

**Less is More**  
**A Rationale for Extended Dosing**  
Roger A. Boshes MD, PhD

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**Philosophy of Science**

1. The study of “knowing” goes back to Aristotle who referred to this domain of philosophy as Metaphysics.
2. Metaphysics includes epistemological knowledge and ontological knowledge, which both concern how we know things to be true.
3. Observation is the basis of scientific knowledge leading to hypothesis formation which is tested and confirmed or disconfirmed.
4. Any hypotheses must have Face Validity (explain the phenomenon in a logical way) and Reliability ( reproducibility) .

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**William of Occam**

1. Medieval Franciscan Monk who studied Philosophy, Physics and Theology.
2. Ontological Parsimony; Any hypotheses that can explain a natural or ecclesiastical phenomenon most efficiently with the fewest possible number of causes, exceptions, or caveats is the preferable explanation.
3. This principle is call the Law of Parsimony or “Occam’s Razor”.

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## Astronomy

**Claudius Ptolomaeus 100-1500 CE**  
 ➤ Astronomer, Geographer, Mathematician  
 Geocentric Universe

**Nicolaus Copernicus 1473-1543**  
 ➤ Polish Astronomer studying in Bologna  
 Heliocentric Universe

**Johannes Kepler 1571-1630**  
 ➤ Astronomer, Mathematician, Optician, developer of improved telescope to study planetary motion, confirming Heliocentric Universe

**Galileo Galilei 1564-1642**  
 ➤ Polymath including Astronomy and Physics  
 Heliocentric Universe

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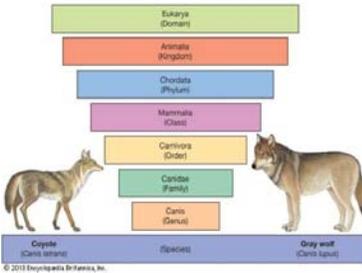
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## Carlolus Linnaeus 1707-1778

Swedish Botanist, Explorer, Physician  
 Defined principles of Natural Genera and Species.

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- Linnaeus' systematic organization of botanical species based exclusively on their morphological characteristics provided an essential building block along with the emerging field of geology to inspire Charles Darwin's (1809-1882) Theory of Evolution.
  
- His description of Morphology of plants' sexual organs (stamens and pistils) were essential for the experiments of Gregor Mendel (1822-1884) which explained the inheritance of qualitative genetic traits and leading to modern genetics.

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**Dmitri Mendeleev 1834-1907**

Scientist, Chemist, Academic

- 1. During the nineteenth Century, the atom was proposed as the smallest particle in nature. The concept of atomic mass evolved from that (John Dalton 1766-1844)
- 2. By 1870, there was 63 know elements. Chemists were trying to understand their structure by observing their shared properties.
- 3. Mendeleev measured the rates and kinds of chemical reactions in order to identify the relative size of each element (speed of reaction) and groupings (shared kinds of reactions).

(Part 1)

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**Dmitri Mendeleev 1834-1907**

Scientist, Chemist, Academic

- 4. Mendeleev created a chemical taxonomy based on these behaviors: the periodic table which is virtually unchanged today. His table had holes for unidentified elements which he correctly predicted. His principle was named Mendeleev’s Periodic Law.
- 5. No only did his law have predictive values, it prefigured atomic theory which ultimately explains chemical structure and interactions.

(Part 2)

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**Schizophrenia**

- 1. Kraepelin “1885” Dementia Praecox  
Early dementia: A progressive encephalopathy with ongoing cognitive deterioration.
- 2. Bleuler “1908” Schizophrenia  
Splitting of the psychic functions  
Dissociation of thought processes and emotions:  
Abnormal associations  
Autistic behavior and thinking  
Abnormal affect  
Ambivalence

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**What we know about Schizophrenias**

1. Schizophrenia is not a unitary disease:
  - Different clinical presentations
  - Different responses to medications
  - Different outcomes
2. Schizophrenia is a pan-neurological condition affecting cognition, perception, sensory, and motor functions.
3. Amelioration of hallucinations, delusions, disorganized thinking and speech does not cure Schizophrenia. The cognitive damage primarily in areas of recent memory, executive function, associative thinking persist.

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**What we do not know about Schizophrenias**

1. The pathophysiological basis for its myriad manifestation.
2. The mechanism of action of psychopharmacological agents in ameliorating positive symptoms of the condition.
3. How much medication should be given and how often to optimize its efficacy.

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**Schizophrenia is a Cognitive Illness**

1. Kraepelin recognized the cognitive decline in adolescence in early years of the acute period of the condition he called dementia praecox.
2. Bleuler considered positive symptoms of hallucinations and delusions as accessory symptoms. He considered associative difficulties, social isolation (autism), constricted affect, and ambivalence as the core elements he renamed Schizophrenia

(Part 1)

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**Schizophrenia is a Cognitive Illness**

- 3. Ross Baldessarini and others including Dr. Oepen, publishes a landmark meta-analysis of pharmacological the treatment of Schizophrenic patients to achieve a productive life. They concluded that virtually nothing had changed in 100 years.

(Part 2)

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**Khan and Keefe 2013**

- 1. Manifesto: The essence of schizophrenia, which renders its victims incapacitated, “is not its psychiatric symptom”.
- 2. Focus on psychosis is a “conceptual fallacy that has greatly contributed to lack of progress” in the treatment of schizophrenia.
- 3. Cognition should be recognized as the “core component” of schizophrenia.

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**Phenothiazine Compounds**

- 1. Promethazine's, compounds were discovered in the 1930's. They were of interest because they produce effects on experimental animals similar to antihistamines which had also recently been identified.
- 2. Phenothiazine's and antihistamines both cause somnolence, but phenothiazine had the unique property of producing altered state called “artificial hibernation”. The animals receiving phenothiazine's were awake but not normally vigilant or reactive. A limb could be moved about by a person without the animal resisting or pulling back to the limb to its original position.
- 3. Surgeons saw in Phenothiazine an ideal treatment produce somnolence and “ artificial hibernation” to pre-medicate surgical patients prior to anesthetic induction with either which were very unpleasant.

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**What do we know about Antipsychotic Medications?**

1. Improvement in behavior, self-care, disorganized thinking perceptions, delusions.
2. Aggressive administration of antipsychotic medication is necessary to optimize recovery. The longer any patient remains psychotic, the poorer the long-term outcome.
3. Little or no improvement in social functioning, insight, cognition.

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**What do we not know about Antipsychotic Medication?**

1. How do antipsychotic agents work? How do they affect thoughts, emotions and behavior?
2. Why do patients respond so unpredictably to antipsychotic medications? Some do well on different medications. Some do well on just one. Some do not do well on any of the numerous medications now available.
3. What do these observations tell us about Schizophrenia?
4. When does antipsychotic medication begin to work and how frequently do we need to give it?
5. What is the minimum effective medication to give if we are not certain of the onset of active of the medication?

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**What have we learned about these Antipsychotic Agents?**

Prolonged dopamine blockade is neurotoxic.

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1. Gur RE, Cowell P, Turetsky BI, Gallacher F, Cannon T, Bilker W, and Gur RC. A follow-up magnetic resonance imaging study of schizophrenia: Relationship of neuroanatomical change to clinical and neurobehavioral measures.  
**Archives General Psychiatry** 1998; 55:145-152
2. Lieberman JA, Tollefson GD, Charles C, Zipursky R, Sharma T, Khan RS, Keefe, RSE, Green AI, Gur RE, McEvoy J, Perkins D, Hamer RM, Gu H, and Tohen M. Antipsychotic drug effects on brain morphology in first-episode psychosis.  
**Archives General Psychiatry** 2005; 62:361-370.
3. Konopaska GT, Dorph-Petersen, KA, Pieri, JN, Wu Q, Sampson AR, and Lewis DA. Effect of chronic exposure to antipsychotic medication on cell numbers in the parietal cortex of macaque monkeys.  
**Neuropsychopharmacology** 2007; 32:1216-1223.

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**Wunderlink et al. (2013)**

- 257 First episode psychotic patients evaluated (Dx of schizophrenia, schizoaffective d/o)
- All treated for 6 months after achieving clinical stabilization.
- 128 Agreed to be randomized to either a MT regimen ( as they had been on for 6 months) or DR regimen (reduced medication or discontinuation).
- Followed for 7 years
- 111 Patients located
- Social function by a standardized instrument evaluating performance, family relations, romance, etc.
- MT patients performed at a level of 17.6 % normal
- DR patients performed at a level of 40.47% normal

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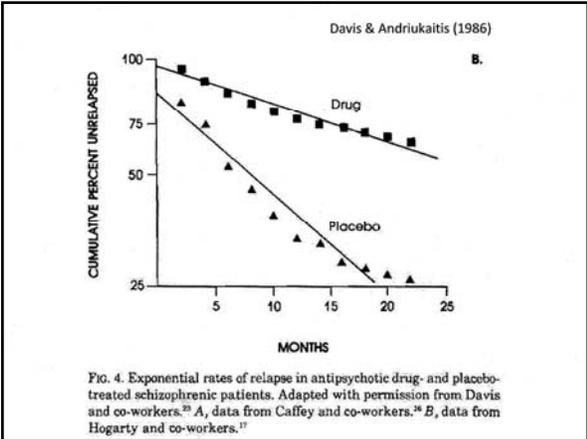
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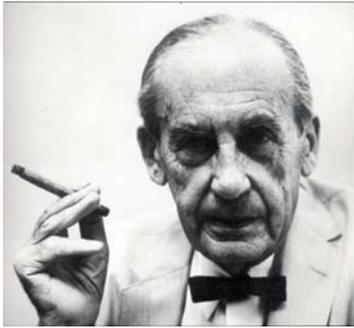
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“Architecture begins where engineering ends.”

Walter Gropius

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The Bauhaus in Dessau, 1925

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The Gropius House, Lincoln, Mass, 1938

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Ludwig Mies Van Der Rohe  
"Less is more"

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Lake Shore Drive Apartments, 1951

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Crown Hall, 1956

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Lake Point Tower, 1968

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Lake Point Tower, 1968

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McCormick Place, 1971

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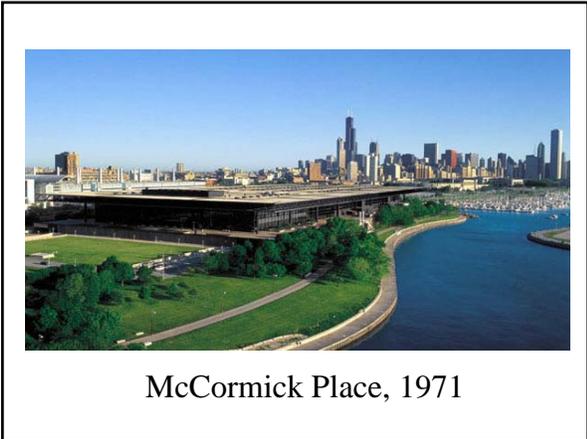
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