Case Study B
Pain Relief Medication

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Case Statement

- ▶ 20 experiments on mice with combinations of marijuana and morphine, of which:
  - ▶ 1 control experiment;
  - ▶ 5 experiments with marijuana only;
  - ▶ 8 experiments with morphine only;
  - ▶ 6 experiments with both drugs.
- ▶ 10 mice used per experiment;
- ▶ Each mouse undergoes a tail flick test.

The tail flick test assesses the effect of drugs on the mouse.

In each experiment, the proportion of mice not flicking their tail can be interpreted as a **measure of the effect of the drug** for the chosen experimental dosage.

First Objective

*Determine the minimum dosage amount of the drugs that achieves **efficacy**.*

The dosage of a drug is said to be **effective** if at least 50% of the subjects are responding.

Second Objective

*Detect whether a **synergy** exists between the two drugs.*

There is **synergy** between two drugs if for some dosages, the combined effect is greater that the effect both drugs would have if they were acting independently, without interaction.

Identifying Synergy with the Isobole Method

The isobole method is a graphical representation which identifies synergy and helps to better understand the concept.

Before constructing the isobole, we must determine the dosage at which the efficacy is 50% for both drugs used separately.
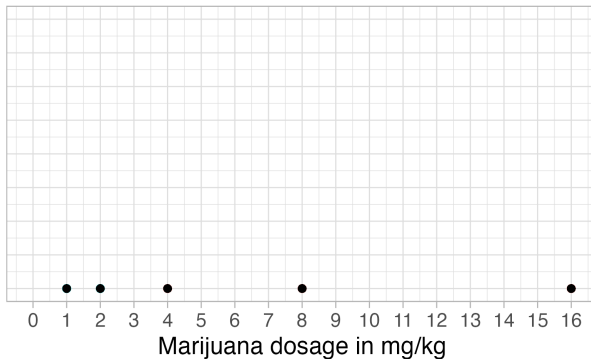
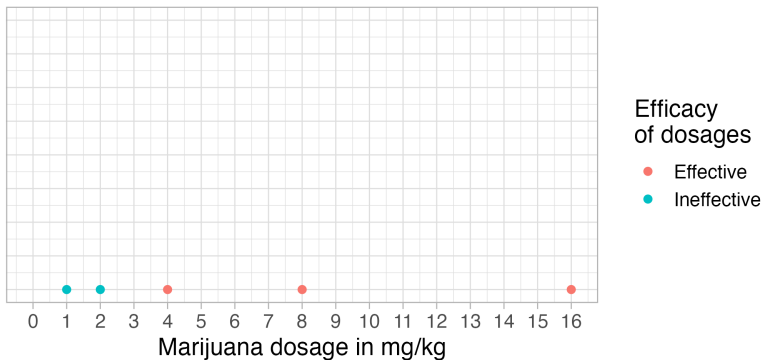Dose-response curves for Marijuana and Morphine
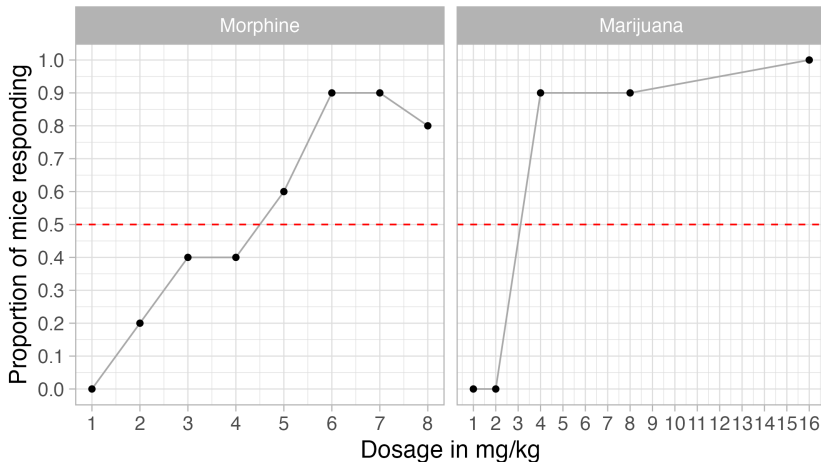
Assumption: The theoretical dosages which give a 50% efficacy level are

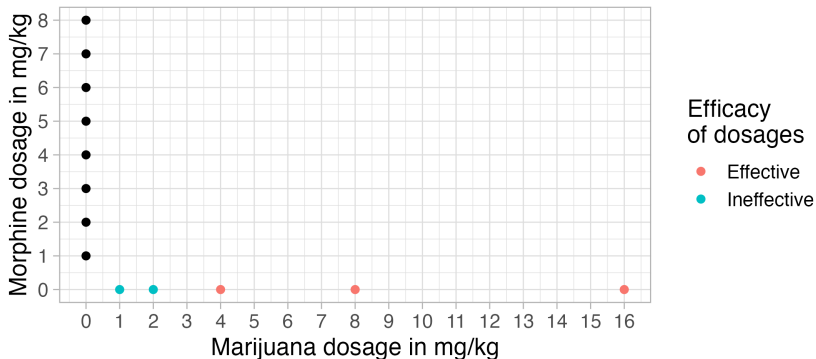- ▶ 3.0 mg/kg of marijuana;
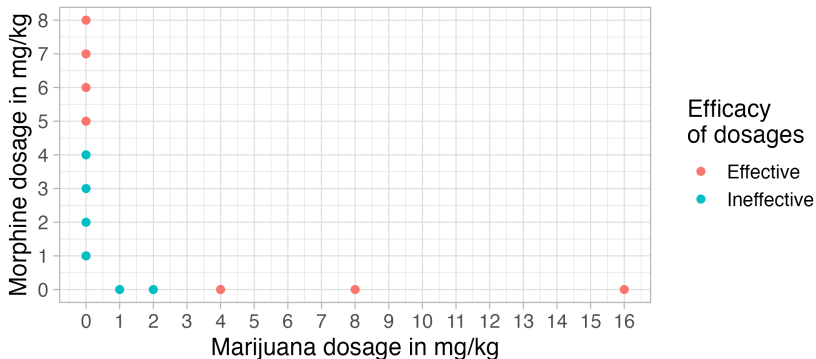- ▶ 4.5 mg/kg of morphine.

Dosages of Marijuana

Marijuana dosage in mg/kg

Dosages of Marijuana

Efficacy
of dosages

● Effective
● Ineffective

Dosages of Marijuana and Morphine

Efficacy
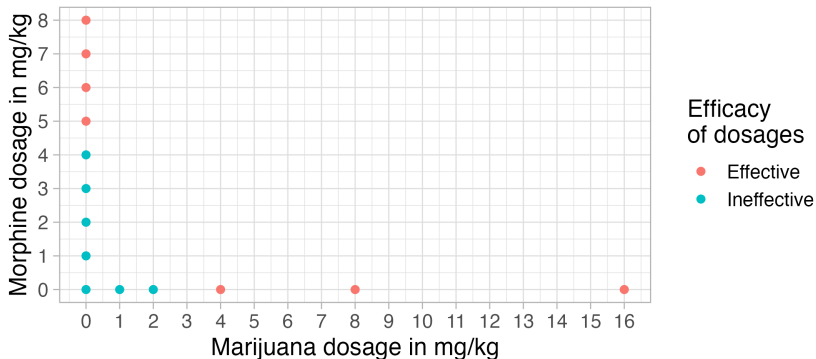of dosages
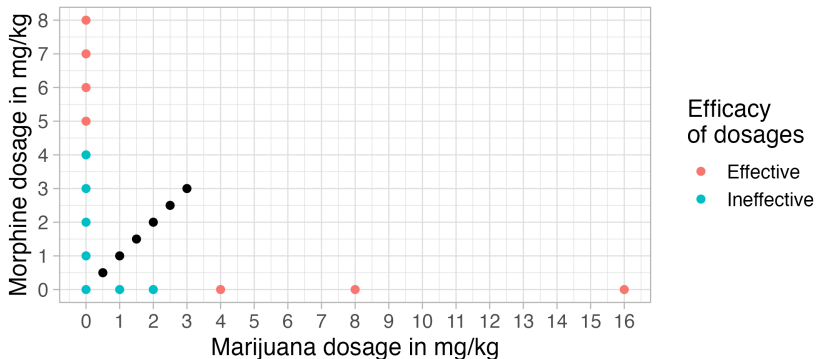
- Effective
- Ineffective
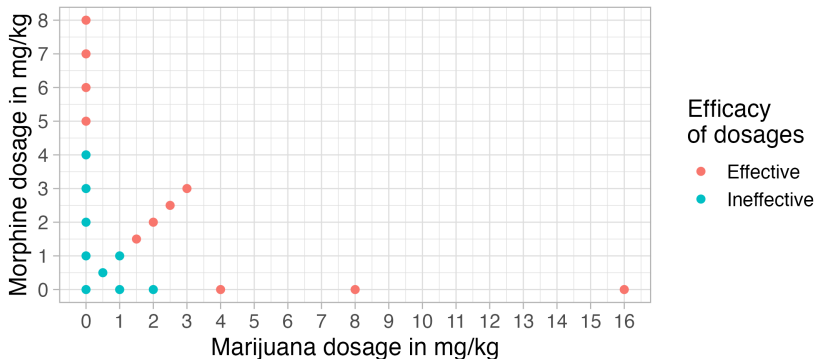
Dosages of Marijuana and Morphine
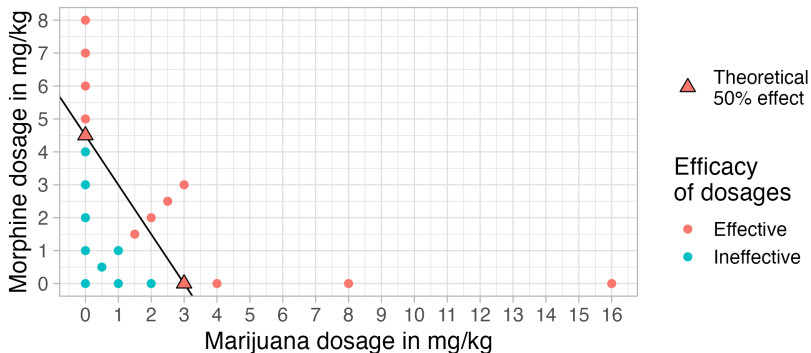
Dosages of Marijuana and Morphine

Dosages of Marijuana and Morphine

Dosages of Marijuana and Morphine

Dosages of Marijuana and Morphine with Isobole

Isobole Insights

▶ The isobole tests whether there is interaction between the two drugs.

▶ If the drugs act independently, then all dosages on the isobole have an efficacy of 50%.

▶ All points above (resp. below) the isobole have an efficacy greater (resp. lesser) than 50%.

▶ A point below the isobole with an efficacy greater than 50% is a departure from independence indicating synergy.

Isobole Conclusion

✓ **First objective, minimal effective dosage:**
  - ▶ 4.0 mg/kg for marijuana alone;
  - ▶ 5.0 mg/kg for morphine alone;
  - ▶ 1.5 mg/kg of each for both drugs.
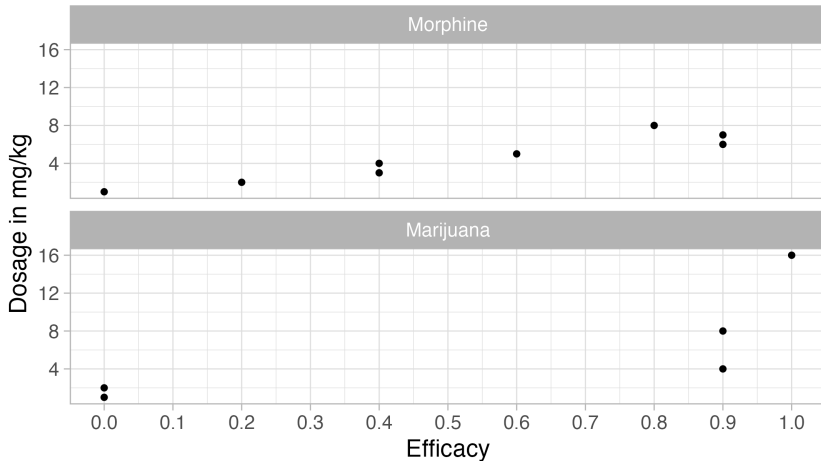
✓ **Second objective, synergy:**
  Dosage of 1.5 mg/kg for both drugs has a
  potential to be synergistic.

Isobole Method Assumptions

Constant potency level
For any chosen efficacy level, the ratio between the dosages of morphine and marijuana must remain the same.

Dosages of Marijuana and Morphine vs Efficacy

- ▶ Only two common efficacy levels, 0.0 and 0.9
- ▶ This is not enough to verify the assumption for this experiment.
- ▶ This weakness is due to dosage choices for marijuana.
- ▶ However, the linear isobole method is used in multiple experiments which are extremely similar.

**Choice of theoretical dosages with 50% efficacy**

For morphine:

- ▶ chosen between 4 and 5 mg/kg;
- ▶ this represents an interval of 1 mg/kg;
- ▶ effect level is between 40% and 60%.

For marijuana:

- ▶ chosen between 2 and 4 mg/kg;
- ▶ this represents an interval of 2 mg/kg;
- ▶ effect level is between 0% and 90%.

▶ The 50% efficacy dosage for marijuana cannot
be pinpointed because of the chosen dosages of
marijuana in the experiment.

▶ Finding that dosage would mean finding a
better minimal effective dosage, which could
result in costs reduction.

▶ The position of that dosage could move the
isobole significantly, making it more or less
strict towards synergistic dosages.

Dosages of Marijuana and Morphine with Isobole
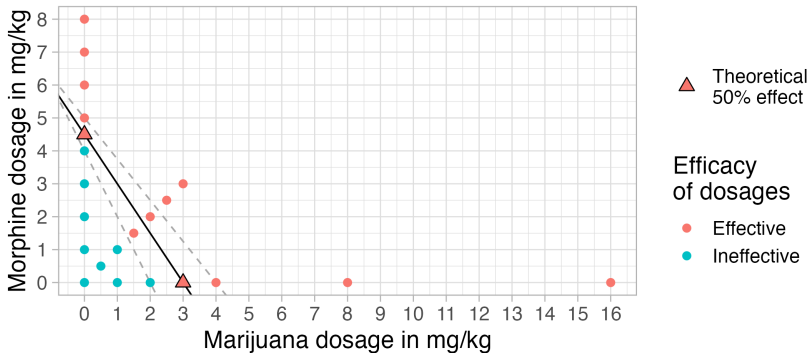
Recommendations

- ✓ **Complete the experiment with trials for at least 4 dosages of marijuana between 2.0 and 4.0 mg/kg.**
- ✓ Experiment with more dosages of morphine between 4.0 and 5.0 mg/kg.
- ✓ Experiment with unequal amounts of marijuana and morphine to find other potential synergies.

Conclusion

▶ Minimal effective dosages have been identified, but there could be significant improvement for marijuana.

▶ One dosage combination has the potential to be synergistic, but only further experimentation will determine if it is the case.

Q&A Session

Thank you for your attention.

Feel free to ask us any question!