Diagnostic tests

Interpretation of results

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Agenda

- Incidence, prevalence, risk, risk ratio (relative risk), odds, odds ratio, number needed to treat, sensitivity, specificity, predictive value of positive test, predictive value of negative test
- Some of these measures explained by examples (development of new antidepressants, testing for E. coli O157)
- Probability theory

- Mammography: Probability that a positive mammogram is truly positive?
- Hiv: Can you get a positive test result if not infected with Hiv?
- Colon cancer: Probability of having cancer given that the test is positive?

Clinical development of antidepressants

- Randomized, blinded clinical trials
- Typically 8 weeks of treatment
- Include a placebo, active treatment group or both
- Approximately 150-200 subjects per treatment group
- Could include multiple doses of the new antidepressant
- Evaluate efficacy and safety of the new antidepressant

Montgomery and Åsberg Depression Rating Scale (MADRS)

- MADRS: rating scale designed to assess the severity of depressive symptoms
- Based on a semistructured interview
- Administered by trained psychiatrists
- MADRS total score is the sum of the score of the 10 individual items
- Symptoms rated on 7-point scales from 0 (no symptom) to 6 (severe symptom) with detailed anchor points
- MADRS total score goes from 0 to 60

Two MADRS items

1. Apparent sadness

Representing despondency, gloom and despair, (more than just ordinary transient low spirits) reflected in speech, facial expression, and posture. Rate by depth and inability to brighten up.

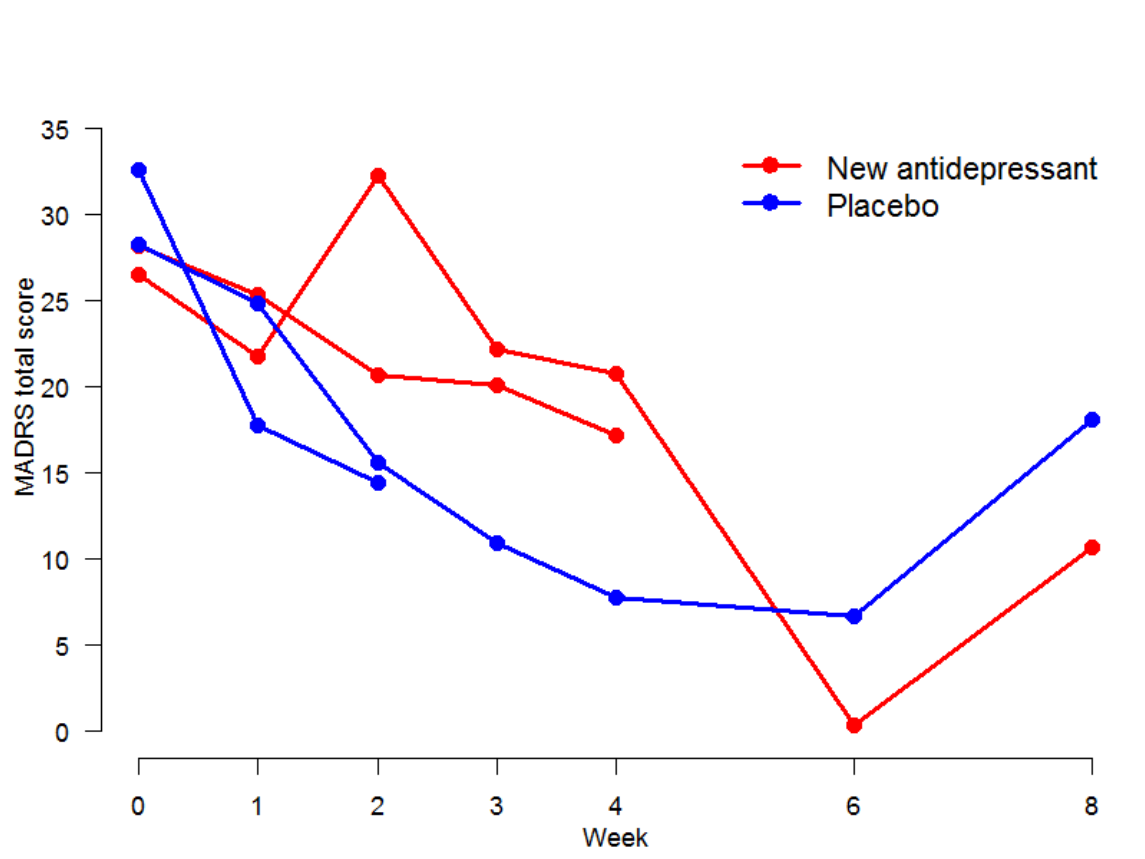
- ☐ 0 No sadness.
- ☐ 1
- ☐ 2 Looks dispirited but does brighten up without difficulty.
- ☐ 3
- ☐ 4 Appears sad and unhappy most of the time
- ☐ 5
- ☐ 6 Looks miserable all the time. Extremely despondent.

4. Reduced sleep

Representing the experience of reduced duration or depth of sleep compared to the subject's own normal pattern when well.

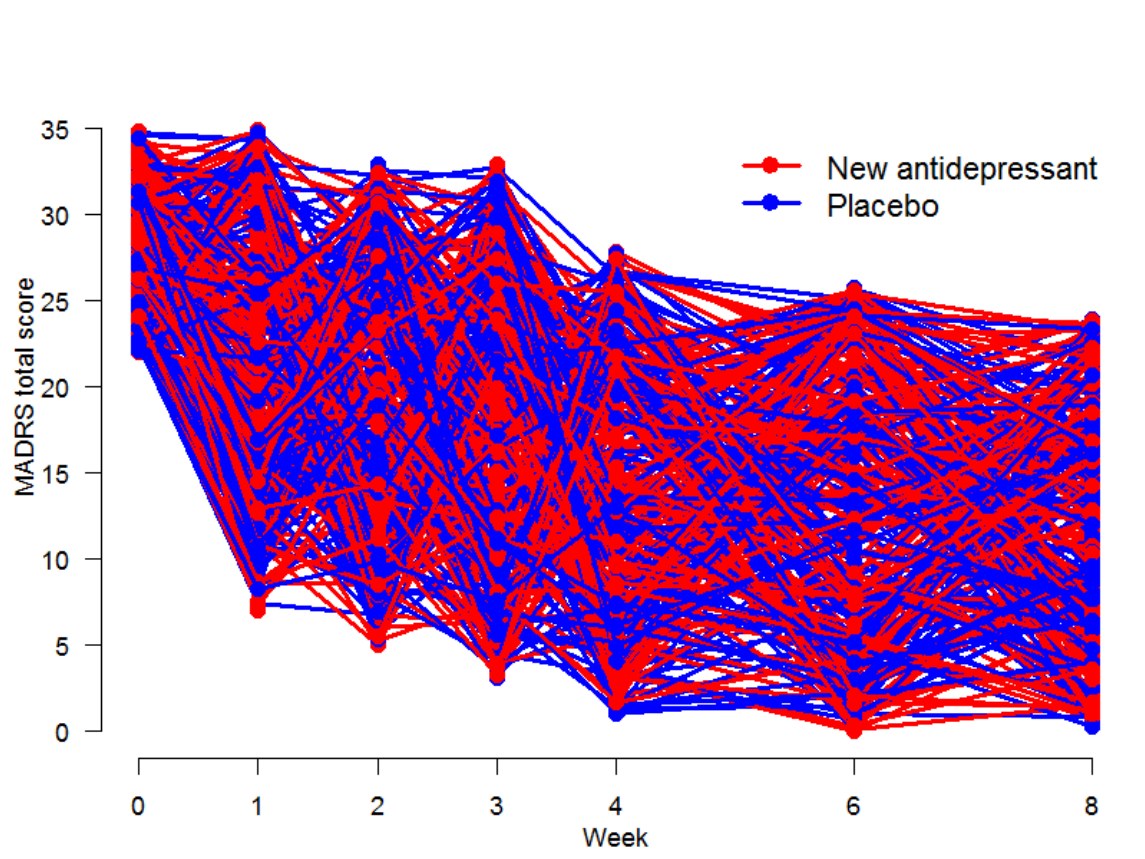
- ☐ 0 Sleeps as usual.
- ☐ 1
- ☐ 2 Slight difficulty dropping off to sleep or slightly reduced, light or fitful sleep.
- ☐ 3
- ☐ 4 Sleep reduced or broken by at least two hours.
- ☐ 5
- ☐ 6 Less than two or three hours sleep.

MADRS total score over time for individual subjects



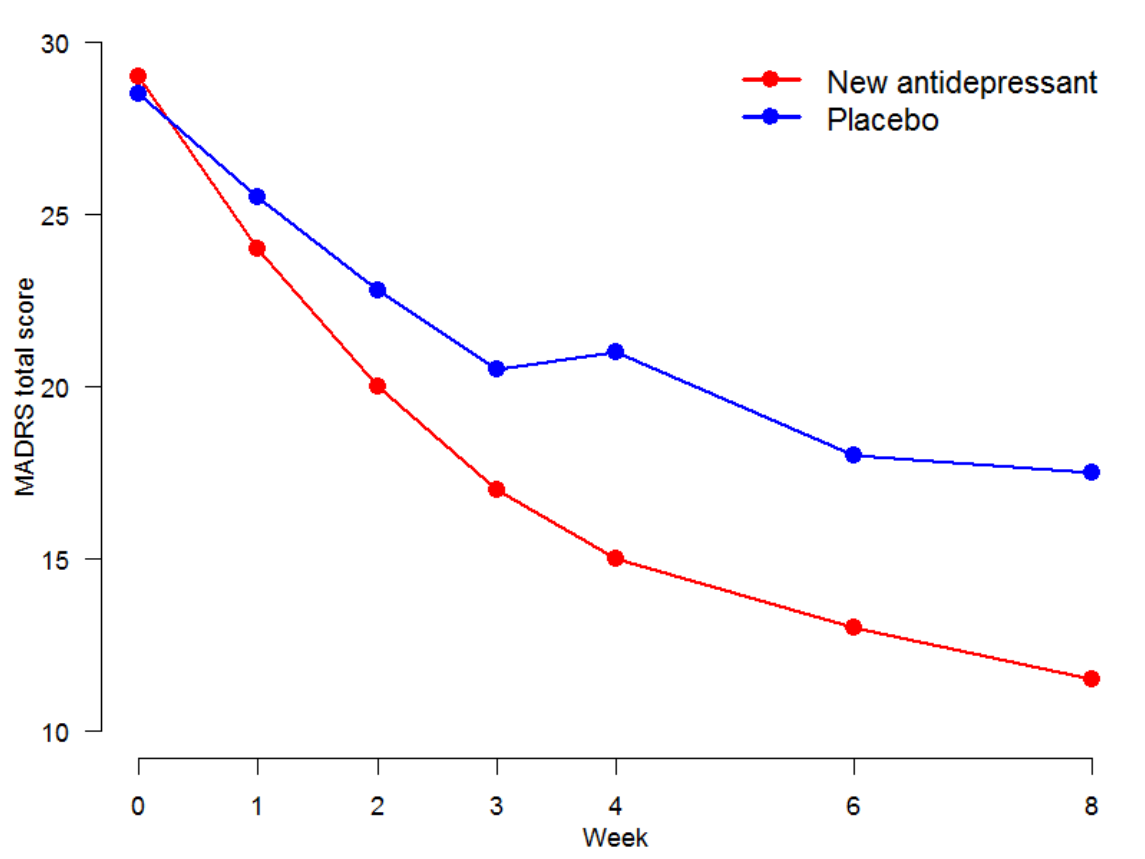
- How should subject dropping out of the trial be handled?

MADRS total score over time for individual subjects



- Is the new antidepressant efficacious?

Average MADRS total score over time by treatment group



- Is the new antidepressant efficacious?

Treatment response at week 8

- Response to treatment: at least 50 % reduction from baseline

	Placebo	New antidepressant
Response	54 (32.7%)	88 (50.6%)
No response	111 (67.3%)	86 (49.4%)
Total	165	174

- How would you report the effect of the new antidepressant?

Treatment effect based on response

- Absolute difference: percentage responding on new antidepressant - percentage responding on placebo = 50.6% - 32.7% = 17.9%
- Relative risk = Risk ratio: percentage responding on new antidepressant / percentage responding on placebo = 50.6% / 32.7% = 1.55, i.e. the likelihood of responding on the new antidepressant is 1.55 times higher than on placebo
- Number needed to treat (NNT): 100 / absolute differrence = 100 / 17.9 = 5.6
    - The number of patients that need to be treated for one to benefit compared with a control in a clinical trial
    - The higher the NNT, the less effective is the treatment

Treatment effect based on response

- Odds ratio (OR) = the ratio of two odds

$$\text{OR} = \frac{p_1/1-p_1}{p_2/1-p_2} = \frac{0.506/(1-0.506)}{0.327/(1-0.327)} = 2.11$$

- Does not mean that the response to treatment is 2.11 times as likely on the new antidepressant as on placebo
- Odds of treatment response is 2.11 times higher in the new antidepressant group than the placebo group

Incidence and prevalence

- What is the difference?

Incidence and prevalence

Prevalence: the number of cases of a disease that are present in a particular population at a given time

Incidence: the number of new cases that develop in a given period of time

Testing for E. coli O157

	Positive	Negative	Total
With E. coli bacteria	57	5	62
Without E. coli bacteria	4	127	131
Total	61	132	193

- How would you quantify the performance of the test method?

Sensitivity and specificity

Sensitivity: The probability of the test being positive when E. coli bacteria are in fact present = true positive rate =
P(+ | bacteria)

Specificity: The probability of the test being negative when E. coli bacteria are in fact not present = true negative rate = P(- | no bacteria)

P(A) : The probability of the event A

P(A | B) : The conditional probability of the event A given the event B

Sensitivity and specificity

	Positive	Negative	Total
With E. coli bacteria	57	5	62
Without E. coli bacteria	4	127	131
Total	61	132	193

- What is the sensitivity and specificity of this test?
- P(+ | bacteria) = ??
- P(- | no bacteria) = ??

Sensitivity and specificity

	Positive	Negative	Total
With E. coli bacteria	57	5	62
Without E. coli bacteria	4	127	131
Total	61	132	193

- P(+ | bacteria) = 57 / 62 = 0.92 = 92%
- P(- | no bacteria) = 127 / 131 = 0.97 = 97%

False positive and false negative

- False positive: Healthy people incorrectly identified as sick
- False positive rate: 1-specificity

- False negative: Sick people incorrectly identified as healthy
- False negative rate: 1-sensitivity

Predictive value of positive test and predictive value of negative test

Predictive value of positive test: The probability of E. coli bacteria being present when the test is positive = P(bacteria | +)

Predictive value of negative test: The probability of E. coli bacteria not being present when the test is negative = P(no bacteria | -)

Predictive value of positive test and predictive value of negative test

	Positive	Negative	Total
With E. coli bacteria	57	5	62
Without E. coli bacteria	4	127	131
Total	61	132	193

- What is the predictive value of positive test and predictive value of negative test of in this case?
- P(bacteria | +) = ??
- P(no bacteria | -) = ??

Predictive value of positive test and predictive value of negative test

	Positive	Negative	Total
With E. coli bacteria	57	5	62
Without E. coli bacteria	4	127	131
Total	61	132	193

- P(bacteria | +) = 57 / 61 = 0.93 = 93%
- P(no bacteria | -) = 127 / 132 = 0.96 = 96%

Mammography

- Prevalence of breast cancer = 1 % = P(breast cancer)
- Sensitivity of mammography = 90 % = P(+ | breast cancer)
- Mammography gives 9 % false positive results = P(+ | no breast cancer)

What is the probability that a positive mammogram is truly positive ?

Mammography

Complete the table for 1000 women

	Positive	Negative	Total
Breast cancer	??	??	??
No breast cancer	??	??	??
Total	??	??	1000

Mammography

- Prevalence of breast cancer = 1 % = P(breast cancer)

	Positive	Negative	Total
Breast cancer	??	??	10
No breast cancer	??	??	990
Total	??	??	1000

Mammography

- Prevalence of breast cancer = 1 % = P(breast cancer)
- Sensitivity of mammography = 90 % = P(+ | breast cancer)

	Positive	Negative	Total
Breast cancer	9	1	10
No breast cancer	??	??	990
Total	??	??	1000

Mammography

- Prevalence of breast cancer = 1 % = P(breast cancer)
- Sensitivity of mammography = 90 % = P(+ | breast cancer)
- Mammography gives 9 % false positive results = P(+ | no breast cancer)

	Positive	Negative	Total
Breast cancer	9	1	10
No breast cancer	89.1	900.9	990
Total	98.1	901.9	1000

P(breast cancer | +) = 9/98.1 = 0.092 = 9.2%

Hiv

- Prevalence of Hiv = 1/10000 = P(Hiv)
- Sensitivity of ELISA = 99.9 % = P(+ | Hiv)
- Specificity of ELISA = 99.99 % = P(- | no Hiv)

What is the probability of having Hiv given a positive test result ?

Hiv

Complete the table for 10000 persons

- Prevalence of Hiv = 1/10000 = P(Hiv)
- Sensitivity of ELISA = 99.9 % = P(+ | Hiv)
- Specificity of ELISA = 99.99 % = P(- | no Hiv)

	Positive	Negative	Total
Hiv	0.999	0.001	1
No Hiv	1	9998	9999
Total	1.999	9998.001	10000

P(Hiv | +) = ??

Hiv

Complete the table for 10000 persons

- Prevalence of Hiv = 1/10000 = P(Hiv)
- Sensitivity of ELISA = 99.9 % = P(+ | Hiv)
- Specificity of ELISA = 99.99 % = P(- | no Hiv)

	Positive	Negative	Total
Hiv	0.999	0.001	1
No Hiv	1	9998	9999
Total	1.999	9998.001	10000

P(Hiv | +) = 0.999 / 1.999 $\sim$ 0.5 = 50%

Colon cancer

- Prevalence of colon cancer = 0.3% = P(CC)
- Sensitivity of investigation = 50 % = P(+ | CC)
- False positive rate = 3 % = P(+ | no CC)

What is the probability of having colon cancer given a positive test result ?

Colon cancer

Complete the table for 10000 persons

- Prevalence of colon cancer = 0.3% = P(Colon cancer)
- Sensitivity of investigation = 50 % = P(+ | Colon cancer)
- False positive rate = 3 % = P(+ | no Colon cancer)

	Positive	Negative	Total
Colon cancer	15	15	30
No colon cancer	299.1	9670.9	9970
Total	314.1	9685.9	10000

P(colon cancer | +) = 15 / 314.1 = 0.0478 = 4.8 %