EPID 765
Pharmacoepidemiology

Lesson 5:

Study Design Solution
- Active comparator
- New user design

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Outline

- Striking example of what can go wrong
- Theory:
  - Brief history of active comparator, new user study design
- Practice:
  - Examples of confounding control by new user, active comparator design

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Hormone Therapy and Coronary Heart Disease

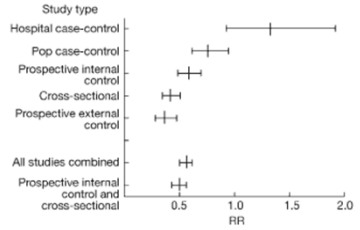

Figure 2 Summary relative risks and 95% confidence interval estimates for studies of estrogen use and risk of coronary disease, by study design. There was significant ($P < 0.001$) heterogeneity by study design

Stampfer & Colditz, Prev Med 1991;20:47-63

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HT and CHD: Experimental


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 7, 2003 VOL. 349 NO. 6

Estrogen plus Progestin and the Risk of Coronary Heart Disease

JoAnn E. Manson, M.D., Dr.P.H., Judith Hsia, M.D., Karen C. Johnson, M.D., M.P.H., Jacques E. Rossouw, M.D.,

RESULTS

After a mean follow-up of 5.2 years (planned duration, 8.5 years), the data and safety monitoring board recommended terminating the estrogen-plus-progestin trial because the overall risks exceeded the benefits. Combined hormone therapy was associated with a hazard ratio for CHD of 1.24 (nominal 95 percent confidence interval, 1.00 to 1.54;

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Plausible Explanations

- Effect modification by time since menopause
  - RCTs: age 70 (HERS) or 60 (WHI)
  - Non-experimental: menopause (age 50)
  - HT could prevent atherosclerosis but cause thrombosis in atherosclerotic vessels
- Confounding bias
  - Control for SES, education reduces "protection"
- **Prevalent user (selection) bias**
  - Missed early events
    - Survivors of treatment
    - Depletion of susceptibles
    - Time-varying hazards
  - Inability to control for RF altered by HT

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New User Design

- Feinstein AR. Sources of 'chronology bias' in cohort statistics. Clin Pharmacol Ther 1971;12:864-79.
  - ***"4. Serial time. …*** the … time that has **elapsed serially since "zero time," which is the inception of each member's exposure to the maneuver under surveillance**."
- Kramer et al. J Chron Dis 1987;40:1073-85:
  - ***"For what period of time?*** The risk posed by a drug for a .. event **is not generally** the same in the **sixth month of chronic therapy** as in the **first or second week**."
- Guess. J Clin Epidemiol 1989;42:1179-84:
  - "The possibility of **temporally non-constant hazard functions** should be considered in the study design. *This requires that drug exposure time be measured not only in relation to onset of the study disease but also in* **relation to start of therapy** *…."*

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New User Design

- Moride, Abenhaim. J Clin Epidemiol 1994;47:731-7:
  - "Our results .. are compatible with .. a **selection process** by which patients who have used the drugs in the past and **tolerated them well remain** on the drugs while patients who are **susceptible** to gastropathy **select themselves out** of the population at risk. This process is analogous to the .. "**healthy worker effect**".. If not taken into account .. it could introduce a **selection bias**."
- Ray, Maclure, Guess, Rothman. Inception Cohorts in Pharmacoepidemiology. Symposium, ICPE 2001
- Ray. Am J Epidemiol 2003;158:915-20:
  - "**First**, prevalent users are "**survivors**" of the early period of pharmacotherapy … **Second, covariates** .. often are **plausibly affected by the drug itself**."
  - "A new-user design **eliminates these biases** by restricting the analysis to persons under observation at the **start of the current course** of treatment"

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Examples

Observational Studies Analyzed Like Randomized Experiments

An Application to Postmenopausal Hormone Therapy and Coronary Heart Disease

Miguel A. Hernán,[a,b] Alvaro Alonso,[c] Roger Logan,[a] Francine Grodstein,[a,d] Karin B. Michels,[a,d,e] Walter C. Willett,[a,d,f] JoAnn E. Manson,[a,d,g] and James M. Robins[a,b]

Background: The Women's Health Initiative randomized trial found greater coronary heart disease (CHD) risk in women assigned to estrogen/progestin therapy than in those assigned to placebo. Observational studies had previously suggested reduced CHD risk in hormone users.

Methods: Using data from the observational Nurses' Health Study, we emulated the design and intention-to-treat (ITT) analysis of the randomized trial. The observational study was conceptualized as a sequence of "trials," in which eligible women were classified as initiators or noninitiators of estrogen/progestin therapy.

Results: The ITT [illegible] and 1-year intervals) of CHD for initiators versus noninitiators were 1.42 (0.92–2.20) for the first 2 years, and 1.12 (0.84–1.48) in others. The ITT HRs were 0.84 (0.61–1.14) in women within 10 years of menopause, and 1.12 (0.84–1.48) in the others (*P* value for interaction = 0.08). These ITT estimates are similar to those from the Women's Health Initiative. Because the ITT approach causes severe treatment misclassification, we also estimated adherence-adjusted effects by inverse probability weighting. The HRs were 1.61 (0.97–2.66) for the first 2 years, and 0.98 (0.66–1.49) for the entire follow-up. The HRs were 0.54 (0.19–1.51) in women within 10 years after menopause, and 1.20 (0.78–1.84) in others (*P* value for interaction = 0.01). We also present comparisons between these estimates and previously reported Nurses' Health Study estimates.

Conclusions: Our findings suggest that the discrepancies between the Women's Health Initiative and Nurses' Health Study ITT estimates could be largely explained by differences in the distribution of time since menopause and length of follow-up.

(*Epidemiology* 2008;19: 766–779)

Causal inferences are drawn from both randomized experiments and observational studies. When estimates from both types of studies are available, it is reassuring to find that they are often similar.[1–3] On the other hand, when randomized and observational estimates disagree, it is tempting to attribute the differences to the lack of random treatment assignment in observational studies.

This lack of randomization makes observational effect estimates vulnerable to confounding bias due to the different prognosis of individuals between treatment groups. The potential for confounding may diminish the enthusiasm for

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Confounding by Indication/Frailty

- Given that we cannot measure indication/frailty
- Other means to control for confounding?
  - Randomization, but clearly not feasible to get timely answers for ALL relevant drug related research questions
  - Restriction, powerful tool to address confounding
- Implicitly restrict to Indication and absence of frailty
- Initiators of treatment alternatives for same indication
  - Guideline, clinical practice
- Active comparator, new user (ACNU) study design

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Active Comparator

- Kramer et al. J Chron Dis 1987;40:1073-85:
  - ***"Compared with what?*** .. it is important to **compare** that risk **with** that of some **other real therapeutic option** for **patients with the same clinical indication**. Just as in a clinical trial investigating treatment efficacy, any epidemiologic study of treatment risks should **compare two or more viable treatment alternatives**."
  - ".. measuring risks **conditionally** on .. indication is .. **essential** to reduce confounding"

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Active Comparator, New User Design

- Strong critique of nonexperimental designs for medical interventions pre-dates active comparator, new user design
  - Based on comparing prevalent users with non-users (maximizes bias)
- Critique of Agranulocytosis and Aplastic Anemia Study led to major methodological developments (Kramer et al., Guess)
- Ray 2003 paper still landmark, first to mention the confounding issue and to clearly outline implementation
- Active comparator idea pre-dates CER!
- Combination of active comparators and new users is a really powerful tool to limit potential for bias in specific settings
- Assumption of no unmeasured confounding still dependent on "equipoise" between treatments (clinical input, guidelines)

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So Much for the Theory, but Does it Really Work?

- Examples from recent studies on antidiabetics @ UNC
  - Guideline (Diab Care 2015;38:140-149)
  - Metformin versus Sulfonylurea
  - DPP-4 versus TZD/sulfonylurea
  - Glargine versus NPH insulin

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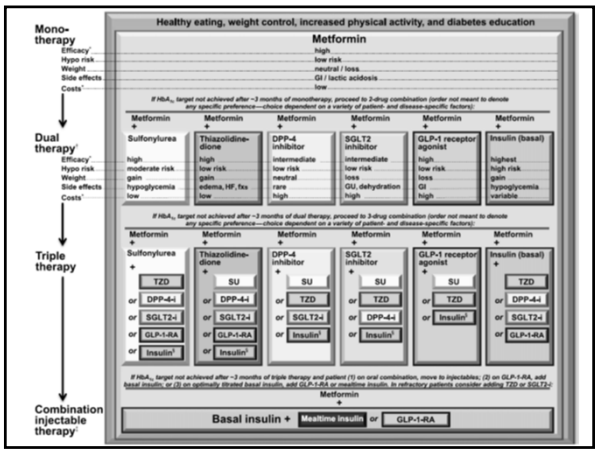

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Metformin

- First line treatment pts. with type 2 diabetes
- Reduction of cancer incidence and mortality?
  - Breast, colon and rectum, liver, pancreas, stomach, prostate, esophagus, etc?
  - Some biology
- Time related biases (Suissa & Azoulay 12, 14)
- Active comparator?
  - Guideline: none
  - Empirically: sulfonylureas

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Initiation of Metformin vs. Sulfonylurea, US Medicare

Table	Metformin	Sulfonylureas
Total	36367 (100.0)	11730 (100.0)
Median of Age (IQR)	72.0 (68.0-78.0)	76.0 (70.0-84.0)
Race		
White	28855 (79.3)	9088 (77.5)
African American	3858 (10.6)	1590 (13.6)
Others	3654 (10.0)	1052 (9.0)
Comorbidity		
Benign Breast Disease	1284 (3.5)	290 (2.5)
Benign neoplasm of breast	55 (0.2)	15 (0.1)
Chronic Obstructive Pulmonary Disease	2737 (7.5)	1136 (9.7)
Congestive Heart Failure	3195 (8.8)	2036 (17.4)
Ischemic Heart Disease	6522 (17.9)	2987 (25.5)
Hypertension	28332 (77.9)	9139 (77.9)
Osteoporosis	4069 (11.2)	1259 (10.7)

Jin-Liern Hong et al., submitted

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Initiation of Metformin vs. Sulfonylurea, US Medicare

Table	Metformin	Sulfonylureas
Medications		
Estrogen	2232 (6.1)	491 (4.2)
Progestin	262 (0.7)	45 (0.4)
Statins	20268 (55.7)	5413 (46.1)
Bisphosphonates	4384 (12.1)	1184 (10.1)
ACE Inhibitors	13715 (37.7)	4354 (37.1)
ARBs	7762 (21.3)	2253 (19.2)
Beta Blockers	14412 (39.6)	4978 (42.4)
Antidepressants	10313 (28.4)	3385 (28.9)
Digoxin	1682 (4.6)	998 (8.5)
Calcium Channel Blockers	10479 (28.8)	3676 (31.3)
Loop Diuretics	5703 (15.7)	2987 (25.5)
Non-Loop Diuretics	14747 (40.6)	3968 (33.8)

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Metformin vs. Sulfonylurea: Medicare Current Beneficiary Survey

Table 3. Characteristics in Metformin and Sulfonylureas at Baseline in MCBS 2006-2009

	MET	SUL
Total	118 (100.0)	79 (100.0)
Median Age (IQR)	74.0 (70.0-80.0)	78.0 (75.0-84.0)
Race		
White	89 (75.4)	59 (74.7)
Other	29 (24.6)	20 (25.3)
Median of BMI (IQR)	29.9 (25.6-34.0)	28.6 (25.1-33.1)
Mean of BMI (Stdev)	30.5 (6.5)	29.9 (6.9)
BMI Category*		
25	24 (20.3)	18 (22.8)
25-30	35 (29.7)	30 (38.0)
30+	58 (49.2)	29 (36.7)
Smoking Status*		
Never	61 (51.7)	48 (60.8)
Ever Smoking	57 (48.3)	28 (35.4)

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Dipeptidyl-peptidase-4 inhibitors

- Introduced (US) in 2006
- Improve glycemic control in type 2 diabetics
- Sitagliptin first in class, saxagliptin (2008), linagliptin (2011) and alogliptin (2012)
- P.O., good tolerability, body-weight neutrality
- 2009: FDA safety communication for acute pancreatitis
- 2011: pancreatic cancer in FAERS (ROR=2.7)
- 2013: increased pancreatic cell proliferation and dysplasia (autopsy study)

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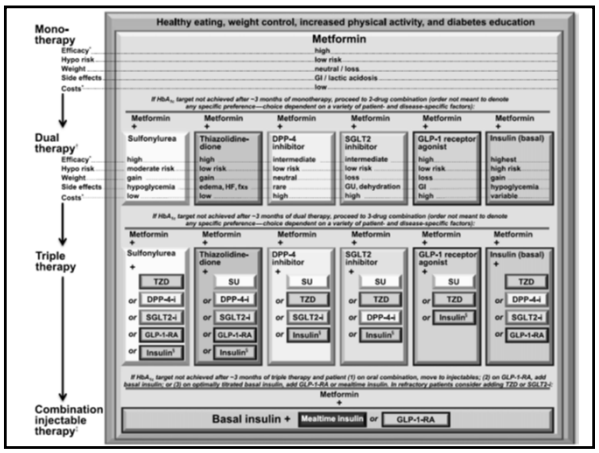

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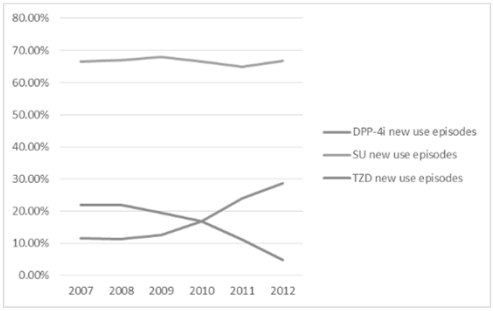
Time Trends in Initiation of Oral Antidiabetics: US Medicare



Gokhale et al., unpublished results

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Dipeptidyl-peptidase-4 inhibitors

Gokhale et al., Diabet Obes Metab 2014

	DPP-4 inhibitors (N = 29 366)		TZD (N = 26 332)	
	n	%	n	%
Mean (s.d.) age, years	75.6 (7.10)		74.6 (6.70)	
66–75 years	16 407	55.87	16 100	61.14
76–85 years	9782	33.31	8130	30.87
≥86 years	3177	10.82	2102	7.98
Male	10 590	36.06	10 609	40.29
White	22 245	75.75	18 628	70.74
Black	3059	10.42	3140	11.92
Other	4062	13.83	4564	17.33
Comorbidities§				
Connective tissue disease	9966	33.94	7763	29.48
Depression	4709	16.04	3712	14.10
Chronic obstructive pulmonary disease	5595	19.05	3999	15.19
Chronic kidney disease	5790	19.72	4031	15.31
Congestive heart failure	7740	26.36	4373	16.61
Diabetic neuropathy	6478	22.06	4813	18.28
Diabetic nephropathy	2660	9.06	1954	7.42
Diabetic retinopathy	5260	17.91	4432	16.83
Diabetic cataract	83	0.28	73	0.28
Gastrointestinal disorders	256	0.87	208	0.79
Alcohol use¶	316	1.08	258	0.98
Tobacco use¶	78	0.27	59	0.22
Pancreatitis	318	1.08	243	0.92

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Dipeptidyl-peptidase-4 inhibitors

	DPP-4 inhibitors (N = 29 366)		TZD (N = 26 332)	
	n	%	n	%
Medication use**				
Insulin	5409	18.42	4445	16.88
Metformin	16 805	57.23	14 282	54.24
Sulfonylureas	13 530	46.07	11 352	43.11
Angiotensin-converting enzyme inhibitors	10 907	37.14	9899	37.59
Angiotensin receptor blockers	8184	27.87	5982	22.72
Statins	19 331	65.83	15 466	58.73
Loop diuretics	8294	28.24	5025	19.08
Other diuretics	7831	26.67	6861	26.06
β-blockers	15 350	52.27	11 288	42.87
Calcium channel blockers	10 334	35.19	8440	32.05
Healthcare utilization§				
Blood tests	2675	9.11	2261	8.59
Lipid panel	25 483	86.78	22 105	83.95
Influenza vaccinations	16 325	55.59	13 427	50.99

Gokhale et al., Diabet Obes Metab 2014

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Dipeptidyl-peptidase-4 inhibitors

- Crude: overall good covariate balance
- Most but not all covariates balanced versus TZD (equipoise), (less so: vs. sulfonylureas!)
- Here (pancreas-CA) not much choice but
  - Which is the better comparator?
  - Choose one, present both, or combine?
  - Allow TZD initiators to be on SULF (vice versa)?
- Treatment changes after baseline different animal but similar in RCT

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Insulin Glargine

- Human insulin analogue
- Implicated with increased risk for cancer (any) in large cohort study from Germany
- Some lab evidence
- Insulin mostly used in type 2 diabetics not controlled by 1st and 2nd line oral antidiab.
- Clincal alternative: human NPH insulin
- New user, active comparator design

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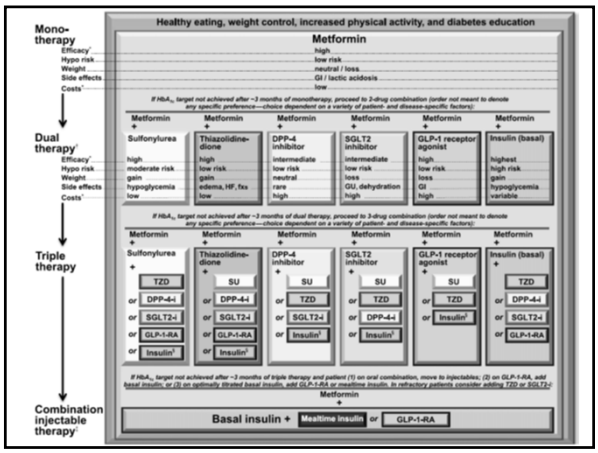

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Confounding Control by Design

	Actual cohorts		Effect on channeling, OR (95% CI)†
	Glargine	NPH	
n	43,306	9,147	
Age (years), mean (SD)	61.3 (14.0)	58.9 (17.2)	1.001 (0.999–1.003)
Sex			
Male	20,369 (47.0)	3,611 (39.5)	1.29 (1.22–1.37)
Female	22,937 (53.0)	5,536 (60.5)	1.00 (reference)
Comorbidities			
Congestive heart failure	8,074 (18.6)	1,645 (18.0)	1.01 (0.93–1.09)
Diabetic nephropathy	11,432 (26.4)	2,345 (25.6)	0.90 (0.84–0.95)
Diabetic neuropathy	9,998 (23.1)	2,110 (23.1)	0.86 (0.81–0.91)
Diabetic retinopathy	11,613 (26.8)	2,364 (25.8)	0.94 (0.89–1.00)
Hypertension	35,314 (81.6)	6,842 (74.8)	1.13 (1.06–1.20)
Pulmonary infection	10,642 (24.6)	2,344 (25.6)	0.98 (0.92–1.05)
Health care use			
Hospitalizations (any reason)			
1	8,961 (20.7)	1,922 (21.0)	1.17 (1.07–1.29)
2	3,144 (7.3)	662 (7.2)	1.15 (1.03–1.28)
≥3	2,512 (5.8)	515 (5.6)	1.25 (1.11–1.42)
Days in hospital (any reason)			
1–2	2,794 (6.5)	618 (6.8)	0.92 (0.82–1.04)
3–5	4,251 (9.8)	913 (10.0)	0.95 (0.86–1.06)

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OK, But What About BMI?

- BMI probably strongest predictor for adding insulin in T2DM and RF for some cancers
- External validation study
  - Estimate **independent** effect of BMI on prescribing glargine VERSUS NPH
  - At time of initiation (same indication)
  - Using EMR data (here: MGH, Ochsner)
- Use known effect of BMI on cancer risk to estimate confounding if BMI unbalanced
- Assumption: BMI effect on treatment choice transportable

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Limiting Confounding by Design

Table 4—*Effect of BMI on channeling between initiating glargine versus initiating NPH: external validation studies*

	Glargine	NPH
MGH		
n	574	412
BMI (kg/m^2), mean ± SD*	32.7 ± 7.53	32.4 ± 8.43
BMI (kg/m^2), *n* (%)		
<19	4 (0.7)	8 (1.9)
19 to <25	77 (13.4)	67 (16.3)
25 to <30	150 (26.1)	105 (25.5)
30 to <35	146 (25.4)	104 (25.2)
35 to <40	114 (19.9)	64 (15.5)
40 to <45	45 (7.8)	36 (8.7)
≥45	38 (6.6)	28 (6.8)

Sturmer et al. Diabetes Care 2013

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Some Differences Remain!

	Actual cohorts		Effect on channeling, OR (95% CI)†
	Glargine	NPH	
n	43,306	9,147	
Age (years), mean (SD)	61.3 (14.0)	58.9 (17.2)	1.001 (0.999–1.003)
Sex			
Male	20,369 (47.0)	3,611 (39.5)	1.29 (1.22–1.37)
Female	22,937 (53.0)	5,536 (60.5)	1.00 (reference)
Metformin	27,347 (63.2)	4,544 (49.7)	1.26 (1.19–1.33)
Niacin	810 (1.9)	108 (1.2)	1.14 (0.93–1.41)
Nonloop diuretics	7,684 (17.7)	1,397 (15.3)	1.04 (0.97–1.11)
Oral contraceptives	593 (1.4)	317 (3.5)	0.71 (0.56–0.90)
Other diabetes drugs	9,416 (21.7)	891 (9.7)	1.87 (1.73–2.01)
Progestins	407 (0.9)	145 (1.6)	1.13 (0.89–1.45)
Statins	23,874 (55.1)	3,792 (41.5)	1.17 (1.11–1.23)
Sulfonylureas	28,399 (65.6)	4,443 (48.6)	1.57 (1.49–1.65)
Testosterone	250 (0.6)	30 (0.3)	1.42 (0.96–2.11)
Theophyline	275 (0.6)	44 (0.5)	1.39 (1.00–1.94)
Thiazolidinediones	14,085 (32.5)	1,954 (21.4)	1.46 (1.38–1.55)

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Useful tips for comparator selection

- Clinical guidelines are a great place to start!
  - Need clinical input on current practices
- Carefully examine the distribution of patient characteristics in the data (e.g., patterns of care studies)
- Empirical tests of "preference score" overlap (Walker, 2013)
  - Transformation of the propensity score
  - Centered at 0.5 irrespective of prevalence
  - >50% with 0.3 ≤ preference score ≤ 0.7 (both arms)

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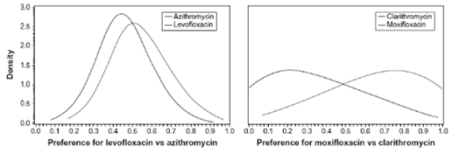
Preference score distributions

Table 2 Numbers of patients and preference overlap for antibiotic pairs taken by at least 5% of patients with community-acquired pneumonia

Antibiotic pair	Patients, n	0.3 ≤ preference ≤ 0.7	
		%	N
Azithromycin	1468	85	1254
Levofloxacin	1407	82	1159
Clarithromycin	369	39	145
Moxifloxacin	320	42	133
Amoxicillin	269	43	116
Clarithromycin	369	43	159
Amoxicillin	269	39	104
Moxifloxacin	320	42	113



Note: Data from the Pennsylvania Pharmacy Assistance Contract for the Elderly program, 2000–2005.[13]

Walker AM, et al. Comp Effect Res. 2013

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What if there is no available active comparator?

Another option: the "inactive" comparator

- *A drug used to treat a different condition, but with evidence of no effect on the outcome of interest*
- Can help reduce time-related biases by synchronizing the start of follow-up
- Equalizes healthcare system interactions

E.g., Antidepressants vs. antihypertensives

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Considerations for inactive comparator selection

1) No association with the outcome
2) Used/administered in the same manner as the active treatment
   - e.g., Chronic vs. acute treatment
3) Sufficient number of users for precise estimation
   - But not a lot of concomitant users of both drugs (who would be excluded)
4) Measurement of risk factors for outcome

D'Arcy et al, Current Epidemiology Reports

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Implementation of New User Design

- To be consistent for all periods, define:
- **Washout Period (WP)** = minimum length of time that a patient must be drug-free prior to becoming eligible for the new user cohort
  - Note: usually includes all comparators!
- **Grace Period (GP)** = maximum length of time that a user can go without the drug before being considered discontinued from drug use (e.g., 15, 30, 90, 180 days)
- **Days Supply (DS)** = imputed number of days supply to use as Days Supply when true value is unknown (e.g., 30 days)

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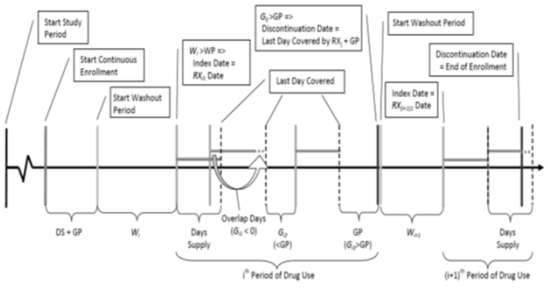
Implementation of New User Design



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Conclusions New User, Active Comparator Study Design

- Conditioning on indication has major impact on potential for confounding by indication and frailty
- Can in practice only be achieved with new user, active comparator design
  (no nonexperimental "placebo"?)
- Carefully assess potential for remaining confounding by indication (clinical input)
- Standard design in nonexperimental PE and CER (need to argue deviations!)

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