New Developments in the Pharmacological Therapy of Schizophrenia

Peter de Boer, PhD
Senior Director Experimental Medicine
Janssen Research and Development

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Terminology

- Category: An ICD-10/DSM-IV diagnosis (e.g., schizophrenia, schizoaffective disorder, schizotypal personality disorder);
- Dimension: A symptom or symptom cluster that occurs throughout the population and that, if of sufficient intensity, may lead to a categorical diagnosis (e.g., aberrant sensory experiences);
- Symptom: A characteristic sign (e.g., a delusion, avolition);
- Target: A biological process affected by a drug.

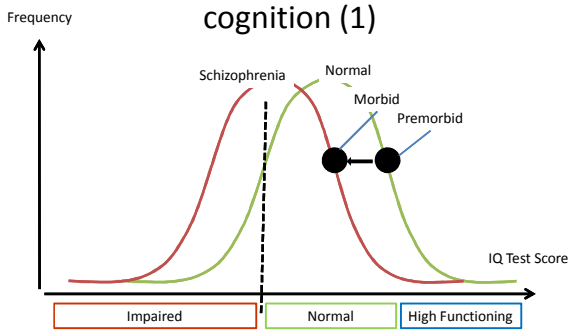
Drug Development

1. Drug development is for a well-accepted and demarcated indication that will become part of the product label (rather than for a symptom – family of symptoms);
2. Symptoms may overlap between disease categories. It is acceptable to develop multiple indications but it is generally not acceptable to develop symptom-specific therapies.

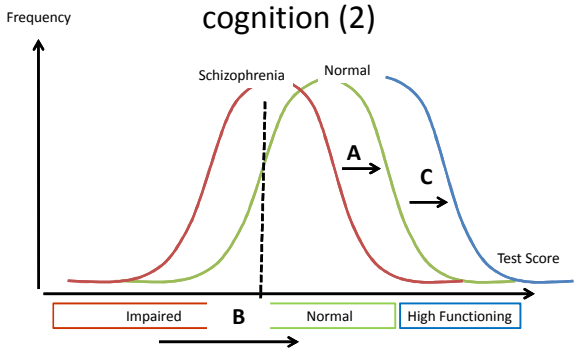
Section 1

WHY CATEGORIES RATHER THAN DIMENSIONS?

Schizophrenia as a disorder of cognition (1)



Schizophrenia as a disorder of cognition (2)



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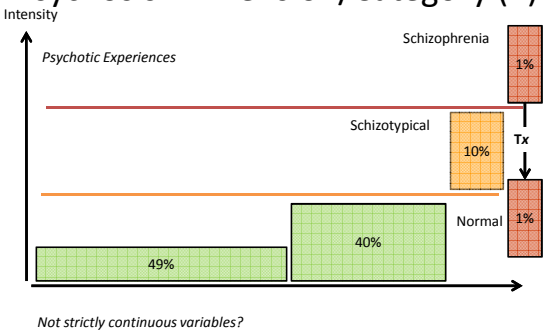
Psychosis: Dimension/Category (2)



Not strictly continuous variables?

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Schizophrenia as a disorder of cognition - issues

1. Cognition is a non-specific term; impaired cognitive performance may have diverse causes (= pseudo continuous);
2. Although schizophrenia may be within the family of 'cognitive disorders' this does not help with identifying it as a diagnostic entity;
3. Issues may exist in identifying the right target population to treat.

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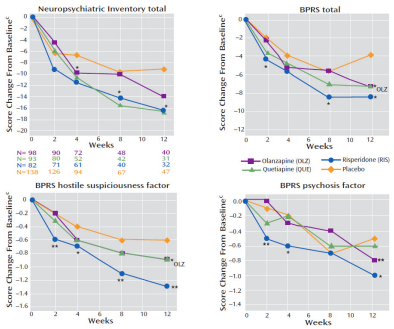
Psychosis in dementia



Sultzer et al., 2008 Am J Psychiatry 165: 844 – 854

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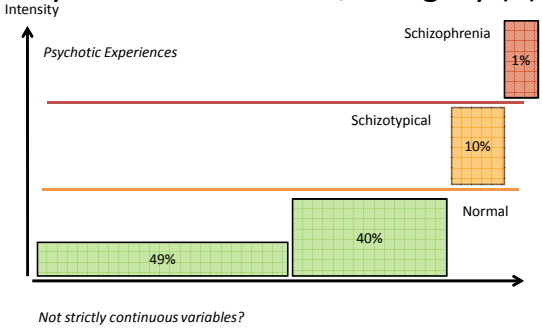
Psychosis: Dimension/Category (1)



Not strictly continuous variables?

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No dopaminergic dysfunction in AD

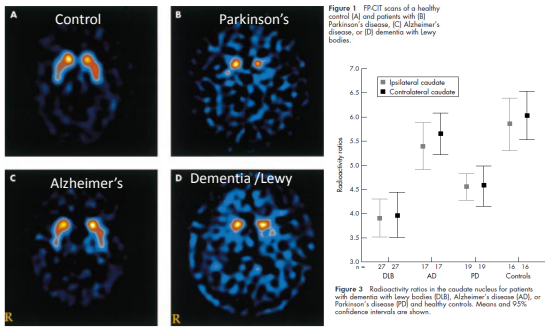

Figure 1 FP-CIT scans of a healthy control (A) and patients with (B) Parkinson's disease, (C) Alzheimer's disease, or (D) dementia with Lewy bodies.

Figure 2 Radioactivity ratios in the caudate nucleus for patients with dementia with Lewy bodies (DLB), Alzheimer's disease (AD), or Parkinson's disease (PD) and healthy controls. Means and 95% confidence intervals are shown.

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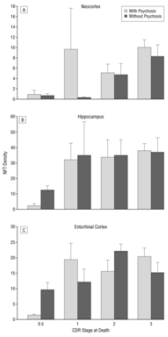
But psychosis in AD may be related to neocortical density of neurofibrillary tangles



Neurofibrillary tangle density densities in individuals with versus without psychosis by brain region (density ± SD [No / mm2])

Brain region	with psychosis	w/o psychosis	*P*
Middle frontal cortex	7.9 (9.7)	2.8 (5.5)	.01
Superior temporal cortex	11.9 (15.2)	5.2 (7.9)	.008
Inferior parietal cortex	7.4 (10.0)	4.0 (7.4)	.006
Hippocampus	36.0 (32.6)	26.7 (28.7)	.5
Entorhinal cortex	19.3 (18.0)	14.1 (10.1)	.3

Farber et al. Arch Gen Psychiatry. 2000;57(12):1165-1173.

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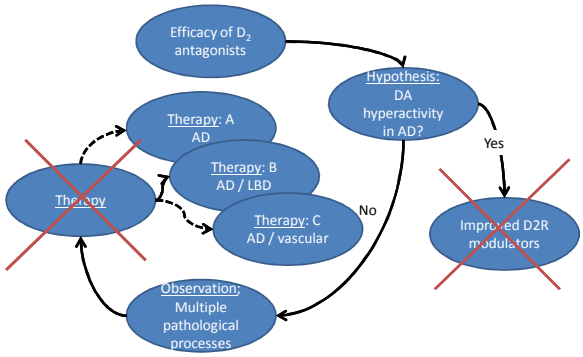
Implication?



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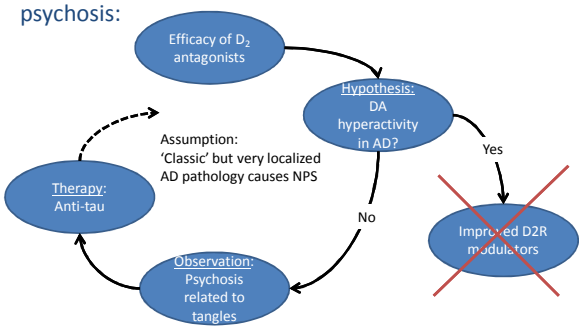
A drug development paradigm based on 'understanding' pathophysiological drivers for psychosis:



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Risperidone in neuropsychiatric symptom clusters in dementia

Efficacy Variables	BPSD population					PAD pop.
	RIS-USA-63		RIS-INT-24		RIS-AUS-5	RIS-USA-232
	1 mg	2 mg	Ris	Hal		
Behave-AD						
Psychotic Agitation(1)	***	***	-	**	***	-
Psychosis(2)	**	*	-	+	**	-
Agitation(3)	***	***	*	***	***	-
CMAI						
Total Aggression	***	***	**	+	***	NA
Total Non-Aggression	*	**	-	-	**	NA
Total	***	***	+	-	***	NA

BEHAVE-AD: Behavioral Pathology in Alzheimer's Disease
CMAI: Cohen Mansfield Agitation Inventory

+: 0.05 <p<0.1, after adjusting for multiplicity, as appropriate
**: p≤0.05*
***: p≤0.01*
****: p<0.001*
-: Not significant at 5% level

(1) Subscales A+B+C+D
(2) Subscales A+B
(3) Subscales C+D

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A clinical phenotype of dementia may result from multiple co-existing pathological processes

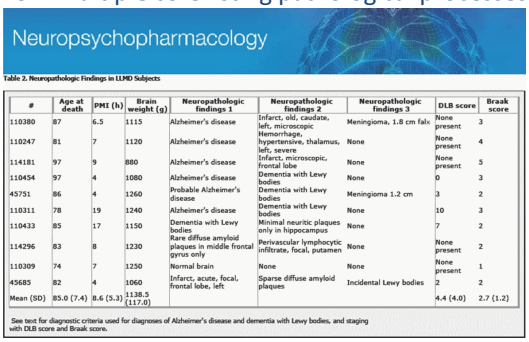

Table 2. Neuropathologic Findings in LLMD Subjects

#	Age at death	PMI (h)	Brain weight (g)	Neuropathologic findings 1	Neuropathologic findings 2	Neuropathologic findings 3	DLB score	Braak score
110380	87	6.5	1115	Alzheimer's disease	Infarct, old, caudate, left, microscopic	Meningioma, 1.8 cm falx	None present	3
110247	81	7	1120	Alzheimer's disease	Hemorrhage, hypertensive, thalamus, left, severe	None	None present	4
114181	97	9	880	Alzheimer's disease	Infarct, microscopic, frontal lobe	None	None present	5
110454	97	4	1080	Alzheimer's disease	Dementia with Lewy bodies	None	0	3
45751	86	4	1260	Probable Alzheimer's disease	Dementia with Lewy bodies	Meningioma 1.2 cm	3	2
110311	78	19	1240	Alzheimer's disease	Dementia with Lewy bodies	None	10	3
110433	85	17	1150	Dementia with Lewy bodies	Minimal neuritic plaques only in hippocampus	None	7	2
114296	83	8	1230	Rare diffuse amyloid plaques in middle frontal gyrus only	Perivascular lymphocytic infiltrate, focal, putamen	None	None present	2
110309	74	7	1250	Normal brain	None	None	None present	1
45685	82	4	1060	Infarct, acute, focal, frontal lobe, left	Sparse diffuse amyloid plaques	Incidental Lewy bodies	2	2
Mean (SD)	85.0 (7.4)	8.6 (5.3)	1138.5 (117.0)				4.4 (4.0)	2.7 (1.2)

See text for diagnostic criteria used for diagnoses of Alzheimer's disease and dementia with Lewy bodies, and staging with DLB score and Braak score.

Sweet et al 2004 Neuropsychopharmacology 29 2242 – 2250

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Psychosis: Dimension or Category - conclusions

1. Psychosis as a phenomenon is common in the general population;
2. However, the underlying causes of psychotic experiences are diverse (see example dementia);
3. Hence, the efficacy of a drug against a symptom / symptom cluster in a specific diagnostic category cannot be extrapolated to another diagnostic category without proof.

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Section 3

REVIEW OF PROJECTS

Preclinical

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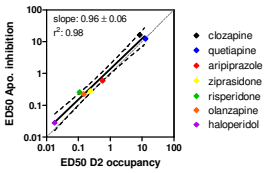
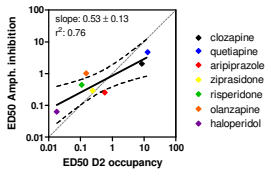
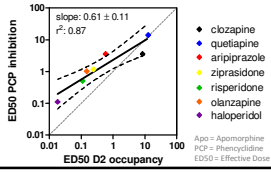
Correlation D2 occupancy / inhibition of apomorphine-induced stereotypy



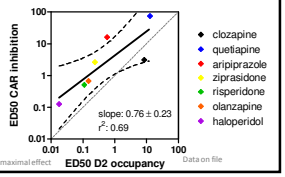
Correlation D2 occupancy / inhibition of amphetamine-induced hyperlocomotion



Correlation D2 occupancy / inhibition of PCP-induced hyperlocomotion



Correlation D2 occupancy / inhibition of conditioned avoidance response



Apo = Apomorphine
PCP = Phencyclidine
ED50 = Effective Dose for 50% of maximal effect

Data on file

Psychiatry, The Pharmaceutical Industry, and The Road to Better Therapeutics

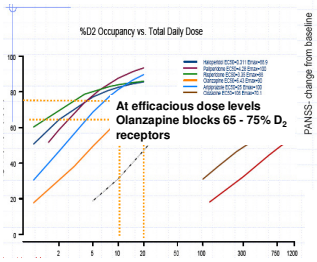
H. Christian Fibiger*
Department of Psychiatry, University of British Columbia, Vancouver, B.C., Canada
*To whom correspondence should be addressed; tel: 250-764-4677, fax: 250-764-4933, e-mail: hcfibiger1@mac.com

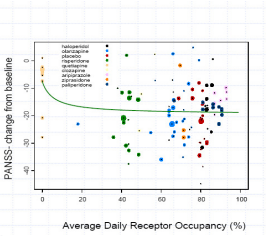
Psychopharmacology is in crisis. The data are in, and it is clear that a massive experiment has failed: despite decades of research and billions of dollars invested, not a single mechanistically novel drug has reached the psychiatric market in more than 30 years. Indeed, despite enormous effort, the field has not been able to escape the "me too/me (questionably) better" straightjacket. In recent years, the appreciation of this reality has had profound consequences for innovation in psychopharmacology because nearly every major pharmaceutical company has either reduced greatly or abandoned research and development of mechanistically novel psychiatric drugs.

The discovery of all three major classes of psychiatric drugs, antidepressants, antipsychotics, and anxiolytics, came about on the basis of serendipitous clinical observation. At the time of their discoveries, the mechanisms by which these molecules produce their effects were unknown, and it was only later that antipsychotics were shown to be D2 receptor antagonists.

For example, what genetic or preclinical data exist that point to the D2 dopamine receptor as a likely target for antipsychotic activity? Presently there are no genetic data that suggest that this receptor is expressed or functions abnormally in psychotic disorders. And without the benefit of the prior clinical validation, it is difficult to see how preclinical data alone would point to the D2 receptor as an interesting potential target for the treatment of psychotic disorders.

Clinical





DA-related – some beliefs.

1. All currently used antipsychotic medications are dopamine D_2 antagonists / weak partial agonists;
2. Dopamine systems are well characterized and > 50 years of model development is available to support drug development;
3. Hence, demonstration of efficacy of a novel drug in a model of dopamine hyperactivity has strong predictive validity for clinical efficacy.

Compound Characterization

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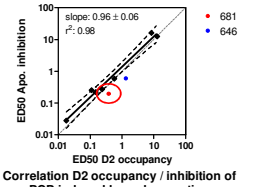
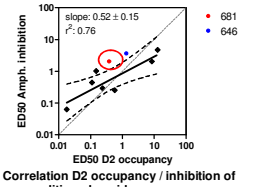
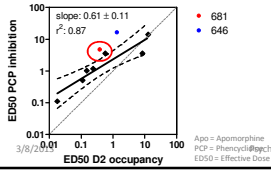
Correlation D2 occupancy / inhibition of apomorphine-induced stereotypy



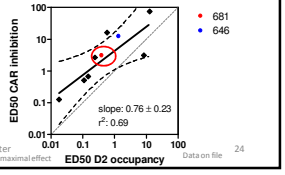
Correlation D2 occupancy / inhibition of amphetamine-induced hyperlocomotion



Correlation D2 occupancy / inhibition of PCP-induced hyperlocomotion



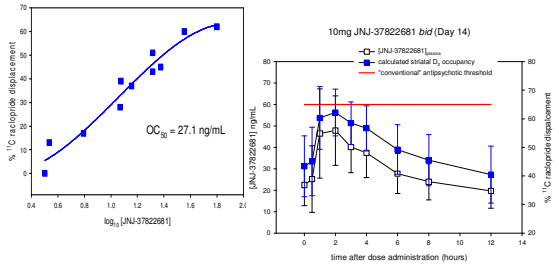
Correlation D2 occupancy / inhibition of conditioned avoidance response



Apo = Apomorphine
PCP = Phencyclidine
ED50 = Effective Dose for 50% of maximal effect

Data on file

Clinical pharmacology



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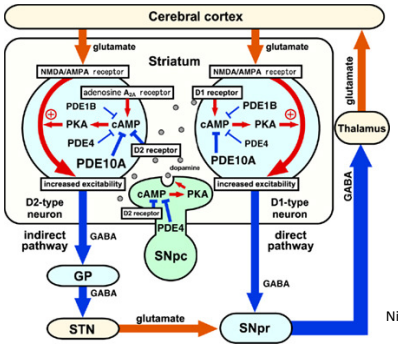
PDE10 inhibitor



In striatum:

D1 agonist
D2 antagonist

Nishi et al., 2011

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Number of subjects included in each treatment group, completers and striatal receptor occupancy throughout the dosing interval as measured with ^{11}C raclopride PET.

Treatment (n) *bid*	Completers (%)	Minimum D_2 occupancy (%)	Maximum D_2 occupancy (%)
Placebo (24)	100	-	-
10mg JNJ-37822681 (16)	100	43.1 ± 11.2	64.1 ± 11.8
20mg JNJ-37822681 (16)	62.5	67.9 ± 6.4	80.7 ± 4.7
30mg JNJ-37822681 (8)	62.5	71.2 ± 3.0	86.7 ± 2.42

The 20 mg *bid* dose was predicted to provide optimal D2 occupancy in time for an antipsychotic effect while the 10 and 30 mg *bid* doses are too low and high, respectively.

3/8/2013 Psychosis Cluster Data on file 26

In vivo, PDE10 inhibitors have a (somewhat) different behavioral profile compared to a D_2 antagonist

Test (acute)	PDE10 inhibitor	D_2 antagonist
Target occupancy (rat striatum)	ED_{50} 1.4 mg/kg *po* (*ex vivo*) (662 ng/mL plasma)	ED_{50} 0.39 mg/kg *sc* (*in vivo*) and 6.26 mg/kg *sc* (*ex vivo*)
↓ 1mg/kg APO-stereotypy (rat)	ED_{50} 1.3 mg/kg *po*	ED_{50} 0.194 mg/kg *po*
↓ 5mg/kg AMPH-stereotypy (rat)	ED_{50} 0.67 mg/kg *sc*	ED_{50} 0.294 mg/kg *sc*
↓ 1.25 mg/kg AMPH-hyperlocomotion (rat)	ED_{50} 8.2 mg/kg *sc* (0.25)	ED_{50} 1.02 mg/kg *sc* (4.6)
↓ 1.25 mg/kg PCP-hyperlocomotion	ED_{50} 2.04 mg/kg *sc* (0.25)	ED_{50} 4.7 mg/kg *sc* (4.6)
DA cell firing SN	No effect on # neurons/tract ↑ spike frequency	Haloperidol: ↓ # neurons/tract
Ro-4-1284-induced hypolocomotion	Reversal: ED_{50} = 2.69 mg/kg *sc* [stimulant activity @ 3.1]	No reversal
Haloperidol-induced catalepsy	Reversal: ED_{50} = 8.2 mg/kg *sc*	*Not done*

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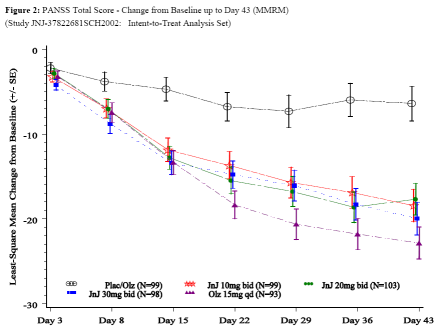
Clinical improvement over time



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Similarly, in sub-chronic drug safety studies different behavioral profiles are observed

Species	Dose	PDE10 inhibitor	D_2 antagonist
Rat – 4wk GLP	L	---	
	M	NOAEL	↓ general activity, narrowing palpebral fissure (sedation)
	H	*No behavioral toxicities*	See above but more intense
Dog – 2wk Non GLP		↓ general activity, ataxia, tremors, catalepsy, yelping, biting	*Not done*
Monkey – 5wk GLP	L (< IC50)	NOAEL	Sleepiness
	M (IC50-2x IC50)	↓ activity, hunched appearance, lethargy, staring, aggression, self-biting, abnormal posture, tremors	Excessive sleepiness, decrease in movement, trance-like state, staring, tremors
	H (10x IC50)	See above + self-mutilation (1M)	See above but more intense

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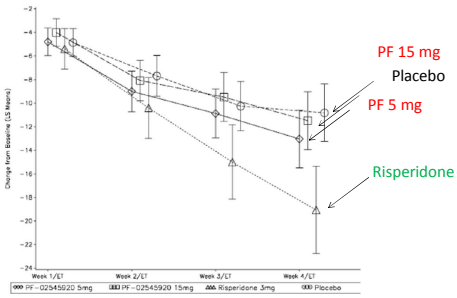
Primary Efficacy Results

Efficacy on the change from baseline on the PANSS total score was significantly greater for RIS vs. placebo, but not for either PF-02545920 group



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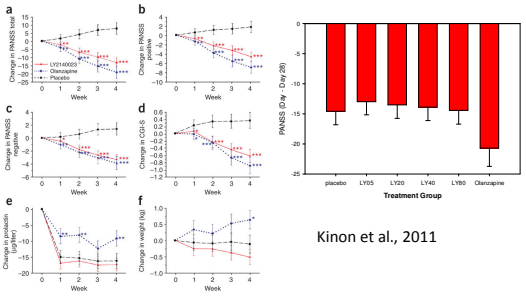
Clinical Effect mGlu2/3 Agonist (Acute Schizophrenia)



Kinon et al., 2011

Patil et al., 2007

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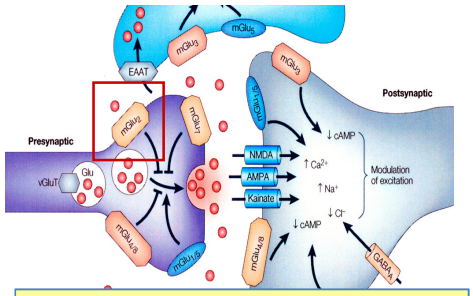
mGlu2: Target and Mechanism of Action



The 'net' effect of mGlu2R stimulation is hypothesized to be a normalization of hyper-glutamatergic transmission

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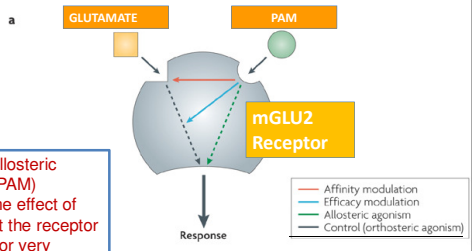
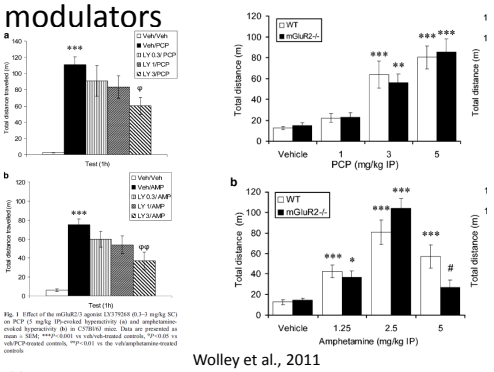
Positive allosteric modulation



A Positive Allosteric Modulator (PAM) enhances the effect of glutamate at the receptor but has no, or very limited, activity at the receptor on its own

mGlu2/3 agonists – positive allosteric modulators



Wolley et al., 2011

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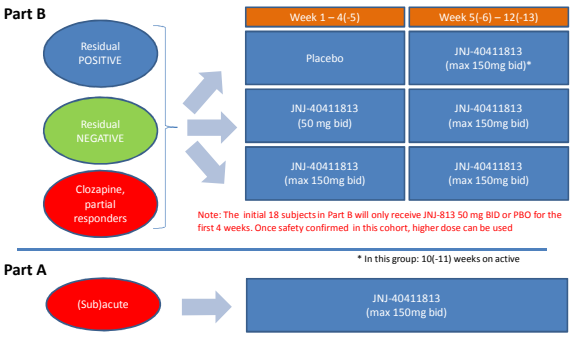
4011813SCH2001 – Overall Design



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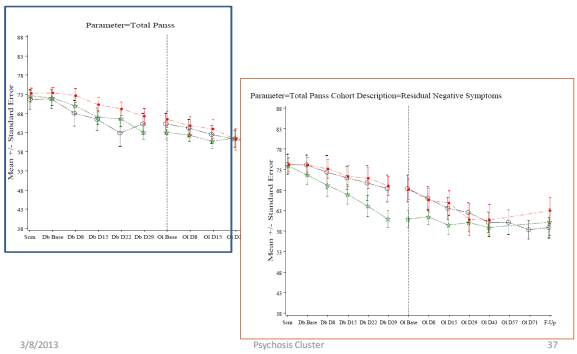
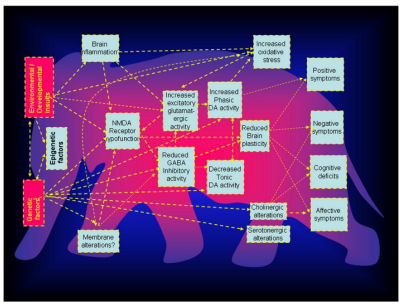
Clinical Effect mGlu2 PAM

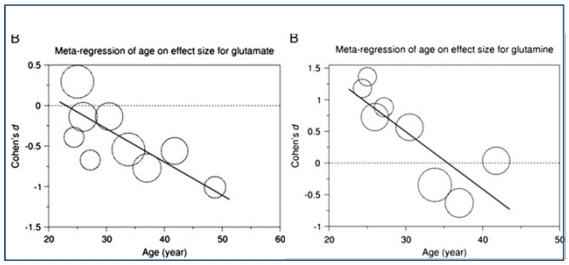


Do we know what to look for?



Keshavan et al., 2011

Elevated Glutamate and Glutamine in Early Course Schizophrenia



Marsman A et al. Schizophr Bull 2011

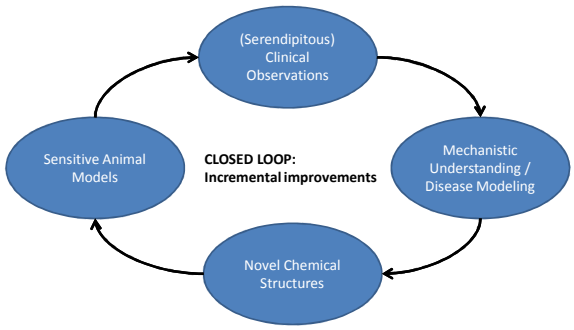
Section 3

SOME COMMENTS ABOUT DRUG DEVELOPMENT

Conclusions

1. Despite contrary perceptions, there still is significant investment in drug development for schizophrenia;
2. Although clinical efficacy can be reasonably well predicted for a dopamine D2 antagonist, recent experience with e.g. PDE10i and mGlu2R stimulation suggests that models do not easily translate to novel MoAs;
3. Rather than a primary focus on 'predictive models', anomalies need explanation;
4. **New drug development for schizophrenia ultimately relies on experiments in patients.**

Drug development: the historical model



Selected Challenges for Novel Drug Development.

1. Understanding of symptoms, biological processes and effects of interventions are interactional;
2. Reciprocal interactions exist between biochemistry and behavior; different psychological processes may have the same biological substrates;
3. Biological understanding is imperfect hence resulting in biased target selection and evaluation;
4. Animal models generally allow for the study of exaggerated normal behavior (i.e. are dimensional).

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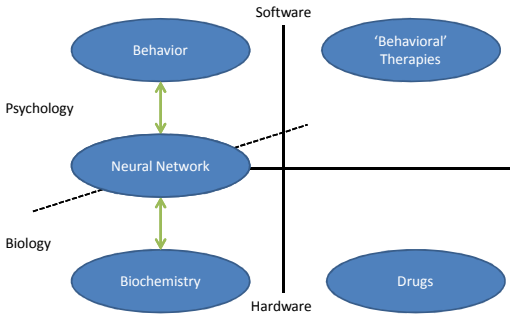
Brain networks supporting different functions use identical biochemistry (2).



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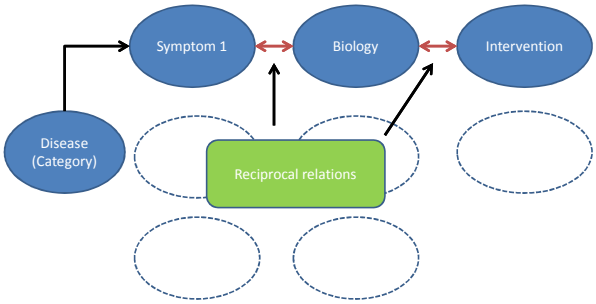
The acquisition of knowledge to support drug development is a non-linear process (1).



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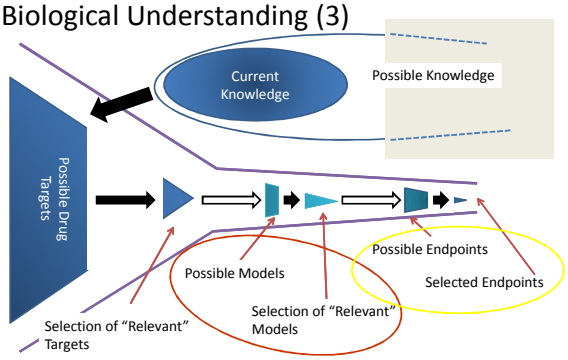
Biological Understanding (3)



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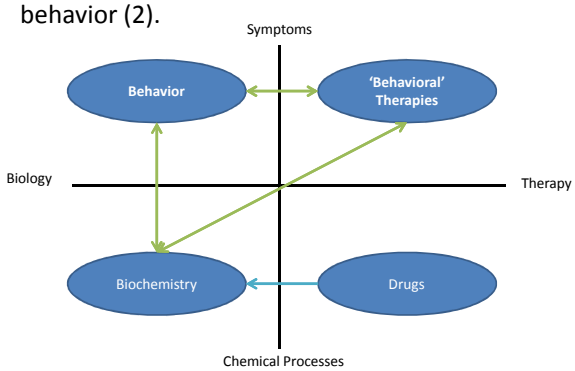
Reciprocal relations between biochemistry and behavior (2).



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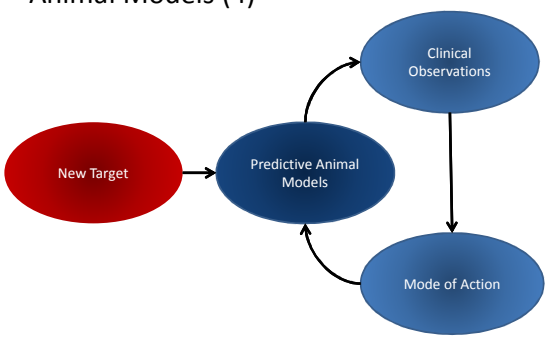
Animal Models (4)



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What to Do with Animal Models?

2 Philosophies:

1. Drug effects in animal models provide relevant information guiding the direction of the clinical indication selection (i.e. animal models have predictive validity for human disease / are translational ⇒ "predictive animal models");
2. Drug effects in animal models provide information about the relationship between plasma concentration and effect (PK/PD relationship) but only in a very broad sense guide indication selection (i.e. animal models have no or limited predictive validity for human disease ⇒ "supportive animal models").

"Predictive" Animal Models

1. Recapitulates (part of) human pathological condition in a biologically plausible manner;
2. Is sensitive to currently available therapy whilst also allowing to investigate the effect of an NME as add-on/adjunct therapy;
3. (Drug) target expression comparable to humans.

➢ Rarely used in drug development (labor-intense, marginally validated, difficult to reproduce)

"Supportive" Animal Models

- Express drug target and target engagement yields a measurable effect ("whatever");
- Effects are gradual allowing study of dose- / concentration effect relations;
- Formation of potentially active metabolites compares to (anticipated) human situation;
- Preferably, "tox-compatible" species.

➢ Most frequently used in support of clinical dosing.

Section 4

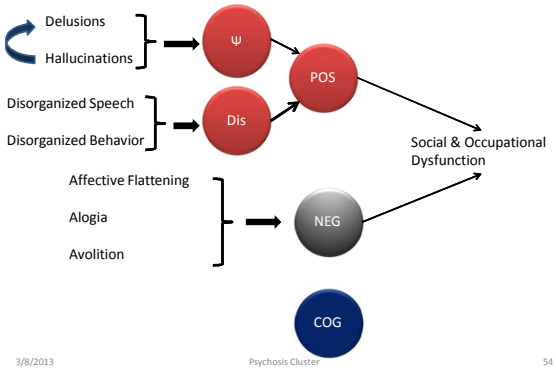
DECONSTRUCTING SCHIZOPHRENIA

Deconstructing Schizophrenia

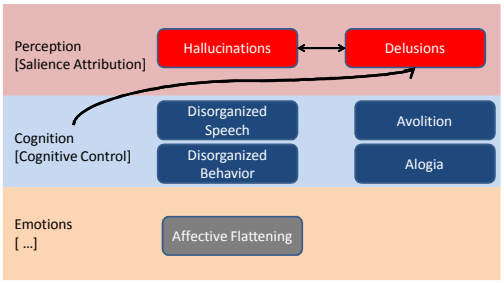
DSM IV TR:

A. Characteristic symptoms: (1) delusions, (2) hallucinations, (3) disorganized speech, (4) grossly disorganized or catatonic behavior, (5) negative symptoms (affective flattening, alogia, avolition);
B. Social/occupational dysfunction;
C. Continuous signs of disturbance persist for at least 6 months;
D. ≠ Schizoaffective- or mood disorder;
E. ≠ Consequence of substance abuse or medical condition;
F. [relation to pervasive development disorders].

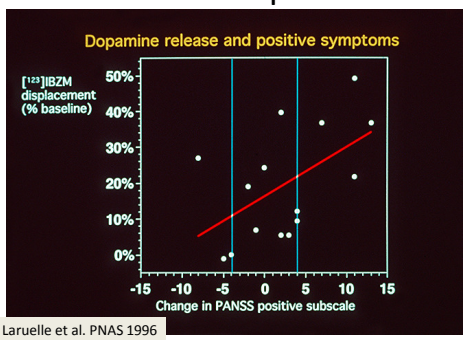
Deconstructing Schizophrenia



Deconstructing Schizophrenia

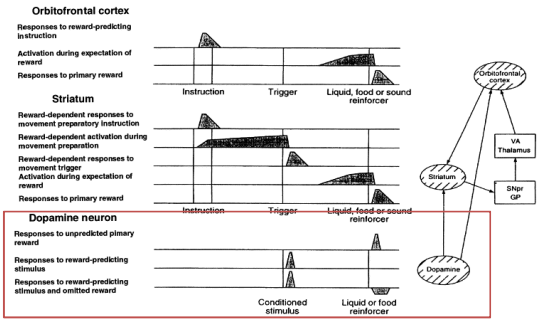


Too much dopamine?



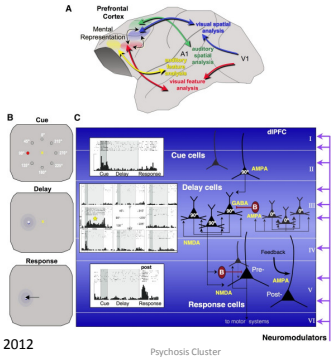
Laruelle et al. PNAS 1996

Salience Attribution: Cortex, Striatum, and Dopamine



Martin-Soelch et al., 2001

Cognitive Control: Frontal Cortex



Arnsten et al., 2012

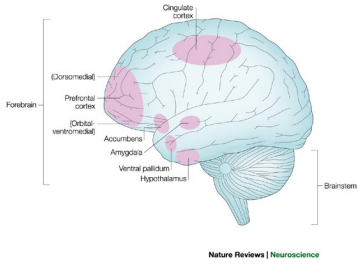
How to understand D_2 antagonists?

1. Dopamine alerts the brain to unexpected events;
2. D_2 receptor antagonists reduce the importance (salience) of stimuli;
3. In agreement, patients report a reduction in the attention to (aberrant stimuli);
4. Rather than anti-schizophrenic, a D_2 antagonist affects a specific cognitive process that is excessively abnormal in schizophrenia.

Potential Targets to Improve Frontal Cortex Function

1. Dopamine D_1 agonists (psychostimulants);
2. Enhancement of NMDA receptor function (GlyT1, mGlu5, …);
3. Nicotinic α_7 agonists;
4. Ampakines;
5. GABA α_5 negative allosteric modulators; GABA $\alpha_{2/3}$ positive allosteric modulators.

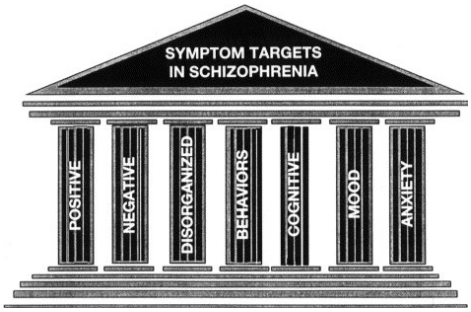
Emotion



Nature Reviews | Neuroscience

NEW BIOCHEMISTRY ?

Beyond the classic schizophrenia clusters



Tollefson and Sanger, 1999 (Eli Lilly & Co)

Schizophrenia Estimated Launch Timeline

- Adasuve A (agitation)(AZ-004) (Alexza; D2 antag)
- Aripiprazole depot M (Otsuka/LUN; D2 partial agonist) (US)
- Cariprazine M (Gedeon Richter/Forest, D3/D2 antagonist)
- Clozapine (oral susp)* M (Jazz Pharma; D4 antagonist)
- Bitopertin (RG1678/RO-4917838) A (Roche; GlyT1 inhib.)
- Ziconapine M (LU 31130) (LUN/Otsuka; 5HT2A/5HT2C/D2 antagonist)
- CYP1020/BL1020 M (BLRX/Cypress Bio; DA antag/GABA agonist)
- Brexpiprazole M (OPC34712) (Otsuka/Lundbeck; D2 partial agonist)
- Aripiprazole lauroxil (ALKS9070) M (Alkermes; D2 partial agonist)

2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 +

- Aripiprazole depot M (Otsuka/LUN; D2 partial agonist) (EU)
- PF-2545920 M (PFE, PDE10 inhibitor)
- CYR 101 M (Mitsubishi; 5HT2A/sigma2 antag)
- ITI-007 M (Intracellular Therapies; 5HT2A antag/DA phosphoprotein modulator/SSRI)
- BP-5063 M (Reviva Pharma; partial D2/5HT1A agonist, D3/D4 antagonist)
- INJ40411813/ADX711 49 M/A (Addex/J&J; mGlu2 PAM

legend: A: Add-on M: Monotherapy

Key Patent Expirations: Abilify (US 4Q14; EU, JP 2015); Fanapt (US 2016); Geodon (EU 2013); Latuda (US 2018); Saphris (US 2015); Seroquel XR (US 2016)

Source: GBI Analysis (Feb 2013), Pipeline, Company Press Releases and websites, Analyst Reports, Decision Resources/Pharmaview, BI reports
Ph2 = 2 yrs; Ph3 to filing = 3.5 yrs; Approval: 12 months. Note: Compounds currently in phase I or preclinical development not included in timeline
TIP: View in SLIDESHOW mode for active links to drug records; (*) = New to timeline

Negative/Cognitive Symptoms in Schizophrenia Estimated Launch Timeline

- TC-5619 A (α7 agonist; Targacept)
- Bitopertin (RG1678/RO-4917838) A (Roche; GlyT1 inhib.)
- CYR 101 M (Mitsubishi, 5HT2A/sigma2 antag)
- EVP-6124 A (Bayer/EnVivo, α7 agonist)
- Lisdexamfetamine A (Shire, Amphetamine)
- AMG-747 A (Amgen, GlyT1 inhibitor) (2019)

Negative

2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 +

Cognitive

- CYP 1020/BL1020 M (BLRX/Cypress Bio, DA antag/GABA agonist)
- TC-5619 A (α7 agonist; Targacept)
- Neboglamine ? (Rottapharm, NMDA-R Gly site PAM; NET inhibitor)
- NBI 98854* A (Neurocrine Biosciences; VMAT2 inhibitor)
- EVP-6124 A (Bayer/EnVivo, α7 agonist)
- CYR 101 M (Mitsubishi, 5HT2A/sigma2 antag)
- AVN-211 A (Avineuro, 5HT6 antagonist)
- ABT-288 A (Abbott, H3 antag.)
- ABT-126 A (Abbott, α7 agonist)
- AQW051 A (Novartis, α7 agonist)
- Eltoprazine A (PsychoGenics, 5HT1B partial agonist)
- Tiprolisant A (BF2.649) (Bioprojet, H3 inverse agonist)

legend: A: Add-on M: Monotherapy

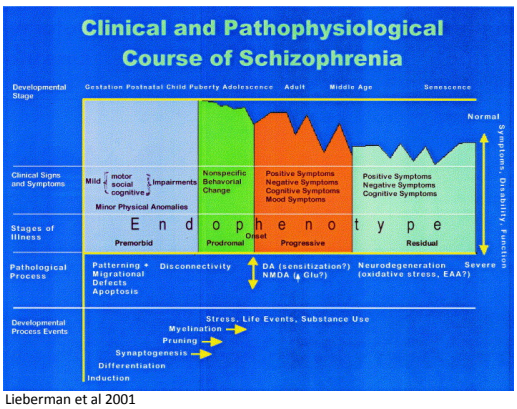
Source: GBI Analysis (Feb 2013), Pipeline, Company Press Releases and websites, Analyst Reports, BI reports
Ph2 = 2 yrs; Ph3 to filing = 3.5 yrs; Approval: 12 months. Note: Compounds currently in phase I or preclinical development not included in timeline
TIP: View in SLIDESHOW mode for active links to drug records;(*) = New to timeline

The Price to Pay: Polypharmacy

Positive Symptoms	D2-selective Antipsychotic	D2-selective Antipsychotic
Negative Symptoms	D2/5HT2A-acting Antipsychotic	GlyT1 Inhibitor
Disorganization	'Clozapine-like' / mood stabilizer	D2/5HT2A-acting Antipsychotic
Cognitive Symptoms		Nicotine α7 agonist
Mood	Antidepressant	Antidepressant
Anxiety	Benzodiazepines	Benzodiazepines, mGlu2
Somatic	e.g. statins, antihypertensives …	e.g. statins, antihypertensives …

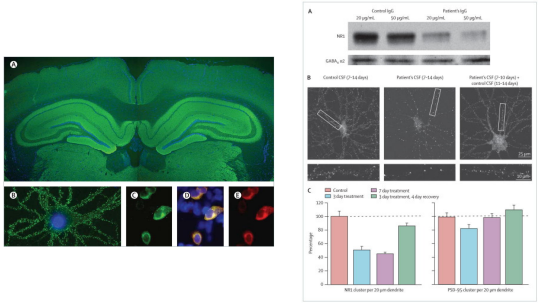
Section 5

A DIFFERENT MODEL?

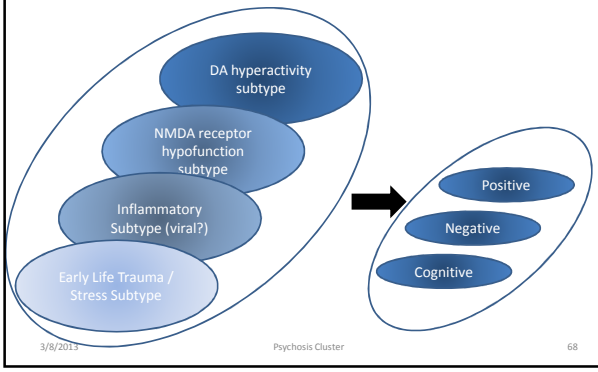


Lieberman et al 2001

Encephalitis and NR1 – NR2 antibodies



The schizophrenias?



Encephalitis and NR1 – NR2 antibodies

Prodromal Phase: Fever, malaise, inability to concentrate, nausea, diarhea, vomiting, headache.

Unresponsive Phase: Not able to follow oral commands, appear mute and akinetic. Catatonic features.

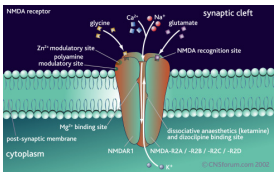
0 2 weeks 4 6

Psychotic/Seizure Phase: Emotional/behavioral disturbances (apathy, fear, depression, psychosis, decline cognitions), ataxia, choreiform movements, seizures.

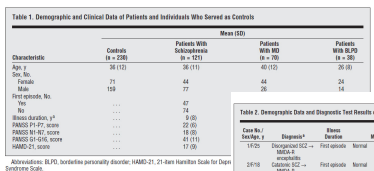
Hyperkinetic Phase: Autonomic instability, dyskinesias .

The Schizophrenia: NMDA Receptor Hypofunction

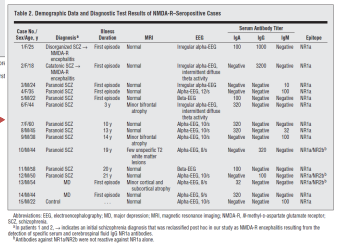
1. Non-competitive NMDA receptor antagonists (ketamine, PCP) precipitate schizophrenia-like behaviors in healthy subjects;
2. Similarly, in patients with schizophrenia, symptoms are exacerbated;



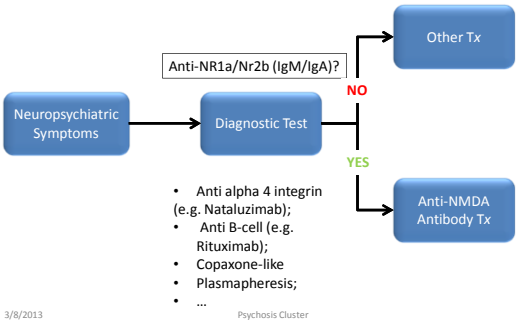
High occurrence in acute schizophrenia



9.9% Schizophrenia
2.8% MDD
0% BLPD
0.4% control



Potential for Drug Development?



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Conclusions

1. Psychiatric symptoms, similar in expression, may have different biological triggers;
2. Hence, the dominant effect of a single drug may differ across populations;
3. The reductionist approach to 'dissect' schizophrenia has not (yet) yielded new treatment approaches. Also, it may lead to polypharmacy;
4. Likely, multiple schizophrenias exist. A better understanding of the diversity of schizophrenia biology may lead to a more individualized treatment approach. However, this promise still needs to materialize.

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