Schizophrenia 2.0
What’s New in the Past 5 Years

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What’s New: Overview

- Genetics – We are starting to identify patho-physiologies
- Cannabis – increases risk and complicates course
- Specialized treatment programs work for FEP
- New antipsychotics and delivery systems
- Mixed results with glutamatergic and nicotinic agents
- Successes: Treating TD with VMAT-2 inhibitors
- The future: Specialization, checklists, teams, and simplification

FEP = first-episode psychosis; TD = tardive dyskinesia; VMAT = vesicular monoamine transporter.

Genetics
Identifying Patho-physiologies

- Complement Component 4, neuronal pruning
- SETD1A, epigenetic control of multiple gene expression
- Greatly reduced fertility among individuals with schizophrenia, especially men
- New mutations – the risk of advancing paternal age

SETD1A = SET Domain-Containing Protein 1A.

Complement Component 4 and Neuronal Pruning during Development

- Schizophrenia’s strongest genetic association at a population level involves variation in the MHC locus
- This association arises in part from many structurally diverse alleles of the complement C4 genes. These alleles generate widely varying levels of C4A and C4B expression in the brain, with each common C4 allele associating with schizophrenia in proportion to its tendency to generate greater expression of C4A


Complement Component 4 and Neuronal Pruning during Development

- C4 mediates synapse elimination during postnatal development in mice, and perhaps in humans
- Excessive complement activity in development may help explain the reduced numbers of synapses in the brains of individuals with schizophrenia


The Complement Cascade

**Loss of Function Mutations of SETD1A**

- SETD1A is a histone methyltransferase that specifically methylates 'Lys-4' of histone H3
- H3 'Lys-4' methylation represents a specific tag for epigenetic transcriptional activation
- SETD1A and SETD1B make non-redundant contributions to the epigenetic control of chromatin structure and gene expression

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**Histone Modification and DNA Methylation**

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**Nucleosomes**

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**SETD1A**

- LoF variants in the SETD1A gene are very rare in the general population
- Singh et al identified a genome-wide significant association between rare LoF variants in SETD1A (which encodes a subunit of histone methyltransferase) and risk for schizophrenia ($P = 3.3 \times 10^{-9}$)
- 7 of the 10 individuals with schizophrenia carrying SETD1A LoF variants also had learning difficulties
- These LoF variants were also found in severe developmental disorders with notable neuropsychiatric phenotypes

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**Reduced Fertility**

- Patients with schizophrenia have reduced fertility compared with the general population (FR = .39)
- Men had a greater impairment in fertility than women, both in patients (FR = .54) and in their unaffected siblings (FR = .81)
- Strong selection exists against schizophrenia
- These variants may be maintained by new mutations

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**Advanced Paternal Age Increased Risk for Schizophrenia**

- After controlling for several confounding factors including maternal age, the relative risk of schizophrenia increased from 1.84 to 4.62 in offspring of fathers with an older age (> 35 years) of fatherhood
- Mother’s age showed no significant effects after adjusting for paternal age
- New mutations may occur in the spermatogonia, possibly because of accumulating replication errors in spermatogonial cell lines
- Patients without a family history of schizophrenia had significantly older fathers than probands with a positive family history of schizophrenia

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**FR = fertility ratio.**

### Advanced Paternal Age

**Advanced Paternal Age
Increased Risk for Relapse after FEP**

- In a 1-year follow-up period, 42 (22%) of FEP patients experienced ≥ 1 relapses
- Advanced paternal age (OR = 1.05, 95% CI: 1.01 – 1.10), medication nonadherence (OR = 2.37, 95% CI: 1.12 – 4.99), and female sex (OR = 2.44, 95% CI: 1.14 – 5.24) independently contributed to a higher risk of relapse
- Analysis between different paternal age groups found a significantly higher relapse rate with paternal age > 40


### Advanced Paternal Age

**Psychotic-Like Symptoms**

- Between 2% and 12% of adults in the general population report experiencing psychotic-like symptoms (eg, seeing a vision others couldn’t see, hearing voices others couldn’t hear)
- Paternal age was significantly associated with experiencing psychotic-like symptoms (χ^2(2) = 13.34, \(P = .010\)). Relative to respondents whose fathers were aged 25 to 29 at the time of their birth, those with fathers aged > 35 had 2.12 × higher odds (95% CI: 1.08 – 4.16) of psychotic-like symptoms


### Cannabis Increases Risk
and Worsens Course

- Dose-response between heaviness of use and risk for psychosis
- Earlier age of onset and better cognitive functioning at onset
- Continued use after onset associated with earlier relapse

### Cannabis

**Effects on Risks and Outcomes**

- In a meta-analysis, enrolling 66,816 individuals, higher levels of cannabis use were associated with increased risk for psychosis in all the included studies
- A logistic regression model gave an OR of 3.90 (95% CI: 2.84 – 5.34) for the risk of schizophrenia and other psychosis-related outcomes among the heaviest cannabis users compared to the nonusers
- Current evidence shows that high levels of cannabis use increase the risk of psychotic outcomes and confirms a dose-response relationship between the level of use and the risk for psychosis


### Cannabis in the Prodrome

**Increases Likelihood of Transition**

- Escalation of premorbid use in the 5 years prior to onset was highly associated with increased risk for onset (eg, increasing from no use to daily use, HR = 3.6, \(P < .0005\))
- Daily use approximately doubled the rate of onset (HR = 2.2, \(P < .0005\)), even after controlling for simultaneous alcohol/tobacco use
- Cumulative cannabis exposure was associated with an increased rate of onset of psychosis (\(P = .007\)), independent of gender and family history


### Prior Cannabis Use in Prodrome

**Better Cognition But Earlier Onset**

- Prior cannabis use, compared to none, is reported to be associated with less cognitive impairment in schizophrenia
- BACS Composite scores in individuals with FEP were significantly higher in individuals with psychosis with prior cannabis use compared to individuals with psychosis and no prior cannabis use
- Patients with substance use (n = 627) had about 3 years earlier age at onset (23.0 years; SD = 7.1) than the abstinent group (n = 492; 25.9 years; SD = 9.7). Only cannabis use was statistically significantly related to earlier age at onset. Gender or family history of psychosis did not influence the results

Cannabis Relapse after FEP

- After 2 years, one-third of the patients had a diagnosis of schizophrenia and more than 40% had a diagnosis of affective psychosis. Rates of relapse were 31% after 1 year and 43% at 2 years.
- Cannabis use after illness onset and poor insight were the best predictors of relapse.


Specialized Treatment Programs for FEP Effective and Cost-Effective

- 2-year programs are associated with improved functioning and satisfaction (but their prosthetic effect decays over time after the programs are discontinued).
- 2-year programs are cost-effective.
- Many prescribers, even in trial sites, are not following pharmacological treatment guidelines.
- Modifiable risk factors for cardiovascular disease and cancer are already prevalent at FEP.

Team-Based, Coordinated, Specialty Care for FEP – RAISE

- The 223 recipients of NAVIGATE remained in treatment longer, experienced greater improvement in quality of life and psychopathology, and experienced greater involvement in work and school compared with 181 participants in community care.
- The median duration of untreated psychosis was 74 weeks. NAVIGATE participants with duration of untreated psychosis of < 74 weeks had greater improvement in quality of life and psychopathology compared with those with longer duration of untreated psychosis and those in community care.

RAISE = Recovery After an Initial Schizophrenia Episode.

Team-Based Specialty Care for FEP is Cost-Effective

- The cost-effectiveness of NAVIGATE, a comprehensive, multidisciplinary, team-based treatment approach for FEP and usual CC was compared in a cluster randomization trial.
- Effectiveness was measured as a one standard deviation change on the QLS-SD.
- The NAVIGATE group improved significantly more on the QLS and had higher outpatient mental health and antipsychotic medication costs.
- The incremental cost-effectiveness ratio was $12,081/QLS-SD, with a .94 probability that NAVIGATE was more cost-effective than CC at $40,000/QLS-SD.

CC = Community Care; QLS-SD = Quality of Life Scale.

Guidelines vs Reality in the Treatment of FEP

- The authors identified 39% of the sample who might benefit from changes in their psychotropic prescriptions.
- Of these, 9% received prescriptions for antipsychotics at higher than recommended dosages; 32% received prescriptions for olanzapine (often at high dosages), 23% for > 1 antipsychotic, 37% for an antipsychotic and also an antidepressant without a clear indication, 10% for psychotropic medications without an antipsychotic, and 1% for stimulants.


RAISE Metabolic Risk Factors at Baseline

- 48% were obese or overweight, 51% smoked, 57% had dyslipidemia, 40% had prehypertension, 10% had hypertension, and 13% had metabolic syndrome.
- Prediabetes (glucose based, 4%; hemoglobin A1c based, 15%) and diabetes (glucose based, 3%; hemoglobin A1c based, 3%) were less frequent.
- Antipsychotic treatment duration correlated significantly with higher non-HDL-C, triglycerides, and triglycerides to HDL-C ratio and lower HDL-C and systolic blood pressure (all P ≤ .01).
- Olanzapine was significantly associated with higher triglycerides, insulin, and insulin resistance, whereas quetiapine fumarate was associated with significantly higher triglycerides to HDL-C ratio (all P ≤ .02).

New Antipsychotic Medications and Delivery Systems

- Cariprazine
- Brexpiprazole
- Aripiprazole LAI
- Aripiprazole Lauroxil LAI
- Paliperidone Palmitate – 3-month

LAI = long-acting injectable.

Cariprazine

- Cariprazine is indicated for the treatment of schizophrenia and for acute treatment of manic or mixed episodes associated with bipolar I disorder
- The efficacy of cariprazine could be mediated through a combination of partial agonist activity at central dopamine D2 and serotonin 5-HT1A receptors and antagonist activity at serotonin 5-HT2A receptors

DCAR = desmethyl cariprazine; DDCAR = didesmethyl cariprazine.

Cariprazine forms 2 major metabolites, DCAR and DDCAR, that have in vitro receptor binding profiles similar to the parent drug
- The half-lives based on time to reach steady state, estimated from the mean concentration-time curves, are 2 to 4 days for cariprazine, and approximately 1 to 3 weeks for DDCAR
- Mean concentrations of DCAR and DDCAR are approximately 30% and 400%, respectively, of cariprazine concentrations by the end of 12-week treatment

Brexpiprazole

- Indicated for adjunctive treatment of MDD; recommended starting dosage is .5 mg or 1 mg, once daily, taken orally with or without food; titrate up to the target dosage of 2 mg once daily. The maximum recommended daily dosage is 3 mg
- And for the treatment of schizophrenia (the recommended starting dosage is 1 mg once daily; titrate to 2 mg once daily, then to 4 mg based on the patient's clinical response and tolerability. The maximum recommended daily dosage is 4 mg

MDD = major depressive disorder.
### Paliperidone Palmitate – 3-Month

- The PP3M formulation utilizes NanoCrystal technology similar to the PP1M but with increased particle size, allowing for an extended sustained release.
- Paliperidone palmitate undergoes hydroxylation into the active moiety paliperidone via esterases in muscle tissue.
- PP3M is available in dose strengths of 273 mg, 410 mg, 546 mg, and 819 mg paliperidone palmitate.

### Paliperidone Palmitate – 3-Month

- PP3M dissolves slowly after intramuscular injection before being hydrolyzed and absorbed systemically due to its low water solubility.
- The administration of PP3M will occur only after ≥ 4 injections of PP1M, which is after paliperidone has reached steady-state concentrations.

### Aripiprazole LAI

- Only to be administered by intramuscular injection in the deltoid or gluteal muscle.
- For patients naïve to aripiprazole, establish tolerability with oral aripiprazole prior to initiating aripiprazole LAI.
- Recommended starting and maintenance dose is 400 mg administered monthly as a single injection. Dose can be reduced to 300 mg in patients with adverse reactions.
- In conjunction with first dose, take 14 consecutive days of concurrent oral aripiprazole (10 mg to 20 mg) or current oral antipsychotic.

### Aripiprazole LAI

- Aripiprazole absorption into the systemic circulation is slow and prolonged following intramuscular injection due to low solubility of aripiprazole particles.
- Following a single dose administration of aripiprazole LAI in the deltoid and gluteal muscle, the extent of absorption (AUC∞) of aripiprazole was similar for both injection sites, but the rate of absorption (Cmax) was 31% higher following administration to the deltoid compared to the gluteal site. However, at steady state, AUC and Cmax were similar for both sites of injection.

### Aripiprazole Lauroxil

- Depending on individual patient’s needs, treatment with aripiprazole lauroxil can be initiated at a dose of 441 mg, 662 mg, or 882 mg administered monthly, which corresponds to 300 mg, 450 mg, and 600 mg of aripiprazole, respectively.
- Treatment may also be initiated with the 882 mg dose every 6 weeks.
- Administer aripiprazole lauroxil either in the deltoid muscle (441 mg dose only) or gluteal muscle (441 mg, 662 mg, or 882 mg).

### Aripiprazole Lauroxil

- Aripiprazole lauroxil is a prodrug of aripiprazole and its activity in the body is primarily due to aripiprazole.
- After single intramuscular injection the appearance of aripiprazole in the systemic circulation starts from 5 to 6 days and continues to be released for an additional 36 days.
- Aripiprazole concentrations increase with consecutive doses of aripiprazole lauroxil and reach steady-state following the 4th monthly injection.
- With the addition of oral aripiprazole supplementation for 21 days at the time of the first aripiprazole lauroxil dose, aripiprazole concentrations reach therapeutic levels within 4 days.
Glutamatergic and Nicotinic Agents: Mixed Results

- Disappointing results in several clinical trials
- Evidence remains that these are important neurotransmitter systems where we may identify therapeutic opportunities through innovative strategies
- Choline as a nutraceutical

Glutamate: Meta-Analysis of Proton Magnetic Resonance Spectroscopy Studies

- In schizophrenia, there were significant elevations in glutamate in the basal ganglia, glutamine in the thalamus, and Glx in the basal ganglia and medial temporal lobe
- No region showed a reduction in glutamate metabolites in schizophrenia
- Schizophrenia is associated with elevations in glutamatergic metabolites across several brain regions
- Compounds that reduce glutamatergic transmission may have therapeutic potential

Glutamatergic Targets

- Strategies focused on enhancing activity of the NMDA receptor via direct agonists at the glycine site or by inhibition of glycine reuptake have produced modest and often inconsistent evidence of efficacy, as have approaches to reduce excessive glutamate release by lamotrigine or by mGluR2/3 agonists.
- Strategies targeting AMPA receptors have also met with only limited success
- Newer approaches include selective allosteric modulation of NMDA receptor subunits and of mGluR5 receptors. In addition, intracellular pathways downstream of NMDA receptors may also provide new treatment targets, as exemplified by PDE inhibitors

Uncommon Variants Disrupted CHRNA7 Gene

- 2 cases of paternally inherited 15q13.3 duplications in carriers diagnosed with COS, a rare neurodevelopmental disorder of proposed polygenic origin with onset in children before age 13
- 15q13.3 deletion and duplication exhibit pathogenicity for COS, with both CNVs sharing a disrupted CHRNA7 gene
- CHRNA7 encodes the neuronal α7nAChR and is a candidate gene that has been suggested as a pathophysiologically process mediating AOS and other neurodevelopmental disorders

Nicotinic α7 Agonist Non-Smoking Adults with Schizophrenia

- A double-blind, placebo-controlled, parallel-group, 24-week, multicenter trial was conducted to evaluate the efficacy and safety of 3 doses of ABT-126, an α7 nicotinic receptor agonist, for the treatment of cognitive impairment in non-smoking individuals with schizophrenia
- A total of 432 participants were randomized and 80% (344/431) completed the study. No statistically significant differences were observed in either the change from baseline for the MCCB neurocognitive composite score (+2.66 [±0.54] for ABT-126 50 mg vs +2.46 [±0.56] for placebo at week 12; P > .05) or the UPSA-2ER

Glx = glutamate + glutamine.

AMPAR = α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; mGluR = metabotropic glutamate receptor; PDE = phosphodiesterase.

MCCB = MATRICS Consensus Cognitive Battery; UPSA-2ER = University of California Performance-based Assessment-Extended Range.
Deficient cerebral inhibition is a pathophysiological brain deficit related to poor sensory gating and attention in schizophrenia and other disorders. Cerebral inhibition develops perinatally, influenced by genetic and in utero factors. Amniotic choline activates fetal α7nAChRs and facilitates development of cerebral inhibition.

A randomized placebo-controlled clinical trial of dietary phosphatidylcholine supplementation was conducted with 100 healthy pregnant women. Infants’ EEG recordings of inhibition of the P50 component of the cerebral evoked response to paired sounds were analyzed. Criterion for inhibition was suppression of the amplitude of the second P50 response by at least half, compared to the first response.

No adverse effects of choline were observed in maternal health and delivery, birth, or infant development. More choline-treated infants (76%) suppressed the P50 response, compared to placebo-treated infants (43%) at the 5th postnatal week (effect size = .7). A CHRNA7 genotype associated with schizophrenia diminished P50 inhibition in the placebo-treated infants, but not in the choline-treated infants. Neonatal developmental delay in inhibition is associated with attentional problems as the child matures. Perinatal choline activates timely development of cerebral inhibition, even in the presence of gene mutations that otherwise delay it.

At 40 months, parent ratings of children in the phosphatidylcholine group (n = 23) indicated fewer attention problems and less social withdrawal compared with the placebo group (n = 26). The children’s behavior is moderated by CHRNA7 variants associated with later mental illness and is related to their enhanced cerebral inhibition as newborns. CHRNA7, the α7nAChR gene, has been associated with schizophrenia, autism, and attention-deficit/hyperactivity disorder. Maternal phosphatidylcholine treatment may, by increasing activation of the α7nAChR, alter the development of behavior problems in early childhood that can presage later mental illness.

Choline supplementation in pregnancy is not an FDA approved intervention. Prenatal dietary supplementation with phosphatidylcholine and promotion of diets rich in choline-containing foods (meats, soybeans, and eggs) are possible interventions to promote fetal brain development and thereby decrease the risk of subsequent mental illnesses. The low risk and short (6-month) duration of the intervention makes it especially conducive to population-wide adoption. Similar findings with folate for the prevention of cleft palate led to recommendations for prenatal pharmacological supplementation and dietary improvement.
**Tardive Dyskinesia:**
New Treatment Strategies

- Tardive dyskinesia is still around
- Acute EPSE (excessive/disruptive DAD2 blockade)
- Damaged brains (elderly, TBI, DD, HIV)
- AIMS
- VMAT-2
- Tetrabenazine, deutetetabenazine, and valbenazine*

*These medications are not FDA approved for the treatment of TD as of August 1, 2016.
AIMS = Abnormal Involuntary Movement Scale; DAD2 = dopamine D2; DD = developmental disability; EPSE = extrapyramidal side effects; TBI = traumatic brain injury.

**TD is Still Around**

- Legacy cases
- Second-generation antipsychotic medications have less, not zero, risk for inducing TD
- Antipsychotic medication use has expanded to new indications, eg, augmentation of antidepressant treatment, management of conduct disorder, management of agitation accompanying cognitive decline or following TBI
- The Abnormal Involuntary Movement Scale (AIMS) remains the gold standard for TD detection

**TD in the CATIE Trials**
Association with Acute EPSE

- 212 individuals met the Schoeller-Kane criteria for probable TD and 1098 had no history or current evidence of TD
- Participants with TD were older, had a longer duration of receiving antipsychotic medication, and were more likely to have been receiving a conventional antipsychotic and an anticholinergic agent
- The TD participants also had higher ratings of psychopathology, EPSE, and akathisia

CATIE = Clinical Antipsychotic Trials of Intervention Effectiveness.

**TD Risk**
Greatly Increased in the Elderly

- The cumulative rates of TD were 25%, 34%, and 53% after 1, 2, and 3 years of cumulative antipsychotic treatment in a group of 261 neuroleptic-naïve patients aged ≥ 55 identified at the time they were starting antipsychotic drug treatment
- A greater risk of TD was associated with history of ECT treatment, higher mean daily and cumulative antipsychotic doses, and presence of extrapyramidal signs early in treatment
- TD rates for patients beginning treatment with conventional antipsychotics in their 5th decade or later are 3 to 5 × what has been found for younger patients, despite treatment with lower doses

ECT = electroconvulsive therapy.

**Vesicular Monoamine Transporter Type 2**

- The vesicular monoamine transporter (VMAT) is a transport protein integrated into the membrane of synaptic vesicles of presynaptic neurons. It acts to transport monoamine neurotransmitters – such as dopamine, serotonin, norepinephrine, epinephrine, and histamine – into the vesicles, which release the neurotransmitters into synapses as chemical messages to postsynaptic neurons. VMATs utilize a proton gradient generated by V-ATPases in vesicle membranes to power monoamine import.

The Future
Sensible Changes in Practice

• Complexity
• Specialization
• Checklists
• Expected Imperfection
• Teams and Communication
• Simplification (Southwest Airlines)

Complexity — Knowledge

• “Avoidable failures [ineptitude] are common and persistent, not to mention demoralizing and frustrating, across many fields…And the reason is increasingly evident: the volume and complexity of what we know has exceeded our individual ability to deliver its benefits correctly, safely, and reliably. Knowledge has both saved us and burdened us.”


Complexity — Skill

• “But it’s not only the breadth and quantity of knowledge that has made medicine complicated. It is also the execution – the practical matter of what knowledge requires clinicians to do.”

### Advantages of Specialization

- Greater knowledge of the details that matter within the specialist domain
- Learned ability to handle the complexities of the particular job
- Examples: First-episode psychosis, clozapine

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### Checklists

- "In a complex environment, experts are up against two main difficulties. The first is the fallibility of human memory and attention, especially when it comes to mundane, routine matters that are easily overlooked under the strain of more pressing events."
- "A further difficulty, just as insidious, is that people can lull themselves into skipping steps even when they remember them."
- "Checklists seem to provide protection against such failures. They remind us of the minimum necessary steps and make them explicit. They not only offer the possibility of verification but also instill a kind of discipline of higher performance."

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### Starting Clozapine “Pre-Flight” Checklist

- Seizure risk/preemption
- Agranulocytosis monitoring
- Myocarditis monitoring
- Constipation risk/preemption
- Weight gain/insulin resistance preemption
- Dyslipidemia monitoring/treatment

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### Expected Imperfection

- "Perfect safety…doesn’t mean eliminating all mistakes. It means structuring a system that expects and safely deals with mistakes, both the type that can do immediate harm and those that can kill slowly – such as failing to lower someone’s critical cholesterol levels over time. Dealing with failures effectively is the essence of a high-reliability organization."

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### Chronic Biological Illnesses eg, Schizophrenia

- Persistent, enduring; given present knowledge, they cannot be “cured” (we cannot resect a tumor or kill an organism)
- The pathophysiology of the illness produces damage that cannot be reversed and that makes later treatment more difficult
- The “activity” of the illness is associated with the rate at which damage occurs (Systolic BP 180 vs 140 mm Hg; HbA1c 12.0 vs 8.0%)

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### Chronic Biological Illnesses

- The goal of treatment is sustained remission, ie, reduction in activity of the illness to “mild” or less
- Enduring medical involvement is recommended
- Most of the work of management is done by the afflicted patient her/himself
**The Chronic Care Model**

**Teams**

- Novel practice teams
- Decision support guiding evidence-based practice
- Chronic illness "self"-management support


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**Complexity**

**Expected Imperfection**

- "The elevator cars were factory constructed and tested. They were installed by experts. But it was not assumed that they would work perfectly. Quite the opposite. The assumption was that anything could go wrong, anything could get missed. What? Who knows? That’s the nature of complexity. But it was assumed that if you got the right people together and had them take a moment to talk things over as a team rather than as individuals, serious problems could be identified and averted."


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**Complexity**

**Large Construction Projects**

- "It is unnerving to think that we allow buildings this difficult to design and construct to go up in the midst of our major cities...we allow it based on our trust in the ability of experts to manage complexity. They in turn know better than to rely on their individual abilities to get everything right..."
- "They trust instead in one set of checklists to make sure that simple steps are not missed or skipped and in another set to make sure that everyone talks through and resolves all the hard and unexpected problems."


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**Antipsychotic Treatment Algorithm**

**4 Questions Aiming for Remission**

- Start a first-line APM? [Favorable side effect burden; once daily PO dosing; availability of LAI preparation]
- Utilize an LAI preparation? [Prior record of adherence; expressed willingness; social support]
- Is remission achieved with a first-line APM? [If not, transition to olanzapine] [Switching among first-line APMs for efficacy, or combining first-line APMs, is useless]
- Is remission achieved with olanzapine? [If not, transition to clozapine]

APM = antipsychotic medication.

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**Simplification**

- "We only need to train our mechanics on one type of airplane. We only need extra parts inventory for that one type of airplane. If we have to swap a plane out at the last minute for maintenance, the fleet is totally interchangeable—all our on-board crews and ground crews are already familiar with it. And there are no challenges in how and where we can park our planes on the ground, since they’re all the same shape and size."