Limit	N/n	AMSTAR-Plus	P Value
SNRIs (Galling et al[16])	Antidepressants	−1.27	−2.35	−0.19	1/40	3	.02
Serotonin 3 rec ant (Kishi et al,[30] 2014)	Miscellaneous	−1.03	−1.70	−0.36	5/261	3	<.01
Lamotrigine (Premkumar and Pick,[18] 2006)	Mood stabilizers	−0.73	−1.26	−0.20	3/98	2	.01
NaSSA (Galling et al[16])	Antidepressants	−0.72	−1.24	−0.20	6/177	3	.01
Estrogen action (Heringa et al,[24] 2015)	Hormones	−0.63	−0.97	−0.29	10/863	4	<.01
Lithium (Leucht et al,[19] 2015)	Mood stabilizers	−0.63	−0.94	−0.32	6/254	1	<.01
Minocycline (Solmi et al,[26] 2016)	Antioxidants	−0.59	−1.15	−0.03	5/299	3	.04
Topiramate (Zheng et al[37])	Miscellaneous	−0.58	−0.81	−0.35	13/651	4	<.01
Adenosine modulators (Nitta et al)	Miscellaneous	−0.49	−0.82	−0.16	7/484	2	<.01
Azapirones (Kishi et al,[31] 2013)	Miscellaneous	−0.46	−0.79	−0.13	4/153	2	.01
N-acetylcysteine (Sommer et al,[28] 2014)	Antioxidants	−0.45	−0.78	−0.12	1/140	3	.01
Any antidepressant (Galling et al[16])	Antidepressants	−0.25	−0.44	−0.06	25/1130	4	.01
NSAIDs (Nitta et al,[29] 2013)	Antioxidants	−0.24	−0.47	−0.01	8/774	5	.04
Modafinil/armodafinil (Andrade et al,[23] 2015)	Stimulants	−0.23	−0.44	−0.02	8/342	4	.04
TCAs (Galling et al[16])	Antidepressants	−0.71	−1.80	0.38	1/33	3	.20
Testosterone (Heringa et al,[24] 2015)	Hormones	−0.51	−1.19	0.17	1/30	3	.14
NMDA rec ant (Matsuda et al,[36] 2013)	Miscellaneous	−0.48	−1.02	0.06	7/387	3	.08
Oxytocin (Oya et al,[25] 2016)	Hormones	−0.46	−1.19	0.27	6/162	2	.22
Antipsychotics (Galling et al[16])	Antipsychotics	−0.30	−0.78	0.18	9/378	4	.22
Pregnenolone (Heringa et al,[24] 2015)	Hormones	−0.27	−0.65	0.11	4/222	3	.16
SSRIs (Galling et al[16])	Antidepressants	−0.26	−0.54	0.02	14/779	4	.07
SARI (Galling et al[16])	Antidepressants	−0.20	−0.99	0.59	2/86	3	.62
AchEsterase inhib (Singh et al,[33] 2012)	Miscellaneous	−0.17	−0.72	0.38	2/31	4	.54
NRIs (Galling et al[16])	Antidepressants	−0.14	−0.91	0.63	2/97	3	.72
Histamine 2 blockers (Kishi et al,[30] 2014)	Miscellaneous	−0.14	−0.44	0.16	7/366	4	.37
Valproic acid (Schwarz et al,[20] 2008)	Mood stabilizers	−0.09	−0.44	0.26	5/361	0	.61
PUFAs (Sommer et al,[28] 2014)	Antioxidants	−0.09	−0.34	0.16	7/338	3	.49
MAO-B inhibitors (Galling et al,[16])	Antidepressants	−0.07	−0.86	0.72	2/83	2	.86
Carbamazepine (Leucht et al,[21] 2014)	Mood stabilizers	−0.06	−1.15	1.03	3/79	0	.91
DHEA (Heringa et al,[24] 2015)	Hormones	−0.04	−0.32	0.24	4/160	3	.78
Varenicline (Kishi and Iwata,[39] 2015)	Miscellaneous	0.06	−0.21	0.33	4/263	4	.66
Davunetide (Sommer et al,[28] 2014)	Miscellaneous	0.23	−0.18	0.64	2/85	3	.28



Correll et al., JAMA Psychiatry 2017; 74:675-684

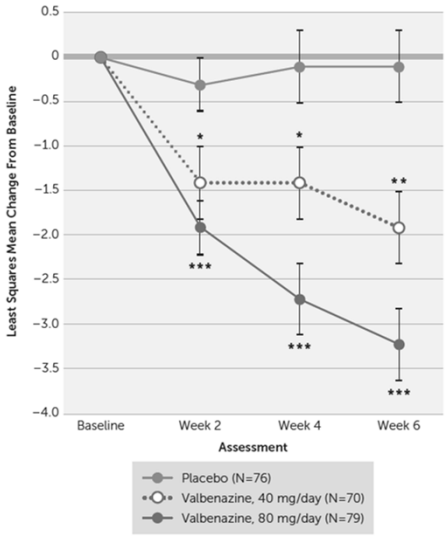
Tardive Dyskinesia (TD)

- 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

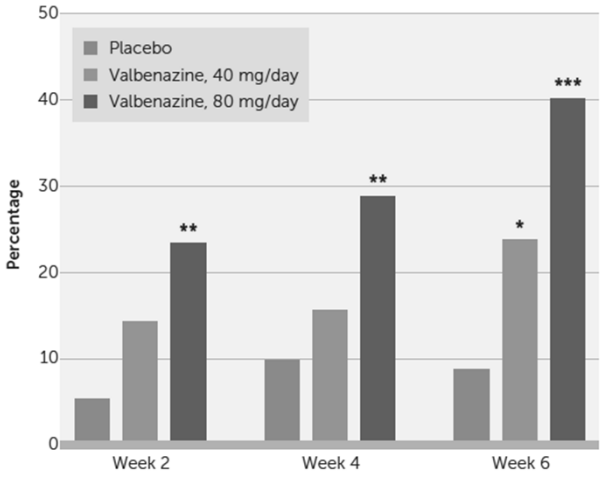
- VMAT-2 inhibitor, structurally similar to tetrabenazine, shares 1 active metabolite with tetrabenazine
- $T_{1/2}$ = 20 hrs
- Phase 3 trial, N=225 patients with TD
- 6 week, double-blind, RCT
- 3 arms: VBZ 40 mg vs VBZ 80 mg vs placebo
- Primary outcome:
  - Change in Abnormal Involuntary Movement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

Change in AIMS score over 6 wks in people with moderate to severe TD



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

Percentage of subjects who experienced ≥50% improvement in AIMS score



NNT=4 for VBZ 80 mg

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

Population	Denmark		Finland		Sweden	
	Life expectancy	Difference	Life expectancy	Difference	Life expectancy	Difference
Men						
General population	75.7	–	75.7	–	78.2	–
Patients with schizophrenia	55.7	20.0	58.6	17.1	59.3	18.9
Women						
General population	80.3	–	82.5	–	82.6	–
Patients with schizophrenia	63.8	16.5	66.9	15.6	65.7	16.9

Laursen et al, 2014 Ann Rev Clin Psychol

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)

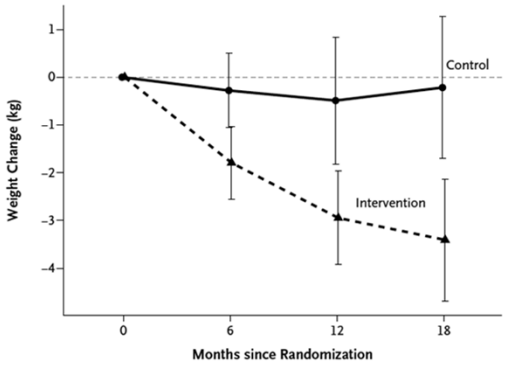
Modifiable risk factors	Schizophrenia	
	Prevalence (%)	RR
Obesity	45-55	1.5-2
Smoking	50-80	2-3
Diabetes mellitus	10-15	2-3
Hypertension	19-58	2-3
Dyslipidemia	25-69	≤5
Metabolic syndrome	37-63	2-3

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 sxs), 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

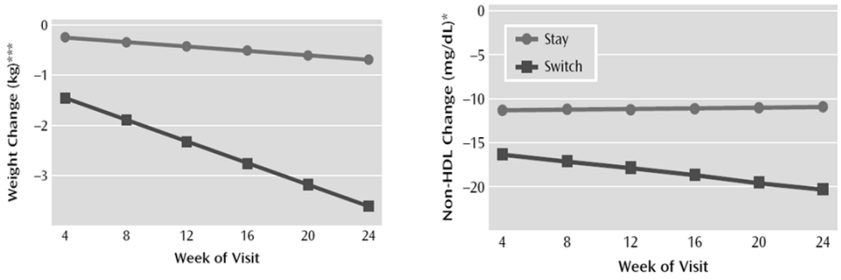
Randomized Trial of Achieving Healthy Lifestyles in Psychiatric Rehabilitation (**ACHIEVE STUDY)**



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.



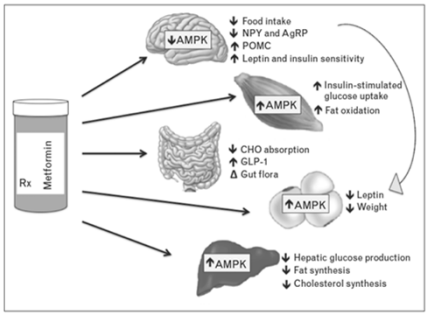
Discontinuation of assigned drug: Switch N=47 (43.9%), Stay N=26 (24.5%)

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



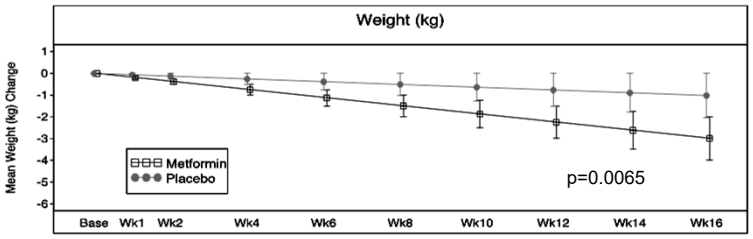
Malin et al., Curr Opin Endocrinol Diabetes Obes 2014; 21: 323-329

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 m^2)
  - 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/m^2 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

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

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!