Prospects for a Disease Modifying Claim in Schizophrenia

David H. Millis, MD, MBA, PhD
Medical Officer
Division of Psychiatry Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

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Disclaimer

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Plan for this talk

1. present a simplified disease model to assist in clarification of terminology
2. use this model to consider what should be considered disease modification, and what should not
3. relate the model to our current state of knowledge about schizophrenia
4. offer conclusions on the potential for a disease modification indication in schizophrenia

“All models are wrong, but some are useful.”
- George Box

Simplified model of humans and diseases

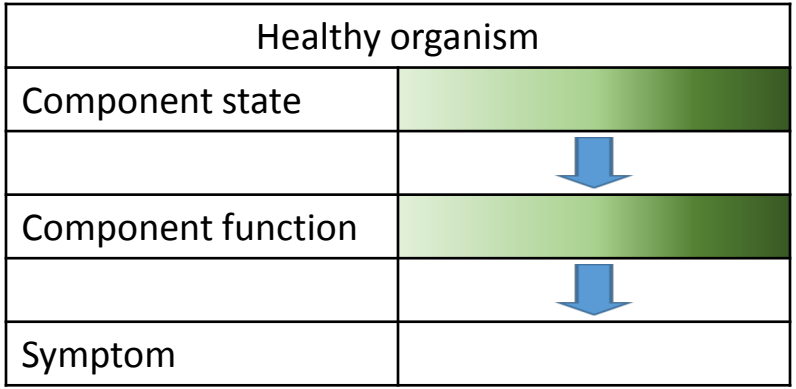
- Human is a collection of interacting biological components
  - Genes, regulatory networks, cells, organs
- Change in a component's state may change the component's functioning
- Change in function at the component level may be observable as a change in function at the organism level

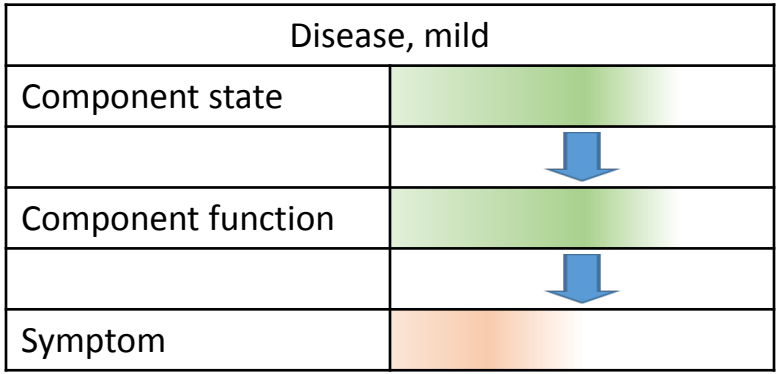
Type of change	Interpretation
State change at component level	Disease etiology
Function change at component level	Disease
Function change at organism level	Symptom Syndrome (collection of symptoms)

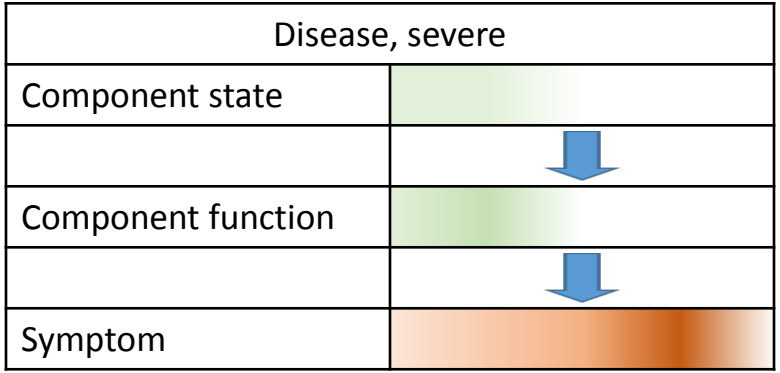
Key elements of this model

- The relationships between component state and component function, and between component function and symptoms, are causal relationships, not just co-occurrence
- Our state of knowledge about these relationships is a key element in designating a drug's action as disease modification
- Observation of a change in syndrome course, in the absence of an understanding of the underlying mechanism of symptom causation, is insufficient for a disease modification claim
  - This is a clarification in our thinking since the 2014 ISCTM presentation by FDA

Healthy and disease states when disease etiology is related to a single component



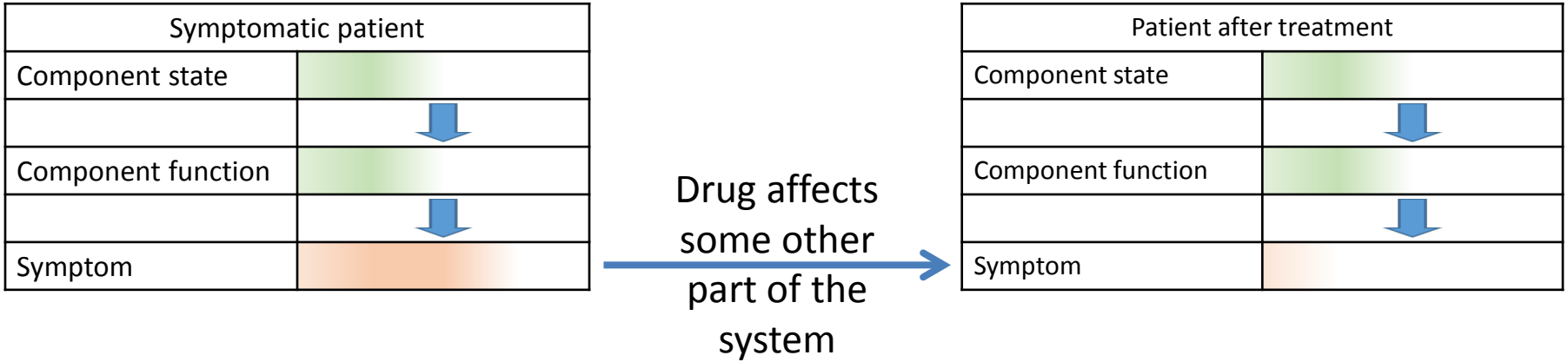




How a drug might affect a disease:

1. the altered biological component is targeted and repaired
   - before symptoms develop:
     - the expected disease never occurs
     - → **prevention**
   - after symptoms develop:
     - all symptoms stop completely
     - → **cure**
2. the altered biological component is targeted, not completely repaired, but is modified
   - the symptoms are not stopped completely, but are reduced
   - → **disease modification**
3. the altered biological component is not targeted; some other body system is targeted and modified to compensate for the loss of the altered component's function
   - the symptoms may stop completely or be reduced, but the disease is still present
   - → **symptom control** (not disease modification)

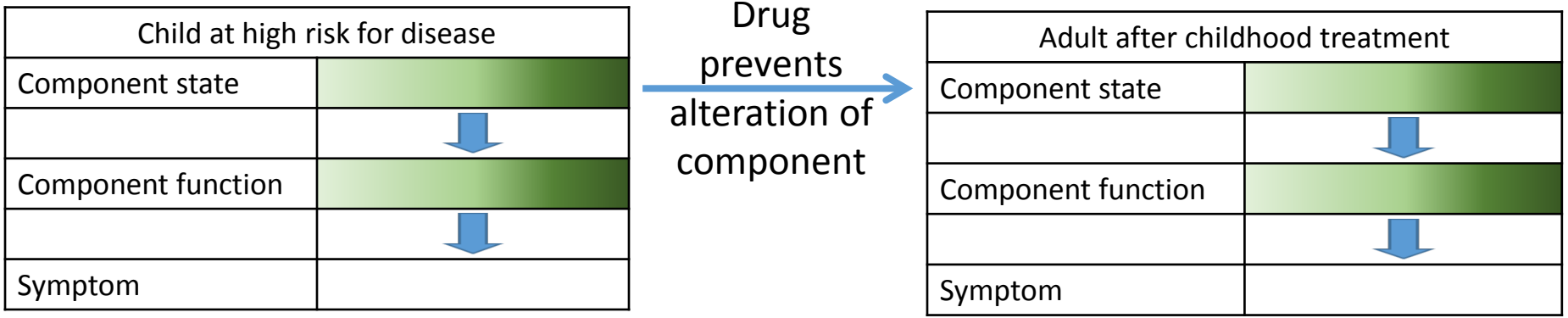
Drug effect: symptom control



Example:

- The etiology of the symptom is unknown.
- A drug that blocks dopamine receptors helps to reduce the symptom.
- We don't know why this works; it's a very nonspecific intervention that affects many components of the system (including some unrelated to the disease).
- If the drug is withdrawn, the symptom returns, because the underlying disease pathology has not been repaired.

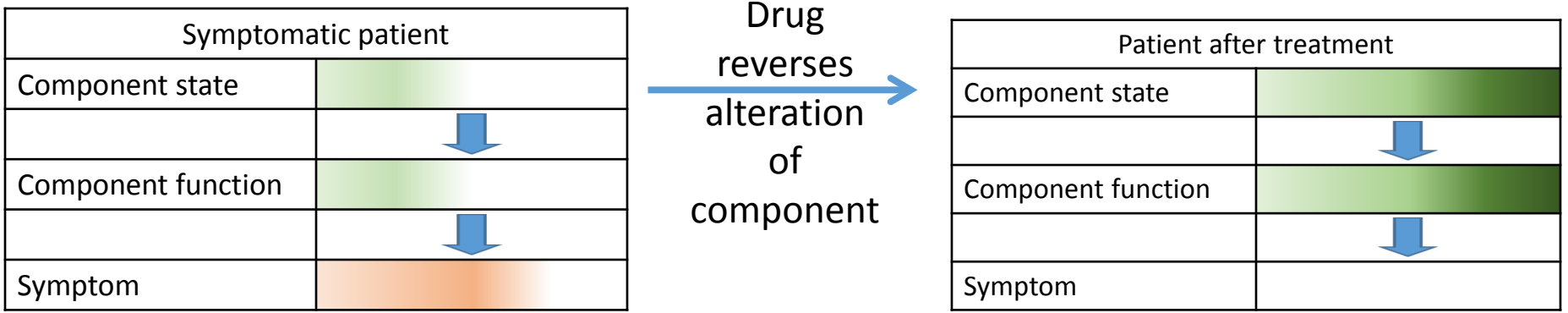
Drug effect: disease prevention



Example:

- The gene for an enzyme required for normal neurodevelopment is not being expressed.
- The drug is a form of the enzyme that can be given exogenously during a critical period in early development.
- Neurodevelopment now proceeds normally.
- The drug is stopped once neurodevelopment is complete.
- The patient never experiences an episode of the illness.

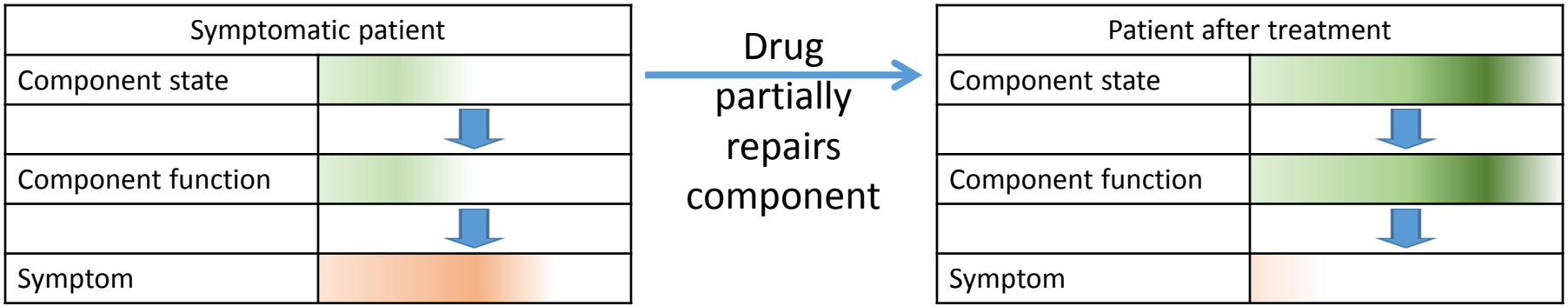
Drug effect: disease cure



Example:

- A gene regulatory network involved in sensory processing is not functioning correctly due to overly-high expression of a single gene.
- The drug performs a histone modification of an upstream regulatory element.
- This turns down the expression of the overly-expressed gene.
- The histone modification is not reversible, so functioning of the network remains normal after the drug is withdrawn.
- The symptom stops, and does not return after the drug is withdrawn.

Drug effect: disease modification



Example:

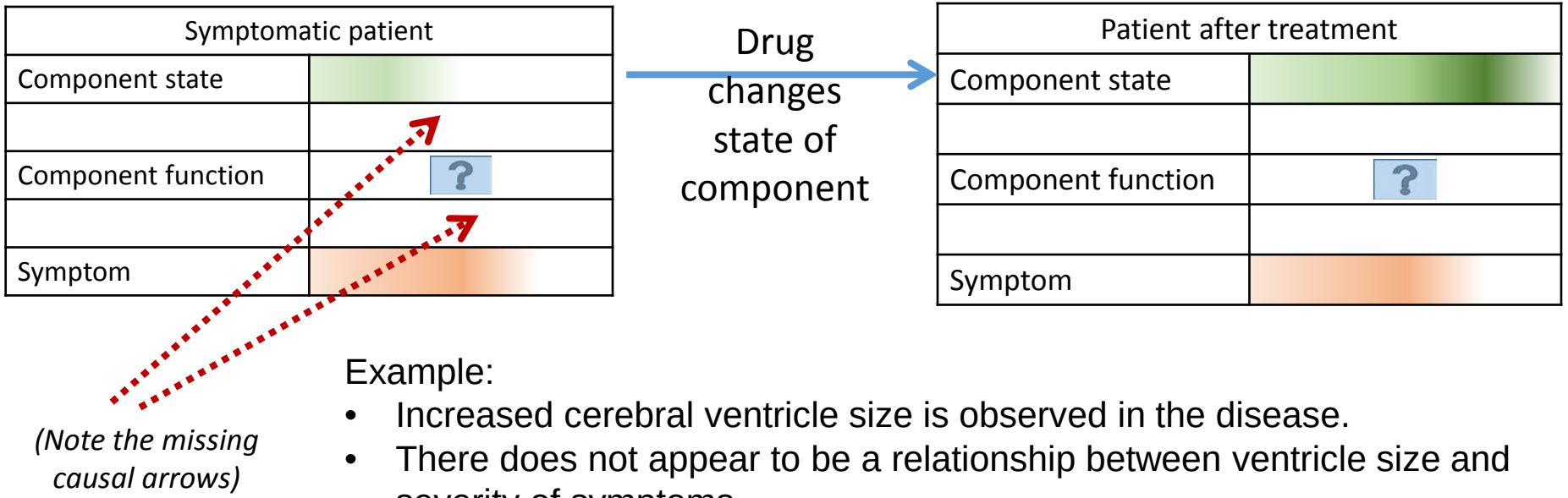
- A gene regulatory network involved in sensory processing is not functioning correctly due to overly-high expression of several genes.
- The drug performs a histone modification of an upstream regulatory element.
- This turns down the expression of two of the overly-expressed genes.
- The histone modification is not reversible.
- Functioning of the regulatory network is not optimal, but is improved.
- The symptom continues, but is less severe, even after the drug is withdrawn.

Knowledge we need about disease to support a claim of disease modification:

1. The underlying pathophysiology that defines the disease is known.
2. A causal relationship between the underlying pathophysiology and disease symptoms has been verified.
   - This is a causal relationship, and not a co-occurrence relationship.

Evidence for disease modification is stronger if the magnitude of change in the symptom is commensurate to the magnitude of the change the drug makes in the underlying pathophysiology.

Drug effect: relationship between component state and symptom is not necessarily causal

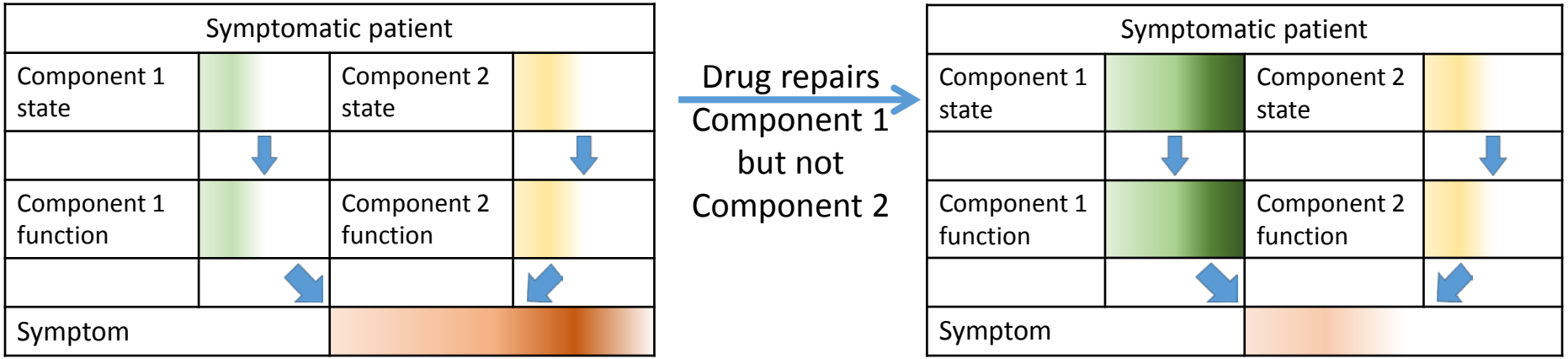


(Note the missing causal arrows)

Example:

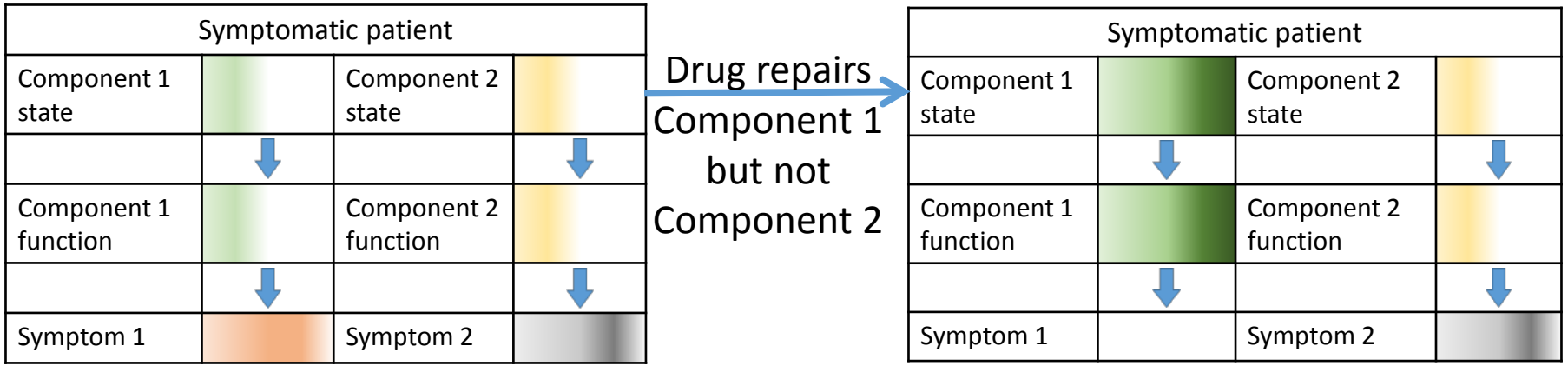
- Increased cerebral ventricle size is observed in the disease.
- There does not appear to be a relationship between ventricle size and severity of symptoms.
- A drug that normalizes ventricle size (and has no effect on other system components) is not expected to have any effect on symptom severity.
- The drug has effected component modification, but not disease modification.

Different pathways to the same symptom



- Symptoms are reduced but still present, even with full functioning of Component 1
- Could explain continued symptoms despite a postulated mechanism for symptom etiology
- May define a subtype of patients in whom disease modification by this drug is possible
  - namely, patients in whom the Component 1 pathway to symptoms is predominant

Different pathways to different symptoms



- The drug helps with some symptoms, but not others
- Whether this is disease modification depends on the relative level of disability caused by the untreated symptom

Disease progression

Q: If the typical course of disease progression is well known, can a drug that alters disease progression be considered to provide disease modification?

A: Possibly, under the following conditions:

1. identification of a CNS component relevant to the disease
2. there is an observable change in the state of this component over time
3. confirmation of a causal relationship between the state change, component functioning, and symptom severity
4. confirmation that the drug has an effect on the change in the component's state

Concerns regarding disease modification label claim for schizophrenia:

- limited knowledge about the causal relationships between changes in state of CNS components and disease manifestations
- unlikely that the diagnostic term “schizophrenia” represents a single component change that is present in all patients
  - more likely that there are multiple component changes that define different biological subtypes
- unclear how to interpret variability in clinical trial results
  - random error? multiple biological subtypes? multiple pathways to symptoms?
- clinical trials that examine the change in disease course may be difficult to interpret without an *a priori* understanding of the relationships between CNS component changes and disease course

Role of clinical trials

- With our current knowledge about schizophrenia pathogenesis, clinical trial designs such as delayed start and randomized withdrawal can contribute to our knowledge of whether schizophrenia is a modifiable disease.
- Findings such as high variability in effect of drug on syndrome course can help point to further basic science studies needed, such as identification of disease subtypes.
- Clinical trials should be considered part of the iterative process of refining our knowledge.
- At this time, using them to finalize a labeling indication for disease modification in schizophrenia may be premature.

A clinical trial interpretability conundrum…

Using a study to simultaneously establish disease modifiability and disease modification can lead to circular reasoning:

- *Q_1:* "How do you know that the drug is disease modifying?"
  - *A_1:* "Because it changes the course of a modifiable disease."
- *Q_2:* "How do you know that the disease is modifiable?"
  - *A_2:* "Because its course is altered by the drug."

Conclusions

1. Disease modification is not just a regulatory concept. It reflects the degree of completeness in our knowledge about the underlying mechanisms of a disease, and of how a treatment intervention could potentially alter those mechanisms.
2. Our current level of knowledge is insufficient to confirm whether schizophrenia is a modifiable disease.
3. It may not be appropriate to give a disease modification claim based only on change in the trajectory of syndrome course, in the absence of knowledge of the relationship between pathophysiology and syndrome course. Some other description, such as “syndrome course modification,” could be considered. But we already have an equivalent description, which is “treatment.”
4. New label claims of disease modification could transmit to patients and providers that the biological mechanisms underlying schizophrenia are now better understood than they actually are.
5. Clinical trials can help build our knowledge base on the modifiability of schizophrenia, but they will likely raise new questions that will require further basic science research.
6. We need better understanding of the causal relationships between CNS component changes and syndrome manifestations before we can confidently grant a disease modification indication for the treatment of schizophrenia.

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