

PEREG Lecture 17:  
The Political Economy  
of Pharmaceutical Regulation #1

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# The Power of the FDA over Pharmaceuticals

Patients are two removes from drugs: physician and FDA.

Gatekeeping power – “veto” over product development – is life-and-death say over careers, companies, products, ads, labeling, even patients.

FDA regulates all clinical research with new pharmaceuticals, devices, vaccines, any new product claim (indication).

FDA is primary author and enforcer of human subjects protections in U.S.

# FDA Pharmaceutical Regulation: Theoretical Rationale

1. Flawed Market for Information: Consumers don't know risks, poorly estimate them even if they have facts.

- E.g., product scares
- 2 effects: (a) equilibrium fraud, (b) consumers avoid purchases that would make them better off.

2. Health market dilutes competition among pharmaceuticals:

(a) **NO SINGLE MARKET FOR PHARMACEUTICALS**: numerous mutually exclusive markets for ethical drugs, generates lots of smaller monopolies.

(b) Health insurance gives pharm consumers fewer incentives to shop for best buy, hence less incentive for pharms to develop marginally better buys.

# Another View: Drugs as Credence Goods

1. *Clearly Drugs are not “Inspection Goods”*: Can’t know their value ex ante.
2. *So why might drugs not qualify as “experience goods”?*
  - Limits on patient and physician inference (**self-curing disorders, placebo learning**)
  - Given this, advertising will exploit these information asymmetries and learning constraints
3. Regulation might (might not) improve “consumer welfare”. Evidence from food regulation in early 1900s.

# A SIMPLE MODEL OF PLACEBO LEARNING

Can placebo effects and other behavioral elements of health care be used to understand rationales for regulation?

Approach here: theoretical modeling.  
Evidence is quite incomplete.

# Basic Questions

If we take placebo effects seriously, what are their economic, political, regulatory implications?

Is the health care system (or, the market for medical treatment) a placebo economy? To what extent, and how so?

If so, what implications for regulatory policy?

TODAY: **speculative**. Paper on how placebo effects complicate individual optimization over alternative therapies, over time. To get to Qs above, need

- model of aggregation (how do individual effects add up to “need” or “demand”)?
- pricing and advertising: how would suppliers of medical treatment behave in a world where consumers were placebo constrained?
- What would regulation look like?

# Placebo Effects

For 50 years, something of an accepted fact. FDA regs: must have placebo arm for RCTs, Phase II and Phase III.

Large literature in internal medicine, psychiatry, individual specialties (allergy, CNS, even cancer).

Hjortskov & Goetzsche (1998): what if what we call “placebo effects” is just regression to the mean? Meta-analysis sheds doubt.

# Consensus: Placebo Effect is Genuine Neurological Phenomenon

Possible to reverse placebo effect with naloxone (opioid antagonist)

fMRI studies (Wager et al, F Benedetti & Co.): (1) response to placebo mimics response to SSRIs

Withheld treatment studies (got by IRBs in Italy): “hidden administrations of pharmacological and nonpharmacological therapies are less effective than the open ones.” (Reverse may be true for mice.)

# Interactions of Placebo with “Message” (Priors?)

Branthwaite and Cooper: Study (*BMJ* 1980).

Randomly assign 800 women to

- (1) Brand-name aspirin
- (2) Brand-name labeled placebo
- (3) Unknown (“generic”) aspirin
- (4) Unknown labeled placebo

Result: In response rates  $(1) > (2) > (3) > (4)$

# Model of Placebo Learning

Imagine human learning about medical treatments is subject to contamination of observables by expectations.

Add to this the possibility that diseases may be self-limiting.

What happens to human inference when otherwise rational agents see “felt” history of treatment efficacy and treat it as pharmacologically generated?

What happens to otherwise (dynamically) rational utilization of treatments?

# QUESTIONS

○ Do placebo effects potentially complicate inference by patients and their doctors about the quality of medical treatments? Might this be true even if the existence of placebo effects is known for a given therapy?

○ How might placebo effects interact with advertising and other practices that affect patients' and doctors' initial beliefs about the quality of a therapy?

○ Might placebo effects influence pharmaceutical consumption and dosing? Is it possible that some patients repeatedly consume a drug when a sugar pill would do as well? Might other patients avoid a therapy they need or underdose due to placebo effects?

○ Can a perspective on placebo learning tell us anything informative about religious healing?

○ How might placebo effects interact with the cyclic or self-limiting nature of diseases to influence human inference about the quality of medical or pharmaceutical treatments?

○ Might placebo effects complicate research-based inference on the returns to medical and pharmaceutical investment, advertising, and other expenditures?

# MODEL

Patient (“agent”) is infinitely lived, eventually gets sick

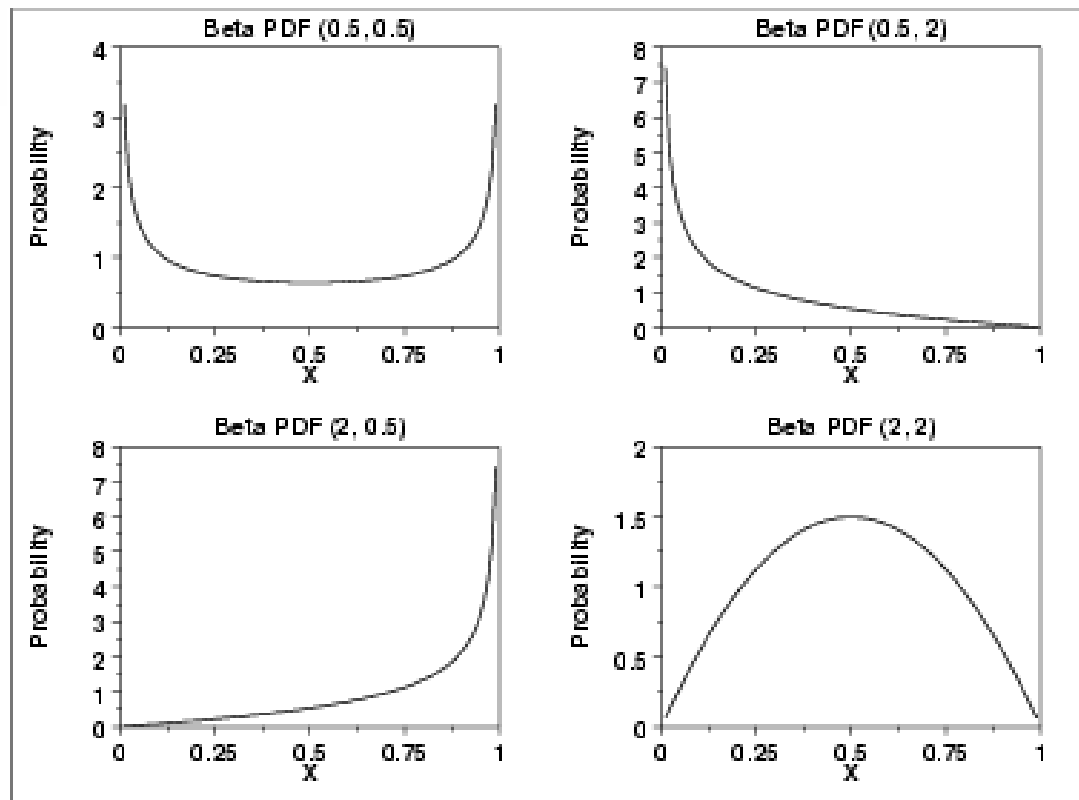
$X_{ijt}^{ILL} \equiv X_{ij}^{ILL} =$  non-treated sickness state in period  $t$

She can try up to  $Q$  treatments for her illness. A default treatment with known curing probability  $\alpha$  exists. Agent starts with an unknown “incumbent” treatment (the unknown with the highest prior). Treatment (“drug”) has an unknown curing probability, distributed Beta.

$$\gamma_{1j} \in \Gamma \equiv [0, 1]$$

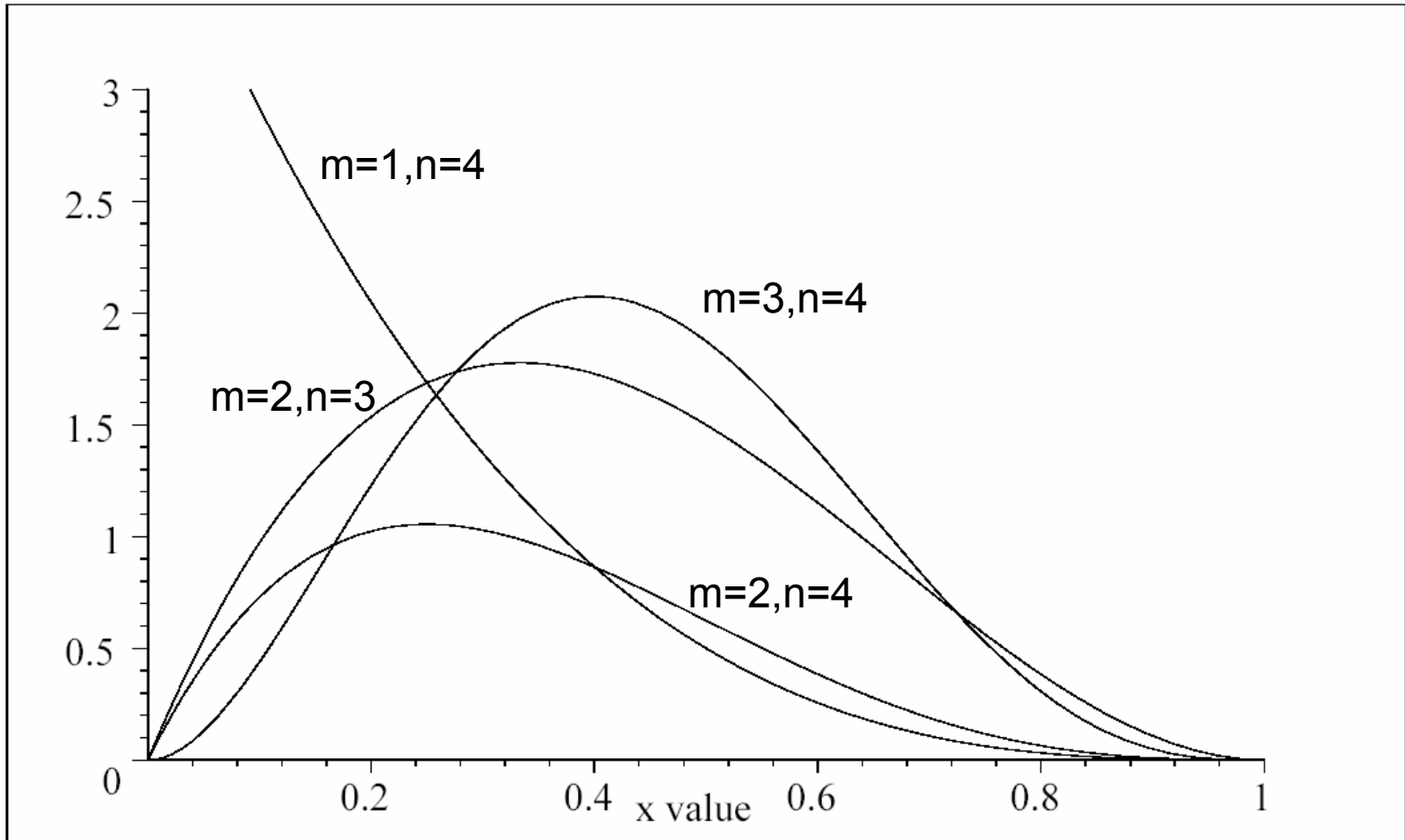
# Beta Distribution

$$\text{pdf is } \phi(x) = \frac{x^{\theta-1} (1-x)^{n-1}}{\int_0^1 u^{\theta-1} (1-u)^{n-1} du}$$



# Plots for Beta distribution with integer-valued parameters, $0 < m < n$

$$\frac{x^{2-1}(1-x)^{3-1}}{\frac{2}{24}}, \frac{x^{2-1}(1-x)^{4-1}}{\frac{12}{120}}, \frac{x^{3-1}(1-x)^{4-1}}{\frac{12}{720}}, \frac{x^{1-1}(1-x)^{4-1}}{\frac{6}{24}}$$



# “Optimal” Inference

1. Assume curing is beta-distributed, s.t.  $0 < m \leq n$ ,

$$\gamma_{1j} \sim \beta(m, n)$$

2. Convenient to think of distribution as representing  $m$  “successes” in  $n$  trials (hence with  $n - m$  “failures”)

3. Upon utilizing treatment, agent observes healing variable  $G_{ijt}$  with mean  $\gamma_{ij}$ . Then without placebo effects, observed health state is

$$Y_{ijt} = (1 - G_{ij}) X_{ij}^{ILL}$$

# “Optimal” Inference

4. Agent observes a history of Bernoulli outcomes, where “1” corresponds to a cure, “0” corresponds to uncured disease. Then after  $\tau$  periods, optimal estimate of curing is

$$\hat{\gamma}_{1j,\tau+1}^* = 1 - \frac{(n - m) + \sum_{t=0}^{\tau} Y_{1jt}}{n + \tau X^{ILL}}$$

5. Because  $G_{ijt}$  is stationary, application of Bayes’ rule gives error as

$$E [\psi_{\tau}^*] = \frac{m + \tau \gamma}{n + \tau} - \gamma_{ij}, \text{ and } \lim_{\tau \rightarrow \infty} \psi_{\tau}^* = 0$$

# Problem 1: What if Expectations about Treatment Influence Curing?

1. Suppose people's ailments are more or less "suggestible." Define suggestibility non-stochastically by

$$\lambda_{ij} \quad (0 \leq \lambda_{ij} \leq 1)$$

2. Now define "apparent" or "felt" curing per-period as  $A_{ijt}$  (non-stationary). Human agent observes not  $Y_{ijt}$  but  $Z_{ijt}$ :

$$Z_{ijt} = (1 - A_{ijt}) X_{ij}^{ILL}$$

$$E[Z_{ijt}] = X_{ij}^S \left( 1 - (1 - \lambda_{ij}) \gamma_{ij} - \lambda_{ij} \widehat{\gamma}_{ijt}^{felt} \right)$$

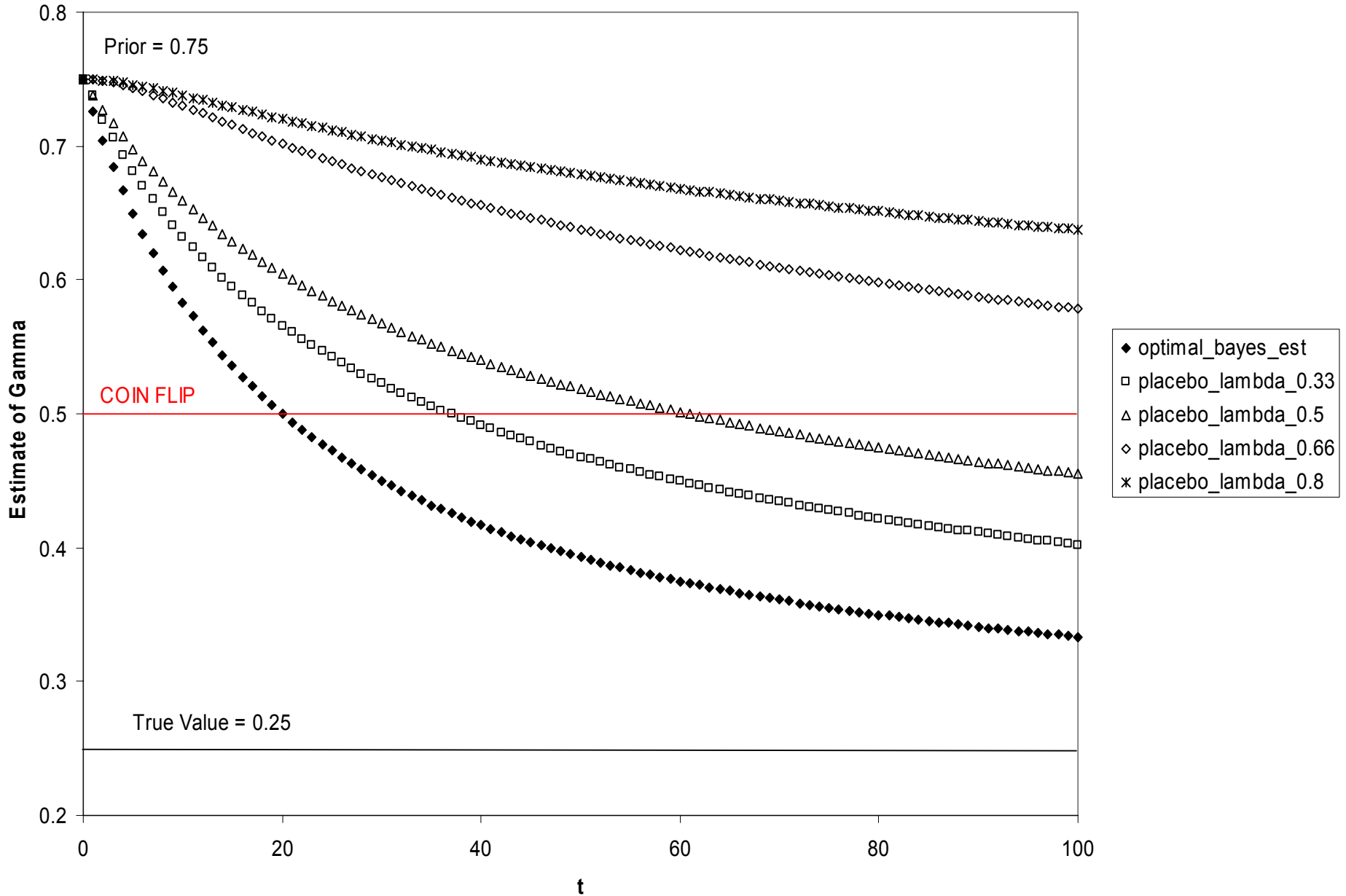
$$E_{zt}[A_{ijt}] = \alpha_{ijt} = (1 - \lambda_{ij}) \gamma_{ij} + \lambda_{ij} \widehat{\gamma}_{ijt}^{felt}$$

# Properties of Placebo Inference

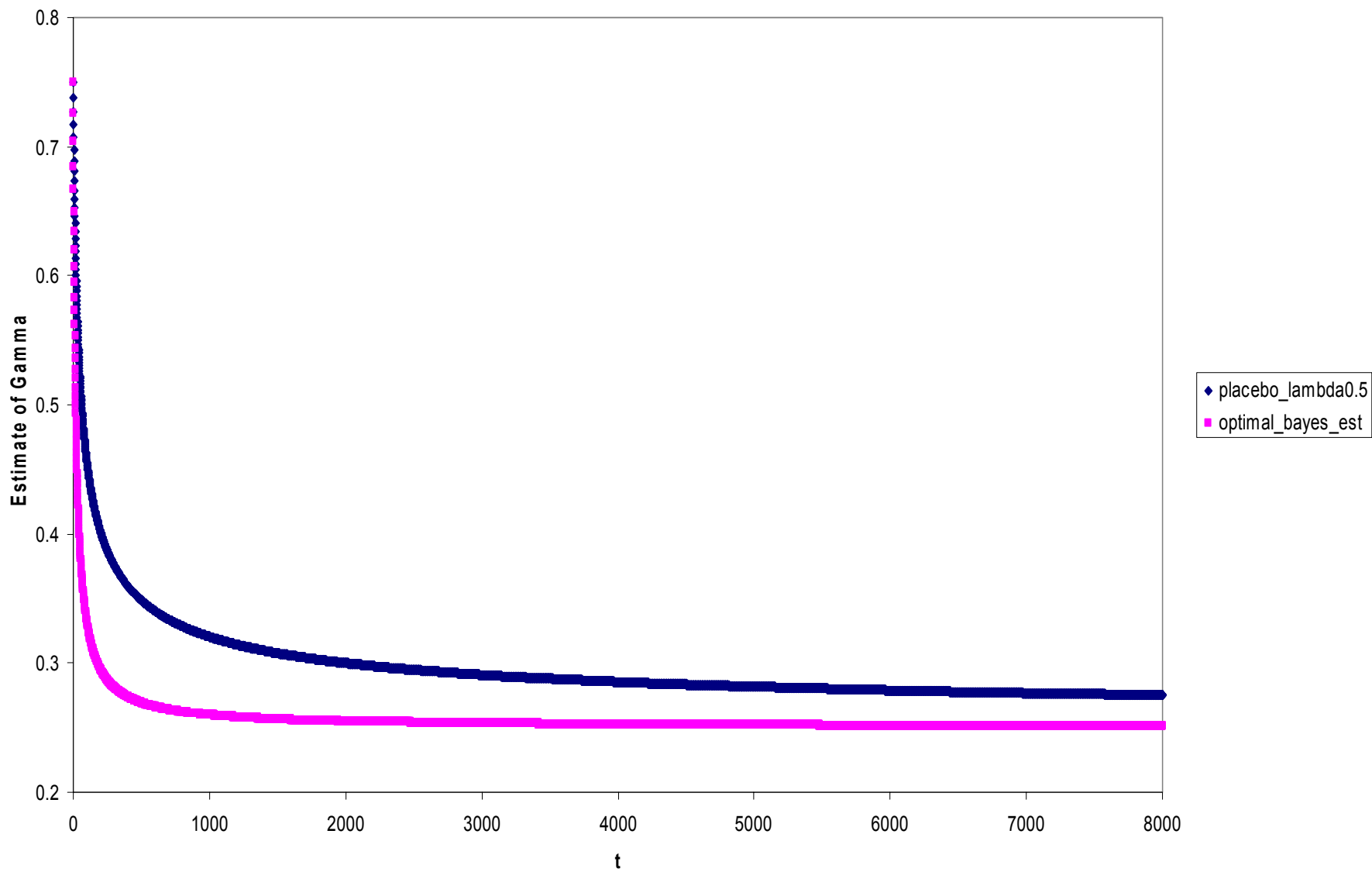
$$E_0 \left[ \hat{\gamma}_{1ij,t=\tau}^{felt} \right] = \frac{m + X_j^{ILL} \left[ \tau \gamma_{1j} + \lambda \left( \sum_{t=0}^{\tau-1} \psi_{1jt}^{felt} \right) \right]}{n + \tau X_j^{ILL}}$$

1. Short-run (“small-sample”) Bias but long-run consistency.
2. But also “inefficiency”: placebo learning agent makes poor use of his own history; arrives at the truth more slowly.

# Convergence of Placebo Estimates to Truth (Gamma = 0.25), by Suggestibility



Convergence of Placebo Estimate and Optimal Estimate to Truth (0.25)



# Problem 2: Placebo Learning under Self-Limitation

1. Some diseases may be self-limiting (influenza, volleyball-induced calf strain experienced while professor is on frivolous leave in Palo Alto). Let per-period “remission” be given by  $W_{ijt} \in [0, 1]$ , s.t.  $E[W_{ijt}] = \omega_{ijt}$ . Now agent observes

$$Z_{ijt}^{felt, W} = X_{ij}^{ILL} (1 - A_{1jt}) (1 - W_{jt})$$

# Modeling Remission

$W_{jt}$  is binary, where “1” is remission in period  $t$

$W_{jt}$  has first moment  $\omega_{jt}$

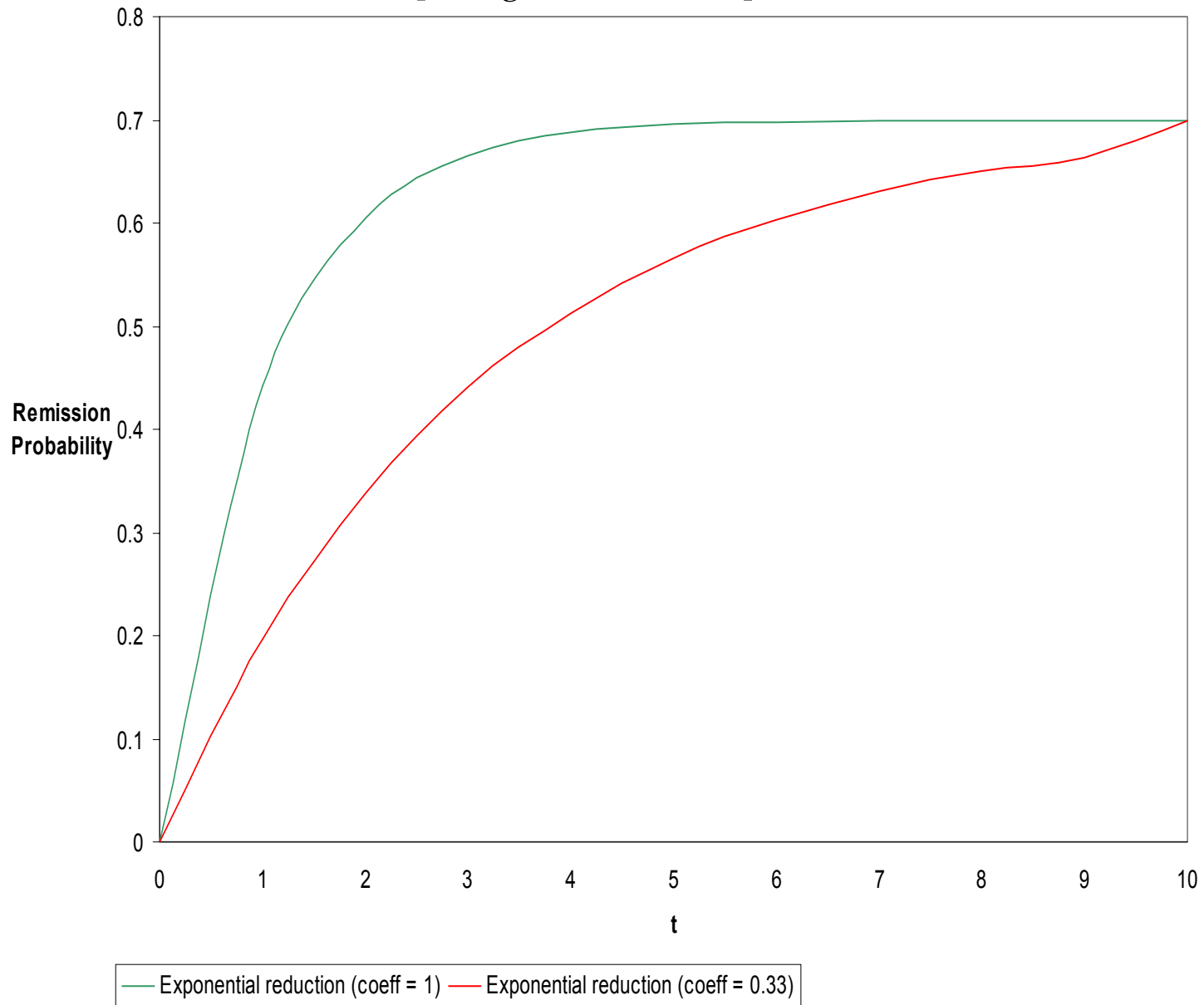
Moment  $\omega_{jt}$  moves from 0 to  $\omega_j^{\max}$

Convergence is monotonic in expectations:

$$(\omega_{jt} - \omega_{j,t-1} \geq 0, \forall t)$$

# Sample Self-Limitation Series

[ $\omega_{\max} = 0.7$ ]



# Self-Remitting Conditions Exacerbate Placebo Learning

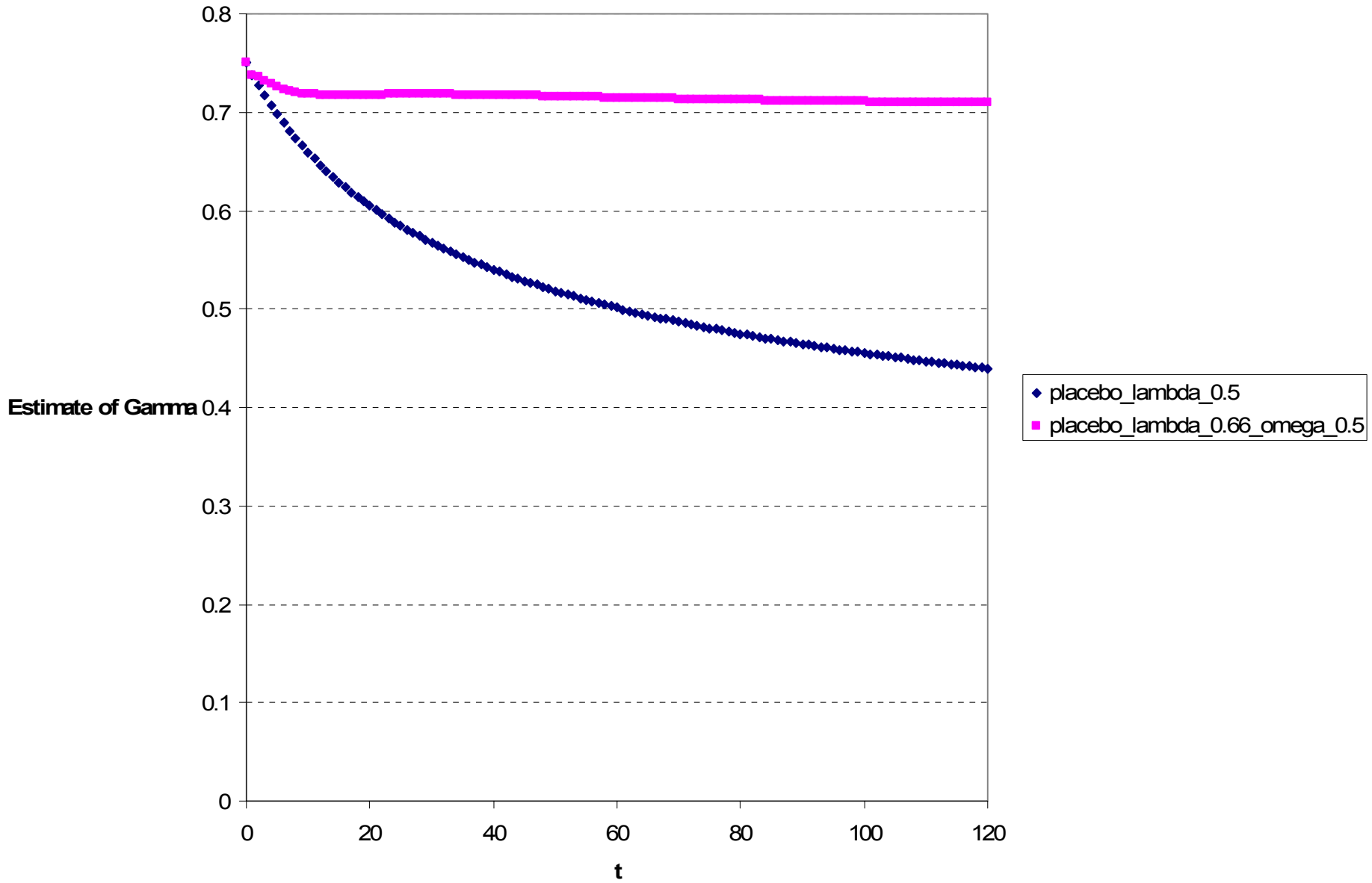
Comment 2: Under reasonably broad set of conditions, asymptotic inconsistency.

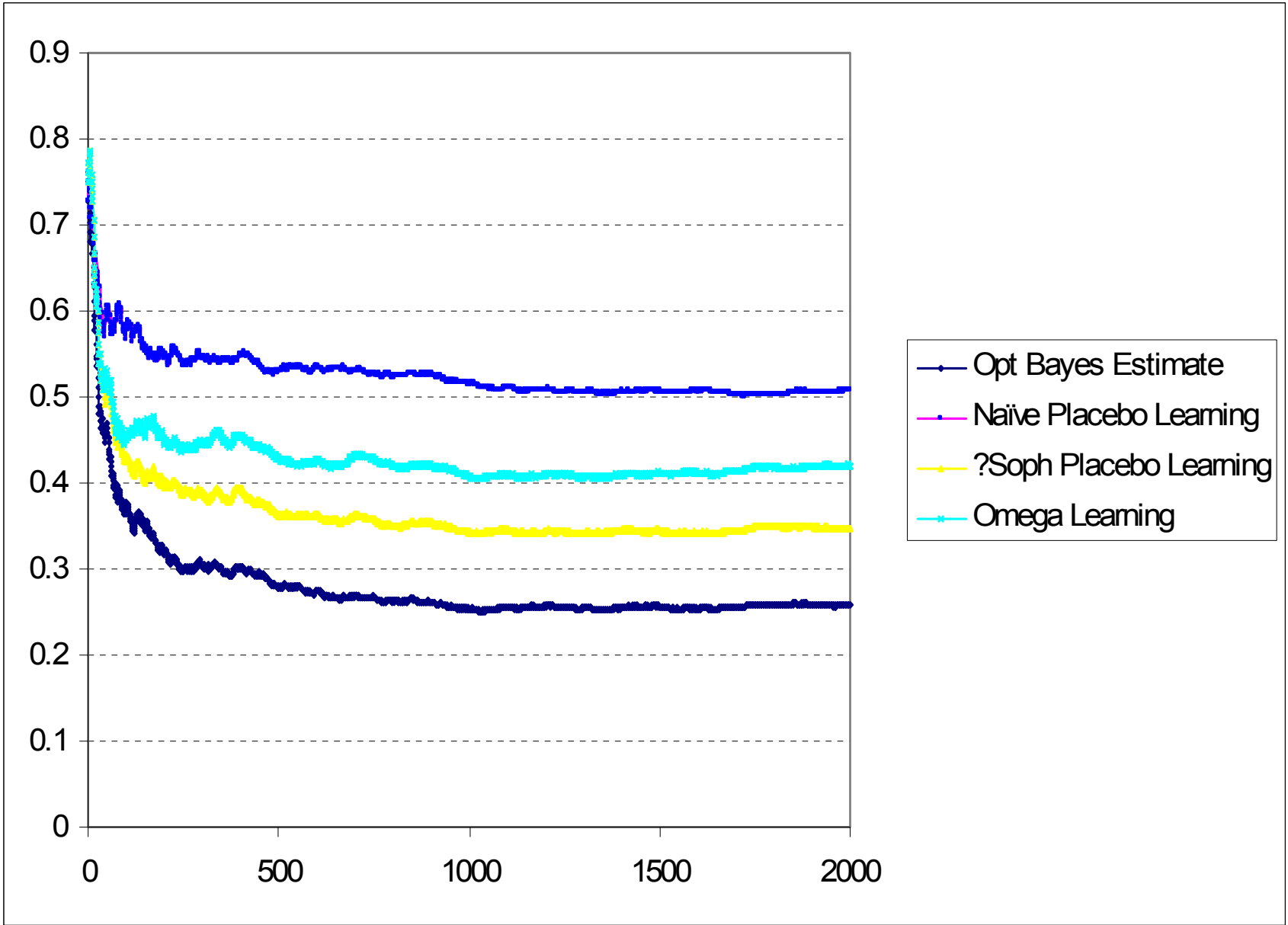
$$\liminf E_t \left[ \psi_{1jt}^{felt,W} \mid H_{1jt}^{felt,W} \right] \geq \left( 1 - \omega_j^{\max} \right) \hat{\alpha}_0^{felt,W} + \omega_j^{\max} - \mu_{1j0} > 0$$

Comment 3: Agent can start with “truth,” end up with inconsistent estimate over numerous cycles of illness and treatment.

➤ I.e., remission can make placebo learning “endogenous.”

Placebo Estimate with and without Self-Limitation





# UTILIZATION UNDER PLACEBO LEARNING

Now add in decision-theoretic model of utilization, and compare “behavior” of optimal agent with that of placebo-learning agent.

1. Assume per-period value of health  $I_t \equiv I$
2. Utilization is binary [ $\sigma_t = 1$  for utilization in period  $t$ , 0 otherwise], with constant per-period cost  $k$  [purchase cost, known side effects]

Agent’s problem is:

$$\sup E_{t=0} \sum \delta^t F \left[ I_t - X_{ij}^{ILL} \left( 1 - A_{ijt} \left[ \gamma_{ij}, \lambda_{ij}, \hat{\gamma}_{ijt}^{felt} \right] \right) - k_i \sigma_{it} \right]$$

# MULTI-ARMED BANDIT

Solution: calculate **Gittins index**, or minimal certain reward that human agent would choose over uncertain treatment, given all agent's information about the treatment.

$$R^i(\hat{\gamma}_{ijt}) = \inf\{\eta \in \mathfrak{R}^+ \mid \sup [\eta, f_t^i + \delta \int f_{t+1}^i(\hat{\gamma}_{ijt}) \mu(d\gamma)] = \eta\}$$

So “default” treatment – which could be no treatment at all – functions as this minimal certain reward

# “Overutilization” as Type I Decision Error

1. I might hang on to bad (inefficacious) medicine too long. (Comment 1, 1a)
2. If a cheap sugar pill would give me the same effect, and the placebo curing is separable from the medicine, I’m overpaying. (Comment 4)
3. If placebo curing separable from medicine, I would do as well by paying less for a cheaper default. (Comment 5)
4. I might “undertreat” a fatal disease whose “early warnings” and “symptoms” are reduced by placebo curing, even as pathology continues unabated. [E.g., 1950s markets for Hoxsey’s cancer cure, later for Laetrile.] (Comment 6)
5. Not considered here: what if side effects are also subject to suggestibility?

# IMPORTANCE OF BELIEFS

Comment 7: Both utilization ( $c_t$ ) and overutilization ( $\varphi_t^I$ ) are increasing in initial beliefs ( $\mu_{ij0}$ ), and this relationship is non-decreasing in suggestibility ( $\lambda$ ).

Key to placebo learning is that false initial beliefs cannot be disproved. Crucial assumption: **both curing probability and suggestibility vary across individuals.**

# HYPOTHESES

1. Overutilization is increasing in suggestibility, given high initial beliefs.
2. Marginal effect of advertising on utilization is higher where suggestibility is higher (for more suggestible agents, more suggestible diseases).
3. Placebo effects greater for self-remitting diseases than for non-cyclic ones.

# POSSIBILITIES

1. Do advertisements work not merely by informing but also by raising patients' initial beliefs about efficacy of treatment?

Aside from Branthwaite and Cooper, no empirical work that addresses this question.

Carpenter, Field, Christakis, King and Kleinman: examine variation in clinical trial placebo response rates before and after the drug is advertised.

# POSSIBILITIES

2. Could more products (“entrants”) make consumers worse off?

With placebo learning, agent becomes attached to treatment.  
Associates curing only with that treatment. Attachment is increasing in risk-aversion.

Do drugs have “associative rents”? Given two pharmacologically equivalent medications, BLUE and YELLOW tablets, agent continually chooses BLUE over YELLOW even though YELLOW is less costly. Medications could be bioequivalent but not “psychoequivalent.”

More entrants might increase chances that consumer ends up in a state of attachment to ineffective treatment.

One conclusion from pharma econ lit:

# RATIONALES FOR REGULATION?

1. Imagine that regulator's function is to compel or provide an estimate of the population average of placebo effect. [This is one historical role of FDA.]

Then [Comment 1a] bias is less, and error is less.

2. Or imagine that, for drugs with population average of efficacy not well above population average of placebo effect, regulator excludes from market altogether.

Under what conditions is patient better off?

# RATIONALES FOR REGULATION?

3. Drugs may be “credence” goods, in part because of placebo learning.

If so, “lemons” problem (Akerlof), and entry restriction can be justified (Leland JPE 1976).

Key here is that agents must believe that the regulator’s intervention is error-reducing.

That is, in order for regulation to work, regulator must be trusted. CREDIBILITY.

# Markets for Patent Medicines

Received wisdom: Proprietary medicines a sideshow to the emergence of pharmaceutical industry in West.

WRONG: (1) Hundreds of millions of dollars spent annually by early 1900s; by 1950, \$2B annual market; (2) from 30,000 to 50,000 commonly consumed or prescribed; (3) accounted for tens of millions in annual advertising expenditures.

## Examples:

“4-44,” a purported cure for stomachache; “4-44 revitalizes your food with sixteen minerals without which you cannot have a sound stomach or vigorous body.”

“Triple Strength Chinese Herb Compound,” which allegedly cured indigestion, dysentery, “biliousness,” dyspepsia, gallstones, malaria, asthma, eczema, rheumatism, and bad breath

Persenico: success “in combating neurasthenic impotence, pre-senility, low vitality and general nervous ailments, particularly...of sexual origin.”

Revivio: “improve your vigor.”

“Dr. Young's Rectal Dilators”: used “natural methods” to strengthen rectal muscles by “imitating Nature’s own process” to prevent “constipation and piles.”

KEY QUESTION: NOT WHY DO PEOPLE BUY THESE THINGS, BUT...

WHY DO THEY KEEP COMING BACK?

# EXTRA SLIDES RE MODEL

# Inference with Placebo Learning

3. Period 0 expectation of  $\tau$ th-period felt estimate of curing (application of Bayes equation to  $Z_{ijt}$  instead of  $Y_{ijt}$ ), is

$$E_0 \left[ \hat{\gamma}_{ij,t=\tau}^{felt} \right] = \frac{m + X_{ij}^{ILL} \left[ \tau \gamma_{ij} + \lambda \left( \sum_{t=0}^{\tau-1} \psi_{ijt}^{felt} \right) \right]}{n + \tau X_{ij}^{ILL}}$$

$$\mu_{ij0} = \inf \left[ \mu^i, \mu^j, \mu^d \right]$$