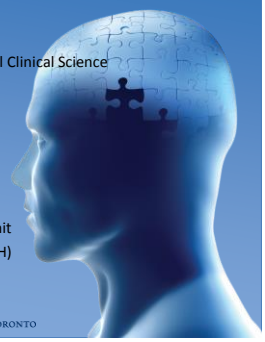
10 Things I've Learned About Schizophrenia

Gary Remington, MD, PhD, FRCPC
Schizophrenia Lead
Division of Brain & Therapeutics
Departments of Psychiatry and Psychological Clinical Science
Institute of Medical Science
School of Graduate Studies
University of Toronto

Chief, Schizophrenia Division
Lead, Subspecialty Clinics
Campbell Family Mental Health Research Unit
Centre for Addiction & Mental Health (CAMH)



camh Schizophrenia Division Complex Mental Illness Program | Psychiatry UNIVERSITY OF TORONTO

Financial Disclosure (2 Years)

Industry

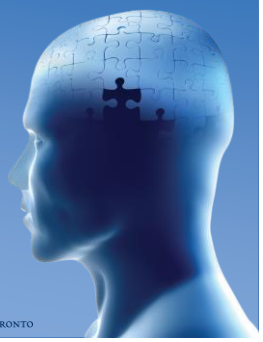
Consultant
Neurocrine Biosciences
Synchroneuron

Research
Novartis

Granting Agencies (PI)

Canadian Institutes of Health Research (CIHR)

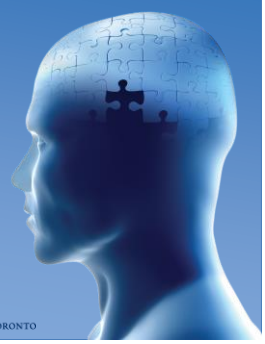
Research Hospital Fund – Canada Foundation for Innovation (RHF-CFI)



camh Schizophrenia Division Complex Mental Illness Program | Psychiatry UNIVERSITY OF TORONTO

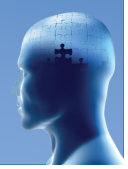
Learning Objectives

To consolidate and review some of the more substantial changes in terms of how we conceptualize schizophrenia.



camh Schizophrenia Division Complex Mental Illness Program | Psychiatry UNIVERSITY OF TORONTO

1. D_2 antagonism is necessary (mostly), but not sufficient, for the treatment of the illness' psychosis domain



Classification of Antipsychotics

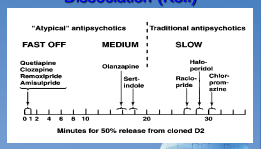
First Generation
D_2 Antagonism
Low Potency
Chlorpromazine
Thioridazine
Mesoridazine
etc
High Potency
Haloperidol
Fluphenazine
Pimozide
etc

Second Generation
5-HT_2/D_2 Antagonism
Asenapine
Clozapine
Lurasidone
Olanzapine
Quetiapine
Risperidone
Sertindole
Ziprasidone
Zotepine

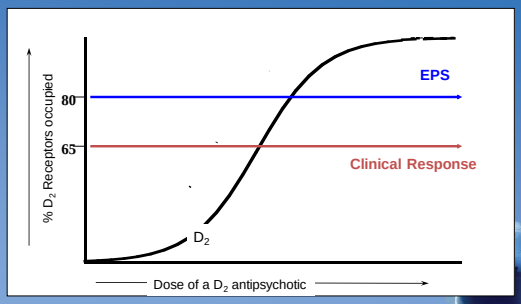
Amisulpride
Sulpiride
Remoxipride

Third Generation
Partial Dopamine Agonism
Aripiprazole

Dissociation (Koff)

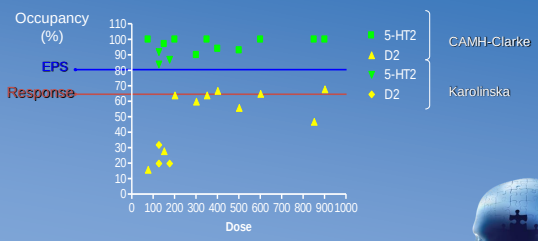


D_2 Occupancy, Clinical Response & EPS



Kapur S, Remington G. Am J Psychiatry 1996

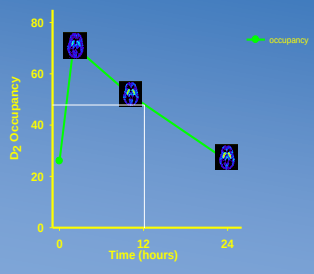
Clozapine: Concomitant 5-HT_2/D_2 Antagonism



Nordstrom et al. Am J Psychiatry 1995; 152:1444-1449
Kapur et al. Am J Psychiatry 1999; 156:286-293

Brain Kinetics of Clozapine on D2 Receptors

Time course of D_2 occupancy in a patient taking 350 mg/hs.



"Extended" Antipsychotic Dosing in the Maintenance Treatment of Schizophrenia: A Double-Blind, Placebo-Controlled Trial

Gary Remington, MD, PhD, FRCPC; Philip Seeman, MD, PhD, FRCS; Alan Feingold, PhD; Steve Mann, BA, MSc; Chekkera Shammi, MBBS, DPM, MRCPsych, FRCPC; and Shitij Kapur, MBBS, PhD, FRCPC

J Clin Psychiatry 2011

Antipsychotic Dosing: Extended, and Transient

Philip Seeman [1], Gary Remington [1, 2, 3]

Clin Schizophr Relat Psychoses 2012

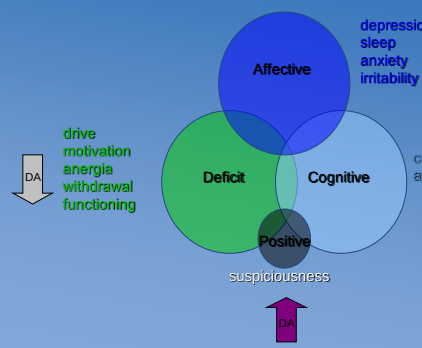
2. Schizophrenia is *not* a disorder of too much dopamine.

Prodrome: Most Common Features

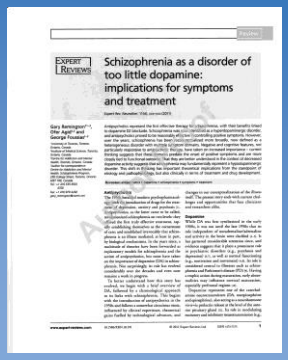
- decreased concentration, attention
- decreased drive, motivation; anergia
- depression
- sleep disturbance
- anxiety
- social withdrawal
- suspiciousness
- deteriorated social functioning
- irritability

Yung & McGorry. Schizophr Bull 1996; 22:353-370

Prodromal Symptoms



Revisiting the Role of Dopamine



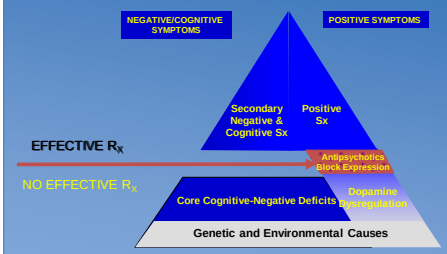
EXPERT REVIEWS

Schizophrenia as a disorder of too little dopamine: implications for symptoms and treatment

Gary Remington*[1], Ofer Agid[2] and George Foussias[3]

3. First episode psychosis represents the end of the illness

Linking Pathophysiology to Therapeutics: A Pragmatic Model

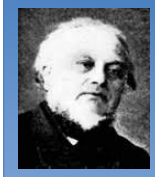


Kapur & Remington, Annual Review of Medicine, 2000

4. Schizophrenia is both neurodevelopmental and neuropgrogressive

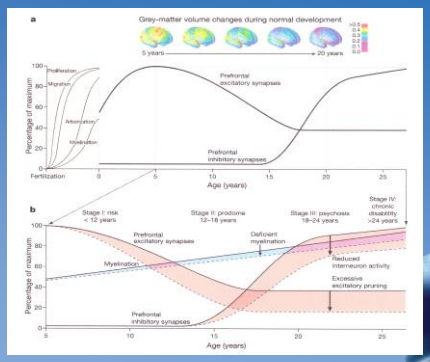
Early Influences

Morel (1853)



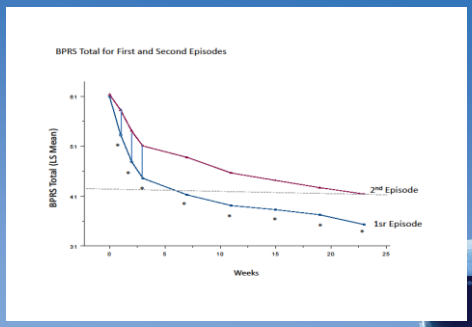
Kraepelin (1896)

Neurodevelopmental vs. Neuroprogressive

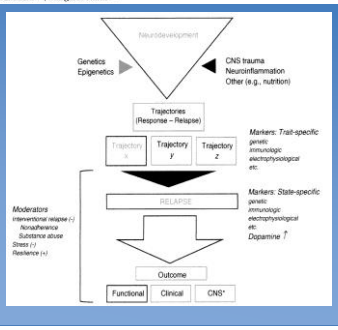


Insel TR. Nature 2011; 468:187-193

Antipsychotic Re-challenge



Responsive to first AP trial and restarted on same medication at same dose (N=38)



Heterogeneity: Outcome

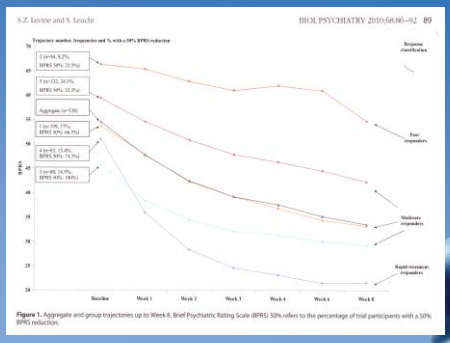


Figure 1. Aggregate and group trajectories up to Week 8. Brief Psychiatric Rating Scale (BPRS) 50% refers to the percentage of trial participants with a 50% BPRS reduction.

Levine S.Z. & Leucht S. Biol Psychiatry 2010; 68:86-92

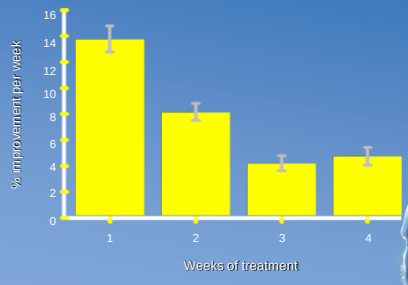
5. Antipsychotics act sooner than later

Antipsychotic Depolarization Block

…antipsychotics must be administered repeatedly to schizophrenics before therapeutic benefits are produced...chronic antipsychotic drug treatment results in the time-dependent inactivation of dopamine neuron firing via over-excitation, or depolarization block.

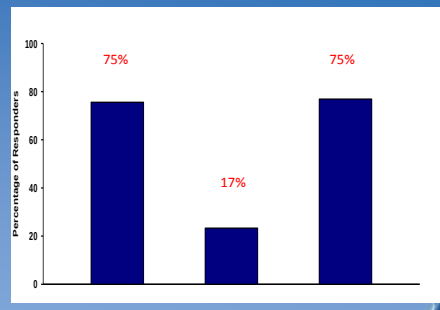
Grace A. J Neural Transm 1992

Weekly BPRS/PANSS Improvement



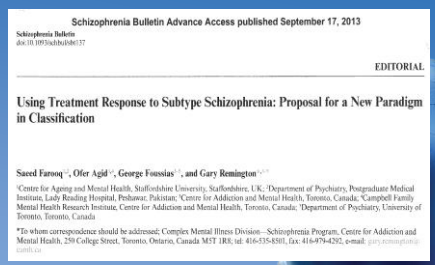
Agid et al. Archives of General Psychiatry 2003

6. Schizophrenia is characterized by subtypes mediated by different mechanisms



Agid et al. J Clin Psychopharmacol 2011

Treatment Response to Subtype Schizophrenia



Schizophrenia Bulletin Advance Access published September 17, 2013

Schizophrenia Bulletin
doi:10.1093/schbul/sbt137

EDITORIAL

Using Treatment Response to Subtype Schizophrenia: Proposal for a New Paradigm in Classification

Saeed Farooq[1,2], Ofer Agid[3,4], George Foussias[3,5], and Gary Remington[3,4,*]

[1]Centre for Ageing and Mental Health, Staffordshire University, Staffordshire, UK; [2]Department of Psychiatry, Postgraduate Medical Institute, Lady Reading Hospital, Peshawar, Pakistan; [3]Centre for Addiction and Mental Health, Toronto, Canada; [4]Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, Toronto, Canada; [5]Department of Psychiatry, University of Toronto, Toronto, Canada

*To whom correspondence should be addressed; Complex Mental Illness Division—Schizophrenia Program, Centre for Addiction and Mental Health, 250 College Street, Toronto, Ontario, Canada M5T 1R8; tel: 416-535-8501, fax: 416-979-4292, e-mail: gary.remington@camh.ca

Three Subtypes of Schizophrenia

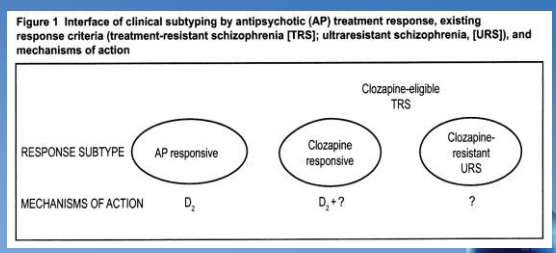


Figure 1 Interface of clinical subtyping by antipsychotic (AP) treatment response, existing response criteria (treatment-resistant schizophrenia [TRS]; ultraresistant schizophrenia, [URS]), and mechanisms of action

Lee J et al. Can J Psychiatry 2015

7. Treatment resistance has at least 2 forms

Subtyping Schizophrenia

Treatment-Resistant ⟹ Ultra-Resistant

Table 1. TRS criteria

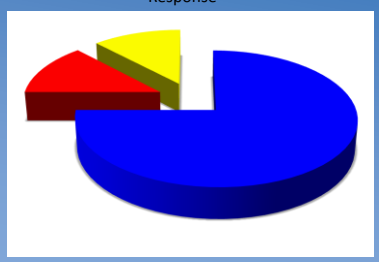
Kane et al. [1] (1988)	Conley et al. [2] (2001)	Mouaffak et al. [3] (2006)
3 antipsychotic trials in last 5 years from at least 2 different chemical classes without significant symptomatic relief (≥1,000 CPZ mg equivalents/day × 6 weeks); no period of good functioning in 5 years	2 antipsychotic trials with no clinical improvement (400–600 CPZ mg equivalents/day × 4–6 weeks); no period of good social or occupational functioning for >5 years; BPRS total score >45 (18-item scale) and score >4 on 2 of 4 positive symptom items	clozapine trial ≥8 weeks; plasma level >350 µg/l and BPRS improvement <20%; no stable period of good social and/or occupational functioning ≥5 years and GAF ≤40; BPRS total score ≥45, CGI score >4, and score ≥4 on 2 of 4 positive symptom items

CPZ = Chlorpromazine; BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impression Scale; GAF = Global Assessment of Functioning Scale.

Remington G. In: Elkis H, Meltzer HY: Therapy-Resistant Schizophrenia, 2010

Antipsychotic Responsive, Clozapine Responsive, Clozapine Resistant

Response



Treatment-Resistant Schizophrenia (TRS) or Clozapine-Eligible Schizophrenia

Table 1 Comparison of published criteria for treatment resistance in schizophrenia with proposed criteria for clozapine eligibility

Published criteria	Ifil et al[2]	Brenner et al[6]	Kane et al[8]	Conley and Kelly[9,10]	Suzuki et al[1]	Proposed criteria for clozapine eligibility
Number of AP trials	Not mentioned	3 (different chemical classes)	3 (2 different chemical classes)	2	2	2
Adequate dose, CPZeq	600 mg or Trifluoperazine 60 mg	≥1000 mg	≥1000 mg	400 to 600 mg	≥600 mg	Upper half of the recommended dosing range[a]
Adequate duration, weeks	24	6	6	4 to 6	6	6, at adequate dose
No significant improvement	Not mentioned	Not mentioned	<20% decrease on BPRS, and either CGI-S ≥ 4 or BPRS ≥ 45	No clinical improvement	CGI-I ≥ 3, or <20 point increase in GAF and FACT-Sz, or <20% decrease of BPRS and PANSS	CGI-SCH positive change >2 (2 = much improved)[b]
Current illness severity	Active psychotic symptoms	Persistent positive and negative symptoms; disability in social, self-care, and occupational domains	BPRS ≥ 45, and CGI-S ≥ 4, and ≥4 on at least 2 out of 4 positive items	BPRS > 45, and CGI-S > 4, and >4 on at least 2 out of 4 positive items	CGI-S ≥ 4, and FACT-Sz ≤ 49 or GAF ≤ 50	CGI-SCH positive ≥ 4 (4 = moderately ill)[c]
Duration of illness with poor functioning, years	2	2	5	5	Not mentioned	

AP = antipsychotic; BPRS = Brief Psychiatric Rating Scale; CGI-S = Clinical Global Impression–Severity; CGI-SCH = Clinical Global Impression–Schizophrenia; CPZeq = chlorpromazine equivalents; GAF = Global Assessment of Functioning; FACT-Sz = Functional Assessment for Comprehensive Treatment of Schizophrenia; PANSS = Positive and Negative Syndrome Scale

[a] Chosen as option based on lack of empiric evidence for establishing dose equivalents[81–83]

[b] A CGI-SCH positive change score of 2 = Notably better with significant reduction of symptoms, but some symptoms remain; increase in the level of functioning.[84]

[c] A CGI-SCH positive symptom score of 4 = Some prominent symptoms with some interference in the level of daily functioning.[85]

Lee J et al. Can J Psychiatry 2015

Ultraresistant Schizophrenia (URS) or Clozapine-Resistant Schizophrenia

Table 2 Comparison of published and proposed criteria for clozapine resistance in schizophrenia

Published criteria	Mouaffak et al[25]	Proposed criteria for clozapine resistance
Adequate dose	Plasma levels > 350 ng/mL	Plasma levels[a] ≥ 350 ng/mL for once a day dosing; ≥ 250 ng/mL for equal divided dosing, or oral dose ≥ 400 mg a day[b]
Adequate duration, weeks	8	8, at adequate dose[c]
No significant improvement	<20% decrease on BPRS	CGI-SCH positive change > 2 (2 = much improved)
Current illness severity	BPRS ≥ 45, CGI-S ≥ 4, and ≥ 4 on at least 2 out of 4 positive items on the BPRS	CGI-SCH positive ≥ 4 (4 = moderately ill)
Duration of illness with no good functioning, years	5	

BPRS = Brief Psychiatric Rating Scale; CGI-S = Clinical Global Impression–Severity; CGI-SCH = Clinical Global Impression–Schizophrenia

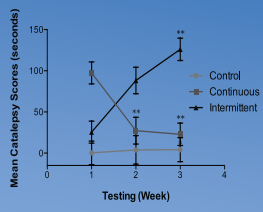
[a] Plasma levels should be taken after 5 days of unchanged clozapine dosing and 12 hours from last clozapine dose.

[b] A daily clozapine dose of 400 mg has been shown to achieve a threshold of 350 ng/mL in various trials, and lies within the dose range advocated for by a field of experts for acute and maintenance treatment.[64–66]

[c] A study identified all clozapine responders within 8 weeks of a change in dose, indicating no increased benefits with continuing people on a particular dose longer to establish benefits.[67]

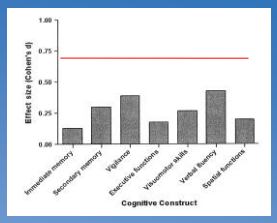
Lee J et al. Can J Psychiatry 2015

Tolerance



8. There are no effective treatments for cognitive and negative symptoms

Cognition in Schizophrenia

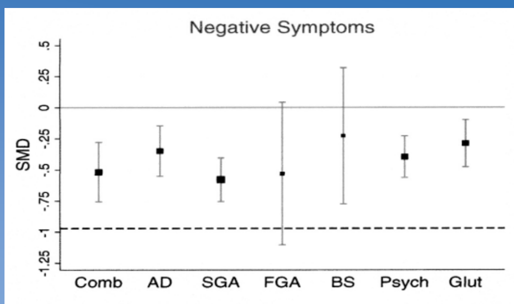


Harvey & Keefe. AJP, 2001
Hagan & Jones. Schizophr Bull 2005

"the advantages for these newer medications [second generation antipsychotics] may h
been overestimated…although there is some evidence that newer antipsychotics are m
effective for improving cognition, it is unclear that this advantage is sufficient to affect
functional outcomes."

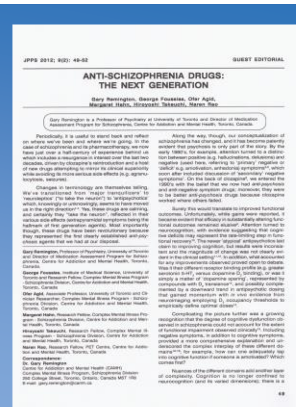
Marder. J Clin Psychiatry 2006

Negative Symptoms: Treatment



Comb – Combination; AD – Antidepressants; SGA – Second Generation Antipsychotics; FGA – First Generation Antipsychotics; BS – Brain Stimulation; Psych – Psychological; Glut – Glutamatergic agents

Fusar-Poli P et al. Schizophr Bull 2015



JPPS 2012; 9(2): 49-52 GUEST EDITORIAL

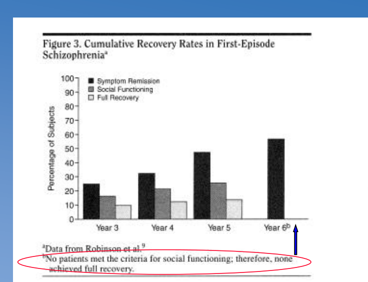
ANTI-SCHIZOPHRENIA DRUGS: THE NEXT GENERATION

Gary Remington, George Foussias, Ofer Agid, Margaret Hahn, Hiroyoshi Takeuchi, Naren Rao

Gary Remington is a Professor of Psychiatry at University of Toronto and Director of Medication Assessment Program for Schizophrenia, Centre for Addiction and Mental Health, Toronto, Canada.

9. Clinical and functional recovery are not parallel events

Symptomatic vs Functional Outcome



*Social/Vocational functioning = appropriate role functioning as a worker, homemaker, or student

Robinson et al. Am J Psychiatry 2004
Schooler J Clin Psychiatry 2006

Clozapine and Functional Outcome

European Neuropsychopharmacology (2014) 24, 1622–1629

ELSEVIER

www.elsevier.com/locate/euroneuro

Relationship between clinical improvement and functional gains with clozapine in schizophrenia

Jimmy Lee[a,b,c,*], Hiroyoshi Takeuchi[c,d], Gagan Fervaha[c,e], Amaal Bhaloo[c], Valerie Powell[c], Gary Remington[c,e,f]

Negative Symptoms and Functional Recovery

Schizophrenia Bulletin Advance Access published July 21, 2006

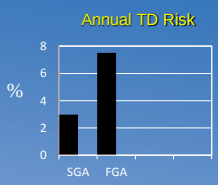
Negative Symptoms in Schizophrenia: Avolition and Occam's Razor

10. Amongst well established side effects….

All antipsychotics are at risk of TD, regardless of drug choice of dose

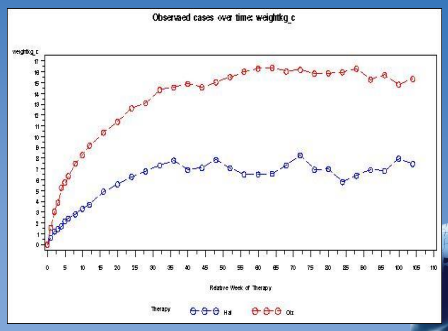
Tardive dyskinesia: eliminated, forgotten, or overshadowed?

Gary Remington



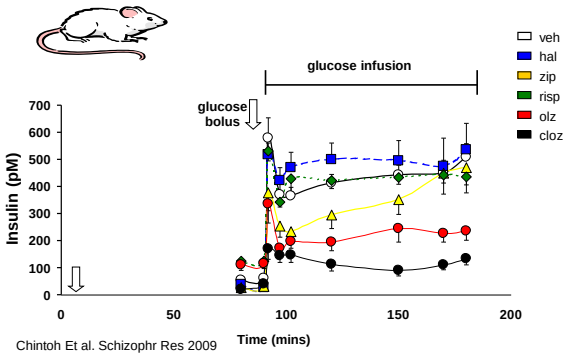
Correll C. Curr Opin Psychiatry 2008

Conventional antipsychotics also carry substantial metabolic risk



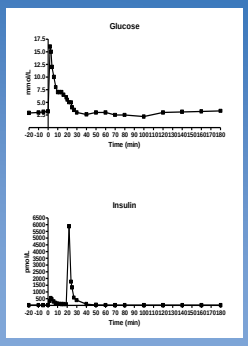
Zipursky et al. Br J Psychiatry 2005

Glucose dysregulation is multi-factorial and, in part, independent of weight



Chintoh Et al. Schizophr Res 2009

FSIGTT and Bergmann's Minimal Model



- Overnight fast
- Glucose and insulin sampled at –20, -10 and –5 min
- Bolus of 50% glucose IV at 0 min
- IV insulin at 20 mins.
- Glucose and insulin sampled via indwelling catheter at 2,3,4,6,8,10, 12,14,16,19,22,24,25,27,30,40,50,60,70 ,80,100,120,140,160,180 mins.
- Computer analysis of glucose disappearance and insulin kinetics
- Measure of insulin sensitivity (SI) and Acute Insulin Response to Glucose (AIRG)

Cohn et al. Can J Psychiatry 2006

Atypical antipsychotics and diabetic ketoacidosis: a review

And the good news….

- Numerous new doors open (e.g. TRS/URS, different symptom domains)
- Personalized medicine