

# ***Nicotinic Agonists for Cognitive Deficits in Schizophrenia: A Case Report***

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# Learning Objectives:

- To increase knowledge regarding the functional impact of cognitive deficits in schizophrenia
- To increase knowledge regarding the relationship between cognitive deficits and negative symptoms in schizophrenia
- To increase knowledge regarding the potential of nicotinic agonists to treat cognitive deficits and negative symptoms



# Functional Impairments in Schizophrenia

Social, Occupational, and Independent  
Living Activities

CATIE (N = 1,438; Age = 40.4)

12% married

60% never married

14.5% some competitive employment

12.6% other employment activity

72.9% no employment activity



# Complex, Multi-Determined Pathways to Functional Impairments

- **Neurocognitive Deficits**
  - Social Cognition
  - Functional Capacity
- **Negative Symptoms**
- Affective Symptoms
- Motivational and Environmental Factors

# Cognitive Impairment—A Core Feature of Schizophrenia

- Not the result of symptoms
- Not the result of antipsychotic medications
- Relatively stable across clinical state changes
- Present before the onset of symptoms
- Exists in an attenuated form in un-affected first-degree relatives



# The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS)— Consensus Process sponsored by NIMH (2003)

- Speed of Processing
- Attention/Vigilance
- Working Memory
- Verbal Learning and Memory
- Visual Learning and Memory
- Reasoning and Problem Solving
- Social Cognition



# MATRICS Consensus Cognitive Battery

- Speed of Processing—Category Fluency, BACS Symbol Coding, Trail Making A
- Attention/Vigilance—CPT, Identical Pairs
- Working Memory—University of Maryland Letter/Number Span, WMS III Spatial Span
- Verbal Learning and Memory—Hopkins Verbal Learning Test (HVLT) Revised
- Visual Learning and Memory—Brief Visuospatial Memory Test (BVMT) Revised
- Reasoning and Problem Solving—Neuropsychological Assessment Battery (NAB) Mazes
- Social Cognition—Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT) Managing Emotions



# Magnitude of Cognitive Deficits

- 1-1.75 standard deviations below the normal mean
- Comparable to performance in 9-16% of healthy controls
- 80% of patients scored at least 1 S.D. below the normal mean on the RBANS
- 50 of patients scored at least 2 S.D.'s below the normal mean on the RBANS
- Modal profile of deficits with most severe deficits in memory, attention, and executive skills and less severe deficits in old learning, vocabulary, and visual perceptual skills
- 20% of patients appear to be neuropsychologically “normal”

# To what extent does a generalized cognitive deficit account for impairment in schizophrenia?

Some factor analyses suggest that cognitive impairment is best accounted for by multiple independent or relatively weakly correlated factors.

Other factor analyses suggest that there is a hierarchical multi-factor model of cognitive test performance in patients with schizophrenia similar to that found in healthy controls. However, there appears to be greater generalization of cognitive ability in schizophrenia than in healthy people. **In these studies, more of the observed cognitive performance variance is determined by generalized cognitive ability (“G”) in schizophrenia than in healthy controls.**

A generalized cognitive deficit in schizophrenia may reflect widespread cortical and subcortical dysfunction.

# Individual Cognitive Ability and Real-World Functional Outcomes

- Performance in specific domains and functional outcomes are modestly correlated
- Episodic memory, working memory, vigilance, and executive functioning are the domains most consistently related (in the range of  $r = .30$ ,  $d = .50$ ) to functional outcomes (e.g. quality of life, work outcomes, social relations, ADL's etc.)
- Composite measures of neuropsychological performance predict 25%-50% of the variance in real-world functional outcomes



# Negative Symptoms--

- Flattened affect
- Asociality
- Anhedonia
- Avolition
- Amotivation
- Alogia
- Inattention

# Negative Symptoms—A Core Feature of Schizophrenia

Similarities shared with cognitive symptoms:

- Not the result of antipsychotic medications
- Relatively stable over time
- Severity of negative symptoms at onset predicts course of illness

## 4 Possible Models of the Relationship between Cognitive Deficits and Negative symptoms (Harvey et al., 2006)

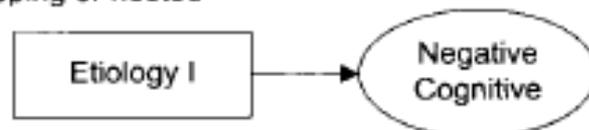
Model 1—Both dimensions are identical features of the illness or alternate manifestations of the same underlying process and would therefore be improved by the same treatments.

Model 2—Both dimensions are separable features of the illness but share similar underlying etiological factors, leading to observed correlations and the possibility that treatment of one dimension will impact the other.

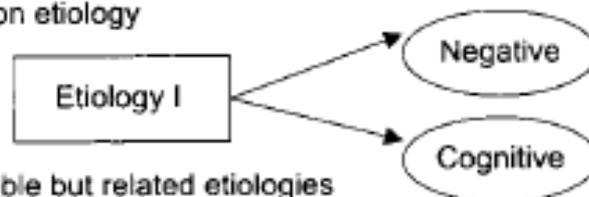
Model 3—Each dimension has a separate but possibly related etiology and therefore treatment of one dimension may impact the other but not as strongly as in Model 1 or Model 2.

Model 4—Each dimension has a distinct etiology and correlations between the dimensions are artifacts of measurement and/or definitions issues or reflect a “third variable”

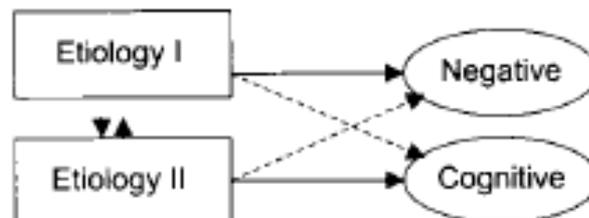
**Model 1: Overlapping or nested dimensions**



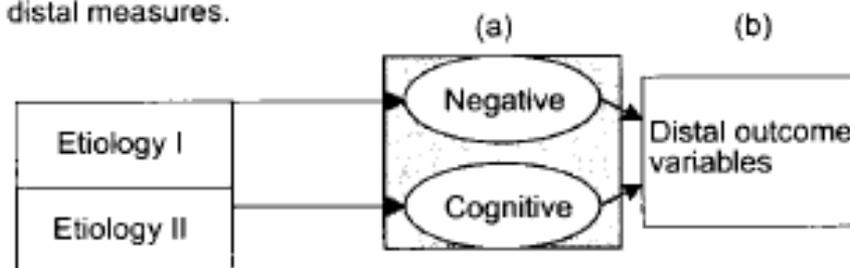
**Model 2: Common etiology**



**Model 3: Separable but related etiologies**



**Model 4: Independent but related due to (a) overlapping measurements or definitions or (b) shared correlations with distal measures.**



**Fig. 1. 4 Theoretical Models of the Nature of the Relationships Between Negative and Cognitive Symptoms.**

# Evidence Against Models 1 & 2

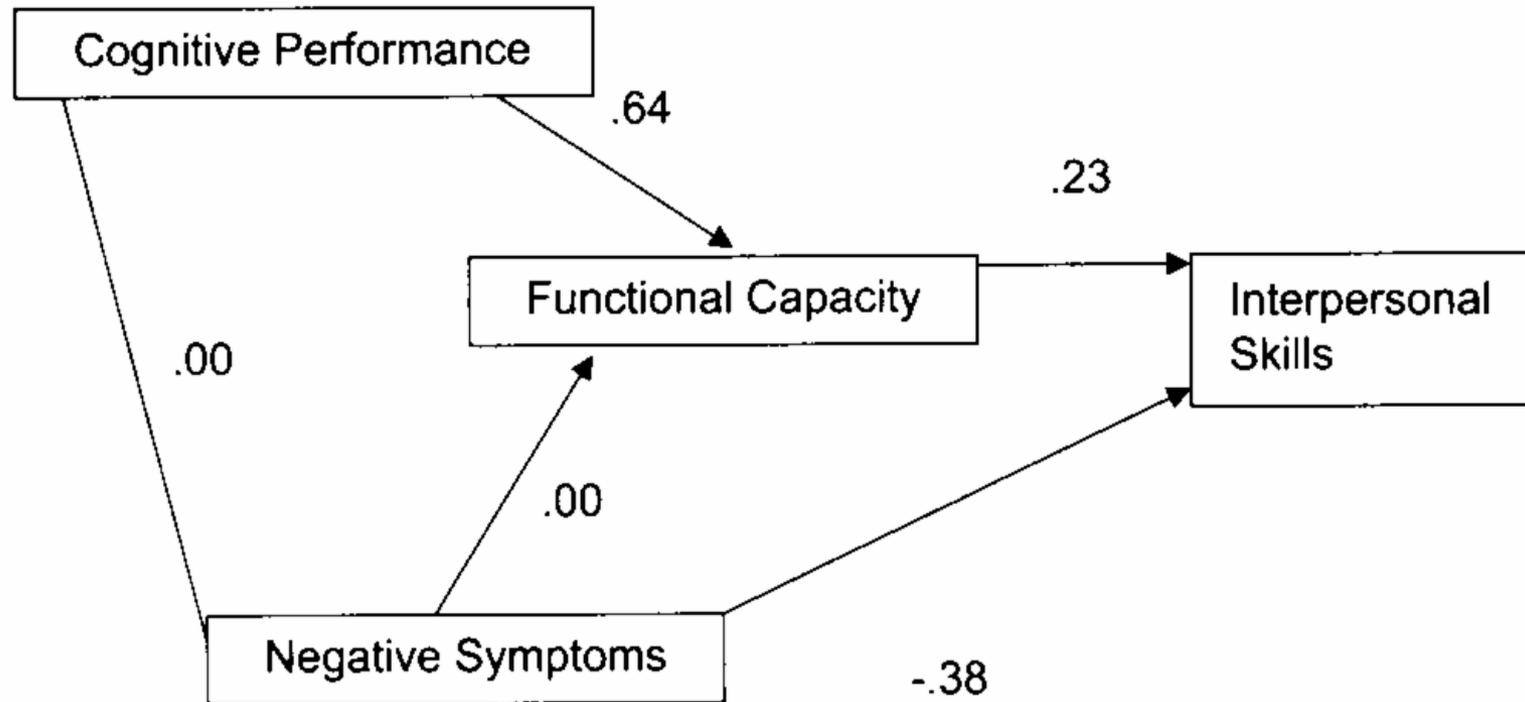
- Cross-sectionally, negative symptoms and neurocognition are only modestly correlated ( $r = .30$ )
- Longitudinal changes in cognitive performance and negative symptoms are unrelated



# Functional Impairment may be the “Third Variable” or shared Distal Outcome

In regression analyses, negative symptoms typically account for about 10% -20% of the variance in functional outcomes above and beyond the variance accounted for by cognitive performance.

# Path Model for Social Functioning (Bowie et al., 2006)



**Fig. 2.** Negative Symptoms, Cognitive Performance, and Everyday Skills Performance. *Source:* Bowie et al.<sup>44</sup>

Neuropsychological performance may be associated with the ability to perform everyday living skills, while negative symptoms are associated with the likelihood of performing these skills.

CATIE—Regression Analysis—  
intrapsychic functioning, negative  
symptoms, and positive symptoms  
but not cognitive performance  
differentiated employed  
individuals from non-employed  
individuals

# Nicotinic Agonists for the Treatment of Schizophrenia

- Neuronal nicotinic systems have been found to be involved in a variety of cognitive functions including learning, memory, and attention.
- Patients with schizophrenia have been shown to have nicotinic receptor deficits in  $\alpha 7$  and also  $\alpha 4\beta 2$  receptors.
- These nicotinic deficits are thought to be related to deficits in early information processing, i.e. sensory and sensory motor gating.

# Sensory and Sensory Motor Gating

Measures of attention gating:

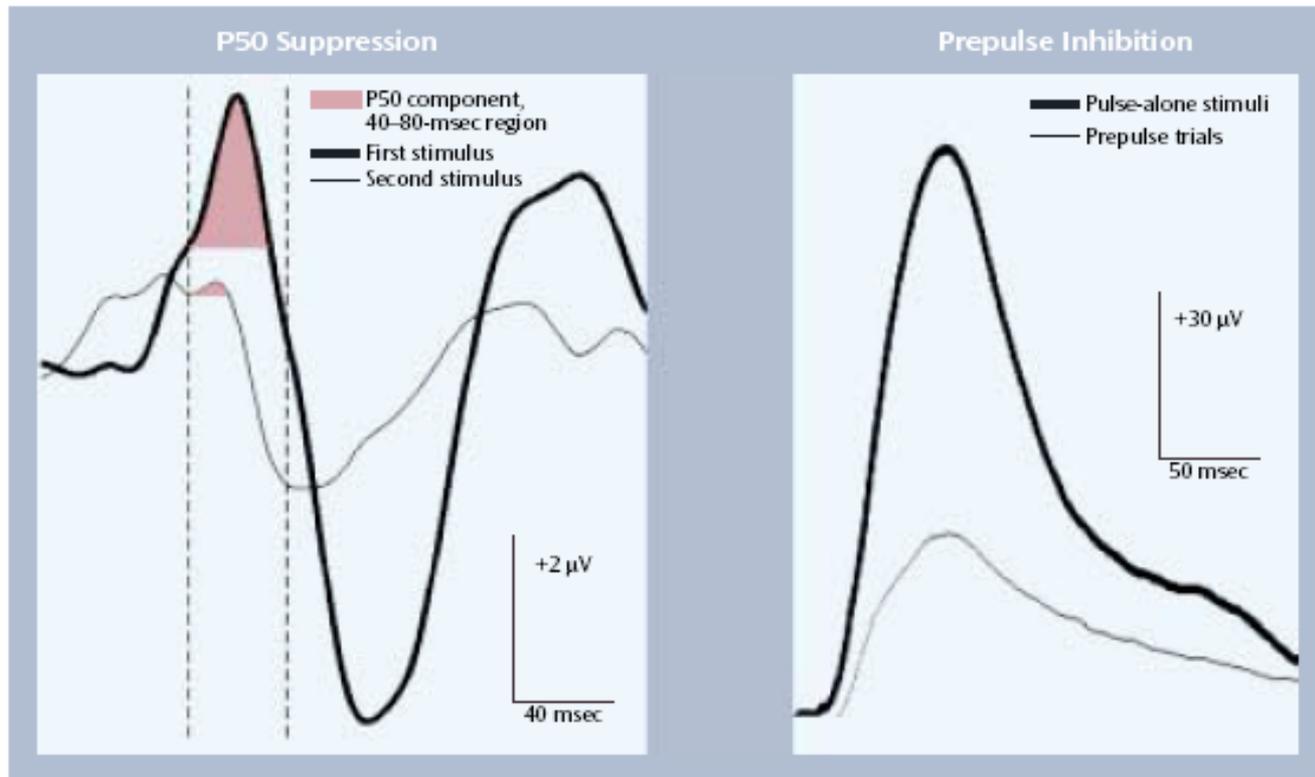
- P50 Inhibition (sensory)

- Prepulse Inhibition (PPI) of startle response (sensory motor)

- Antisaccade eye movements

Deficits in these measures is thought to represent a cognitive endophenotype of schizophrenia.

FIGURE 1. Grand Average P50 and Startle Responses in 12 Normal Subjects Tested for P50 Suppression and Prepulse Inhibition in the Same Session<sup>a</sup>



<sup>a</sup> In the test of P50 suppression, the subjects showed a larger response to the first auditory stimulus (bold waveform) than to the second stimulus (fine waveform). For illustration purposes, the shaded areas indicate the P50 component (positive is up) in the 40–80-msec region. In the test of the startle response, there was a larger response to the pulse-alone stimuli (bold waveform) than to the trials with prepulses (fine waveform).

Studies indicate deficits in P50 suppression in about 75% of patients with schizophrenia and about half of their unaffected first-degree relatives.

Furthermore, P50 suppression has been linked with a genetic marker at the locus of the  $\alpha 7$  subunit of the nicotinic acetylcholine receptor.

# Nicotinic Agonists--Smoking

- The rate of smoking among individuals with schizophrenia is approximately 85%, as compared to 23% for the general population. Approximately 30% of patients with schizophrenia who smoke more than 30 cigarettes per day, and schizophrenics extract more nicotine from cigarettes than other smokers.

- Smoking transiently improves P50 performance to normal levels
- Nicotine (administered transdermally, subcutaneously or nasally) improves smooth eye pursuit, eye tracking, spatial organization, attention, and memory
- Effects of nicotine may be transient due to down regulation

# Galantamine

- Galantamine is both an acetylcholinesterase inhibitor and an allosterically potentiating ligand that modulates nicotinic cholinergic receptors.
- Based upon findings on donepezil for cognitive deficits in schizophrenia, as an acetylcholinesterase inhibitor galantamine may be of little benefit.

The potential benefits of galantamine may be associated with its properties as a nicotinic ligand.

**In schizophrenia, deficits in nicotinic (particularly  $\alpha 7$ ) receptors are particularly evident in the hippocampus and frontal cortex**

- Hippocampal deficits are associated with deficits in attention and memory
- Frontal cortex deficits may be associated with decreased frontal dopamine release

Theoretically, improved nicotinic transmission in the hippocampus should yield improvements in attention and memory.

While, improved nicotinic transmission in the frontal cortex may improve negative symptoms.

# Randomized, Controlled Trials of Galantamine for Cognition in Schizophrenia

- Schubert et al. (2006): 16 schizophrenic or schizoaffective patients stabilized on risperidone were administered galantamine (n=8) or placebo (n=8) in a randomized, double-blind trial. The Repeatable Battery for Assessment of Neuropsychological Status (RBANS) assessed changes in cognitive performance over an eight-week treatment interval.
- Patients treated with galantamine experienced an overall improvement in cognitive performance (RBANS Total scale score; galantamine = 12.1 +/- 12.8 SD, placebo = .5 +/- 13.5,  $t = 2.32$ ,  $p < .04$ ).
- Confidence intervals suggest that RBANS Attention and Delayed Memory subscale performance was robustly improved in galantamine patients by approximately one standard deviation, effectively normalizing cognitive performance in these domains.

Allen et al., (2003) prescribed galantamine as an adjunct to risperidone using a double-blind design. Twenty-four subjects were randomized to placebo and three different doses of galantamine and treated for 28 days. The subjects on galantamine, particularly those on 24 or 32 mgs per day, exhibited significant improvements on tests of attention and verbal fluency.

### Open Label Trial

Bora et al. (2006) report on the use of adjunctive galantamine in 5 patients on clozapine. Neuropsychological assessment was administered before and after 8 weeks of 16 mg/d galantamine treatment. Three of the patients were much improved in sustained attention tasks. Most of the patients were also improved in psychomotor speed and selective attention tasks. Two patients with low pretreatment memory scores seemed to also be improved.

## Case Reports of Improved Negative Symptoms

Rosse and Deutsch (2002) report the case of a patient who was treated with 24 mg per day of adjunctive galantamine for 8 weeks. While on galantamine, the patient's orientation and memory improved and his negative symptoms decreased. The patient's functioning improved considerably as evidenced by increased attention to his personal hygiene and increased participation in household chores.

**Is a deficit in nicotinic receptors a common but topographically, developmentally and functionally divergent etiological factor in cognitive deficits and negative symptoms? If so, does this etiological factor distally manifest in functional impairment?**

# Case Report—Ms X

- The primary objective of this on-going, open-label study is to assess the efficacy of adjunctive galantamine to improve functional impairments in outpatients with schizophrenia over nine months of treatment.
- Primary outcome measures: Quality of Life Scale and Independent Living Scale
- Secondary outcome measures: BACS, PANSS, SANS

# Psychiatric History

Ms X, a married, Caucasian female, enrolled in the study in May 2005 at age 32. As per the subject, she was first diagnosed with schizophrenia at age 13. However, she reportedly went into full remission after treatment which consisted of a two week inpatient hospitalization with antipsychotic medication; however, no outpatient follow-up treatment occurred. Ms X obtained her GED, completed a year of trade school, and enlisted in the military. Ms X served in the military for three and a half years, working as an air traffic controller, until her second psychotic break at age 24, at which time she was hospitalized. Ms X was also hospitalized twice within several years after being discharged from the military.

# Presentation at Enrollment

Ms X was psychiatrically stable but experienced treatment-refractory symptoms including auditory and visual hallucinations, paranoid ideation, mild depression, moderate anxiety, affective flattening, limited social interaction, and an inability to engage in meaningful activity outside of the home. Despite her symptoms, Ms X was able to maintain close relationships with her husband and several family members, take care of many household chores, and actively pursue interests such as gardening and canning. Ms X also had considerable insight into her illness and expressed a deep sense of loss of identity due to her illness and anxiety about a future exacerbation of her symptoms. Per Ms X, her father, who died at age 44 of heart failure, also had a diagnosis of schizophrenia. Ms X had quit smoking 2 months before study enrollment.

# Study Course

*Study Week 1 through Study Week 4 (8 milligrams)*

Reported effects:

- immediate response
- progressive improvement over the first four weeks of treatment
- decrease in depressive symptoms
- decrease in panic attacks
- increase in optimism, motivation, and energy
- increase in social activity
- increase in satisfaction with interpersonal relations
- improved focus
- regained ability to read for pleasure
- no side effects

**After four weeks treatment, Ms X stated, "I want to do more. I want to live life," attributing these positive changes to galantamine.**

## ***Study Week 5 through Study Week 8 (16 milligrams)***

Reported effects:

- continued improvement in mood early on
- continued improvement in functioning
- Increased social activity
- improvement in hearing and sense of smell
- muscular stiffening in arm
- Increase mood lability toward week 8

**"I can multi-task now and I lost that ability when I had my breakdown [as an adult]...I care about myself now."**

## ***Study Week 9 through Self Discontinuation at Study Week 16 (24 milligrams)***

Reported effects Weeks 9-12:

- persistent improvement but with some mood instability

Reported effects Week 12+

- acute exacerbation in psychotic symptoms
- increase in auditory hallucinations
- increase in anxiety
- increase in insomnia
- somatic issues, including abdominal pain, chest pain, hematemesis, excessive perspiration, headache, and increased salivation (all with no significant clinical findings upon evaluation)

# Self-Discontinuation

Although Ms X attributed the increase in her psychiatric symptoms to psychosocial stressors, she indicated that she believed galantamine was exacerbating the severity of her symptoms. She also expressed the belief that she had experienced the most benefit from the 8 mg/day dose and that the benefit had decreased, accompanied by an increase in physical ailments, as the dose was increased. After approximately 16 weeks of study participation, Ms X discontinued taking galantamine in reaction to a bout of chest pain of unknown origin and problems with excessive salivation, as well as ongoing exacerbated psychiatric symptoms.

## ***Two Week Follow-Up***

Two weeks after discontinuing galantamine, Ms X's symptomatology had returned to baseline levels. Her physical ailments had spontaneously resolved. As per the subject, the apparent gains that she had made in functioning while on galantamine, including greater motivation, increased overall activity level, more social interaction, and richer interpersonal relationships, had reversed since discontinuation of galantamine.

Cognitively, Ms X reported losing the gains she had reported at earlier points in the trial, including the ability to read for pleasure and multi-task.

# Baseline and Week 12 Scores

Measure	Baseline	Week 12
Quality of Life Scale (QLS)	58	Not available
Independent Living Scale (ILS)	105	Not available
PANSS	71	67
BACS		
Verbal Memory	-0.32	.28
Digit Sequencing	-0.58	.17
Token Motor Task	0.40	1.22
Verbal Fluency	-1.33	-1.08
Symbol Coding	0.37	0.25
Tower of London	-0.65	-0.65
SANSS	45	26

QLS: Total raw score; a higher score indicates better quality of life. In a group (n = 25) of schizophrenic patients, similar to the group in this study, at the VA PSHCS, the total mean score for the QLS was 71 ( $\pm 15.88$ ).

ILS: Standardized score; a higher score indicates better performance, with scores below 85 considered low, 85 to 100 moderate, and above 100 high.

PANSS: Total raw score; a higher score indicates greater symptomatology. In previous studies with similar samples, the baseline mean scores for the PANSS included scores of 74.3 ( $\pm 18.1$ ) to 75.7 ( $\pm 17.6$ ).

BACS: Standardized z score derived from normal control sample.

SANS: Total raw score; a higher score indicates greater symptomatology. The mean baseline scores from this sample is 52.9 ( $\pm 16.9$ ).

# What Went Right? What do we know?

- Improvement in negative symptoms and functioning appears to have been due to treatment with galantamine and not just a “Rosenthal Effect”
- Pharmacologically-induced significant improvement in negative symptoms is possible
- Improvement was transient
- Improvement in negative symptoms was not accompanied by objective improvement in cognitive performance

# What Went Wrong?

## What don't we know?

- Were the subject's physical complaints signs of decompensation or side effects from the galantamine?
- Did galantamine precipitate decompensation?
- What would have happened if we had maintained an 8 mg/day dose?
- Do the benefits of galantamine persist for only 8 weeks?
- Are patients habituating to galantamine?

# What don't we know?

How much or for how long can potentiation of existing nicotinic receptors compensate for a receptor deficiency?

# Where do we go from here regarding galantamine for schizophrenia?

- Randomized, controlled trials
- Control for antipsychotic, other CNS medications, smoking, and clinical features
- P50 testing
- Fluctuating dose of galantamine
- Other nicotinic agonists