PAIN RELIEF MEDICATION

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Ms. AL QOH, Oumaima
Mr. ARRIETA, Francisco
Ms. CAMENISCH, Lucia
Ms. GIANSANTE, Manuela
Ms. SCHMIDT, Emily
Ms. VALERA, Camille

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Agenda

- Problem Statement
- Objectives
- Results
- Recommendations & Conclusions

Case Statement

- 20 experiments performed 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.

What is a Tail Flick?

- 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

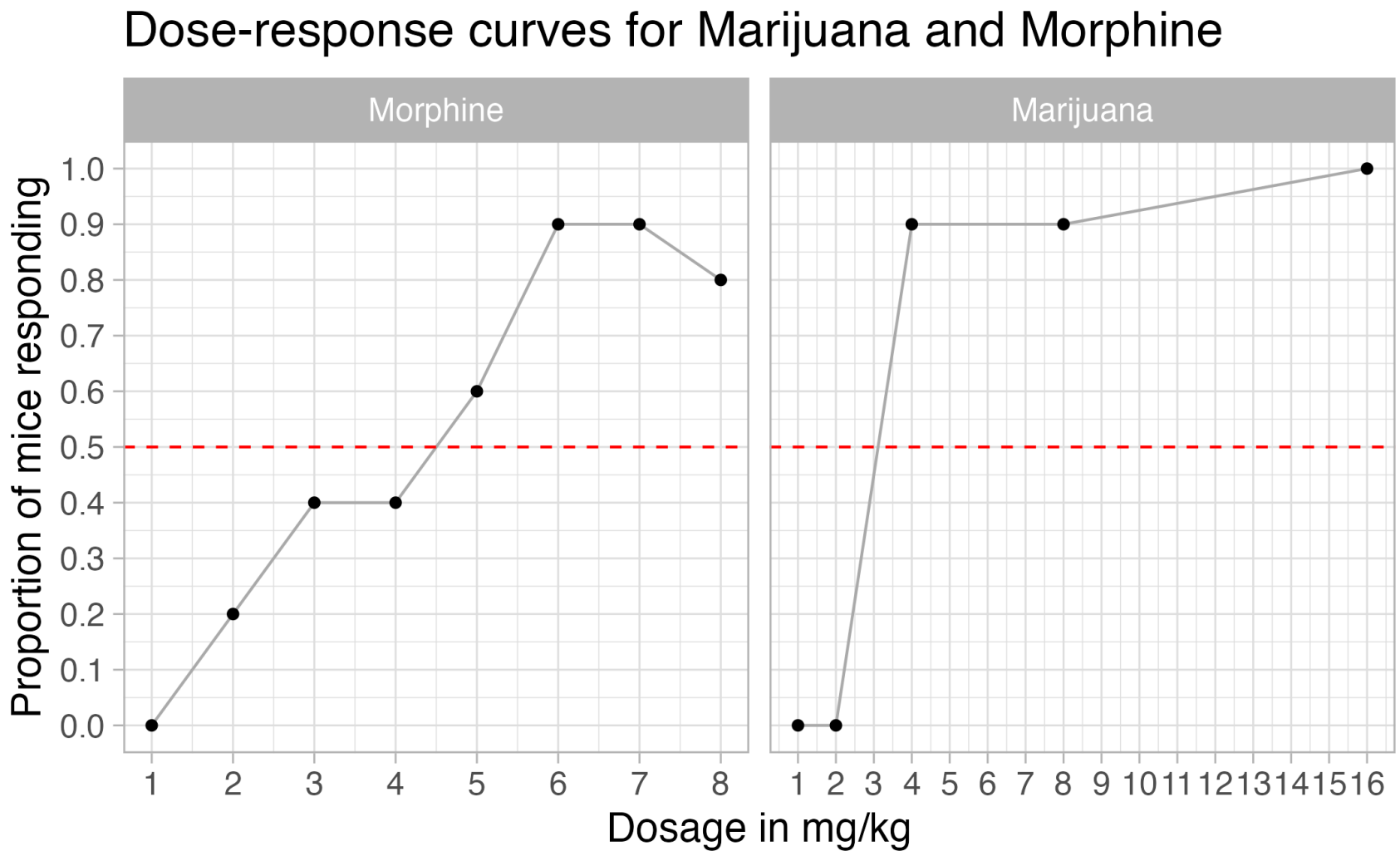
- Detect whether a **synergy** exists between the two drugs.
- There is **synergy** between two drugs if for some dosages, the combined effect is greater that the effect both drugs would have if they were acting independently, without interaction.

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.

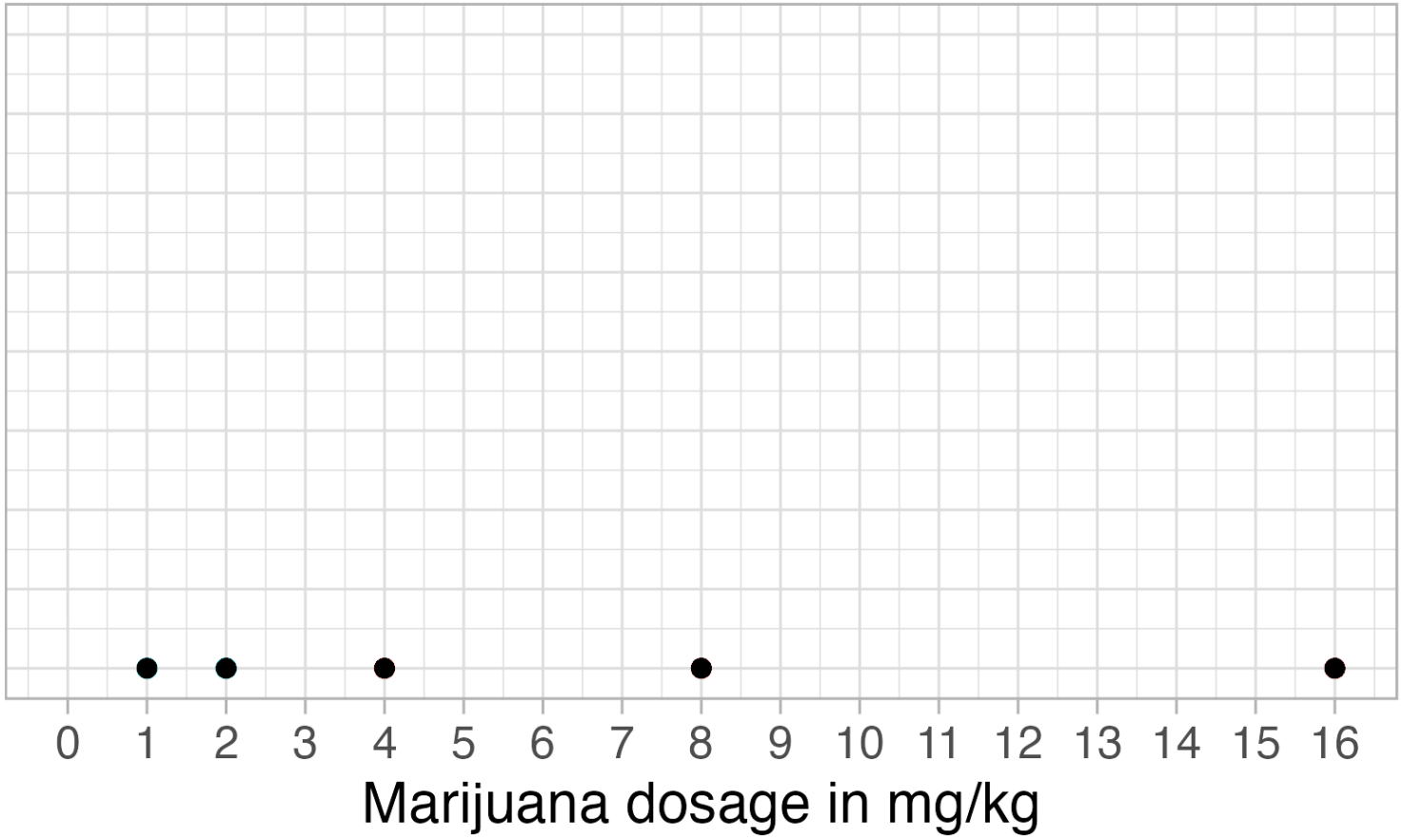
Dosages per Medication



ASSUMPTION

- The theoretical dosages which give a 50% **efficacy** level are
  - 4.5 mg/kg of morphine;
  - 3.0 mg/kg of marijuana.

Dosages of Marijuana



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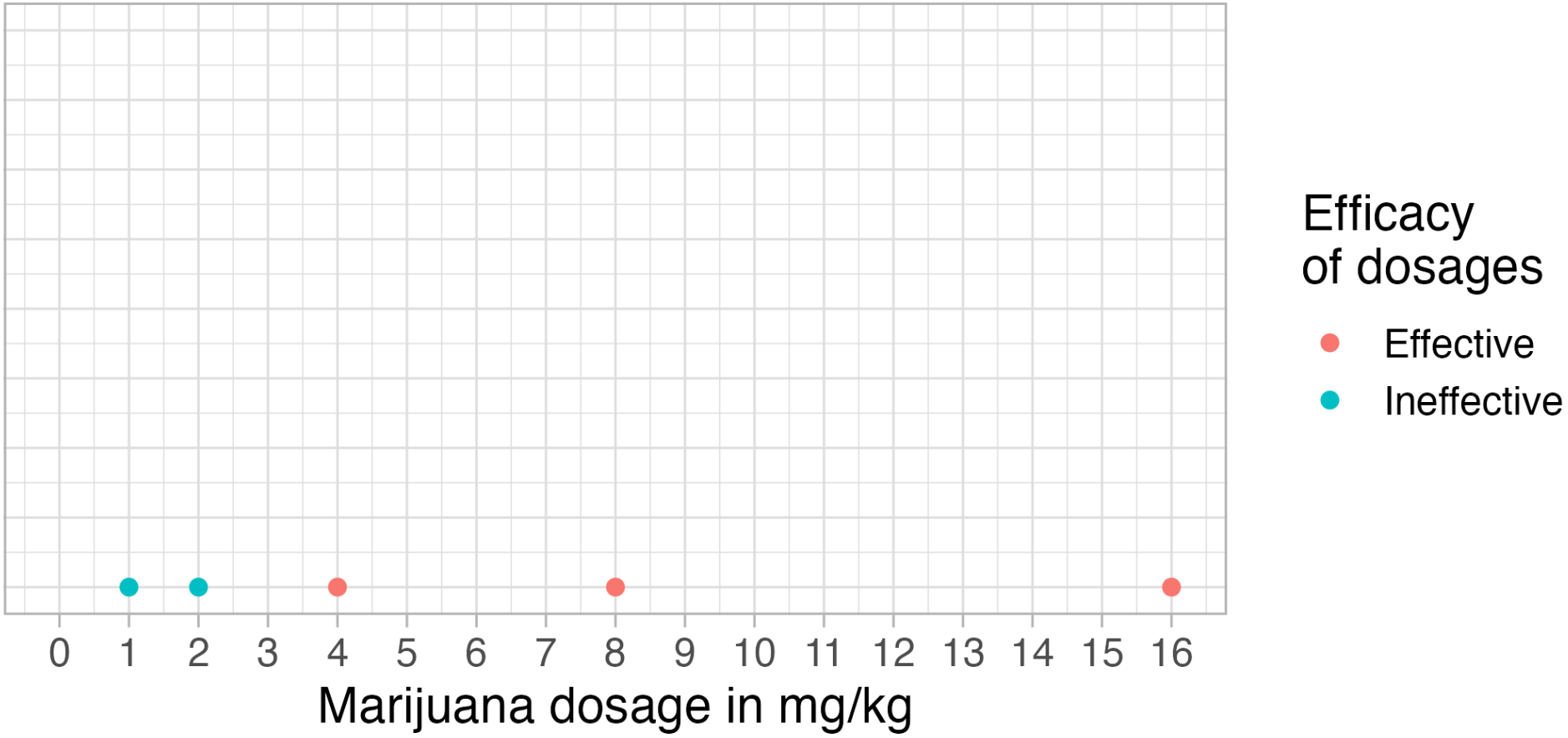

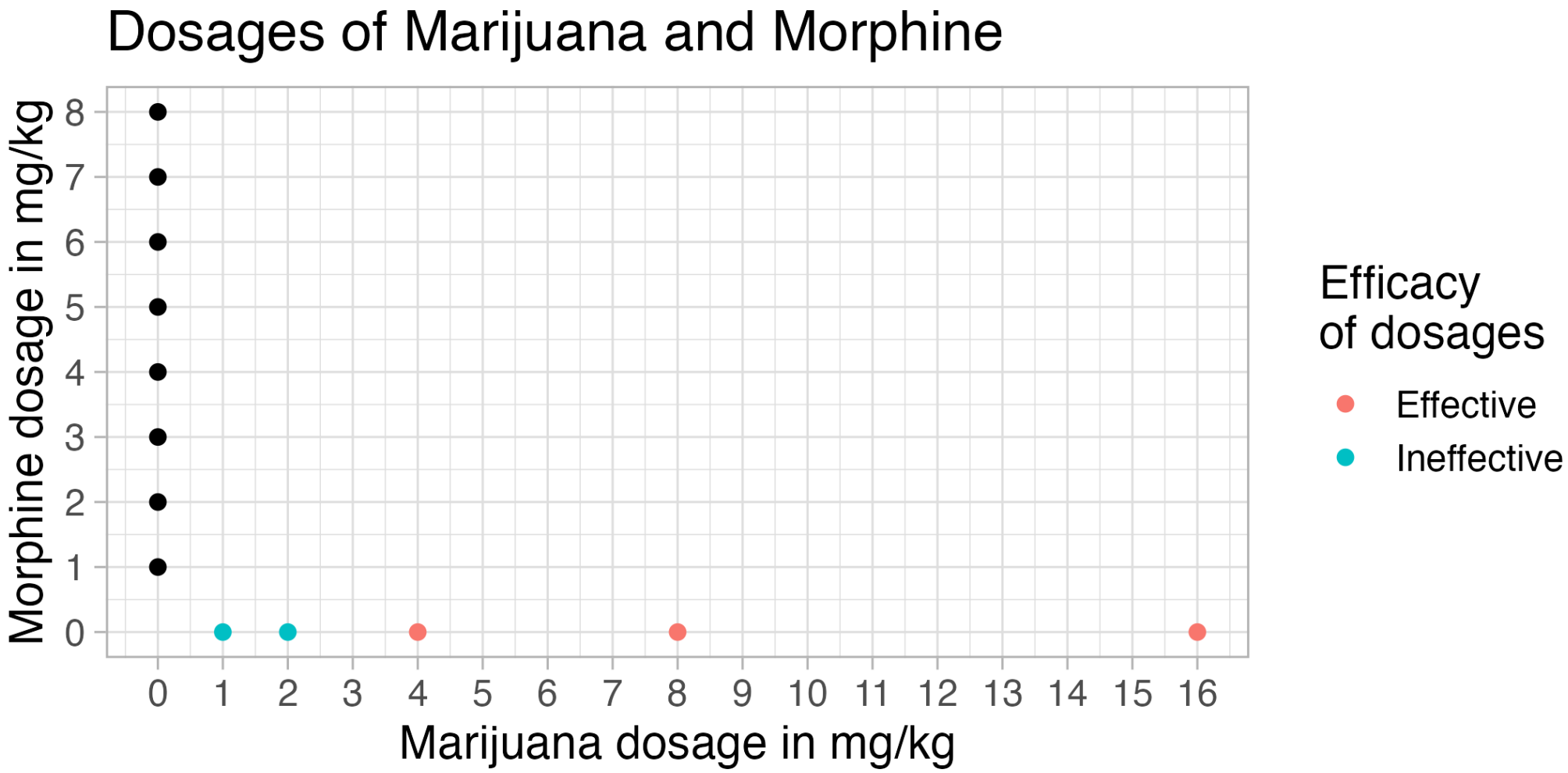
Dosages of Marijuana and Morphine
Morphine dosage in mg/kg
0
1
2
3
4
5
6
7
8
Marijuana dosage in mg/kg
0
1
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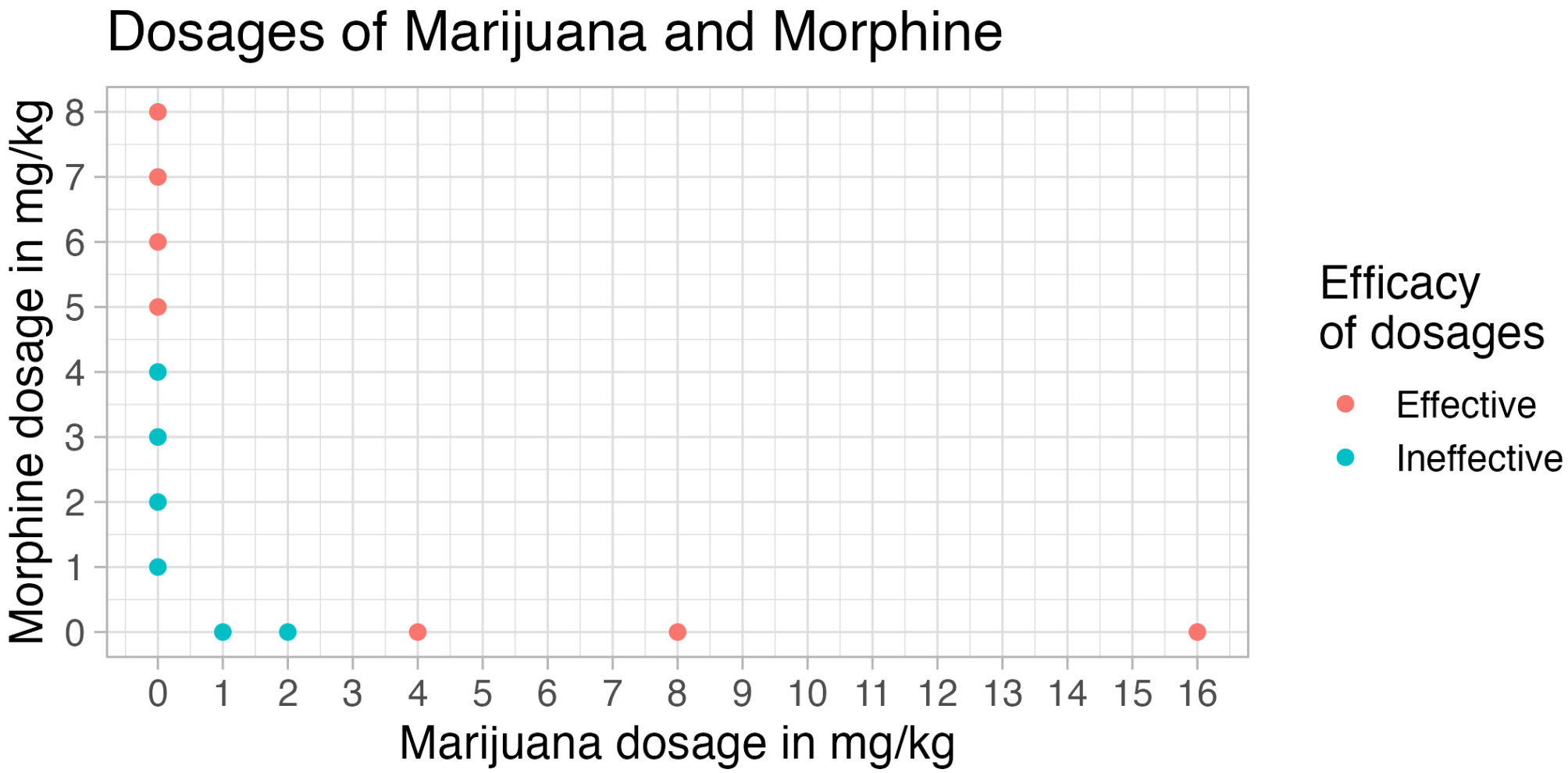
16
Efficacy of dosages
Effective
Ineffective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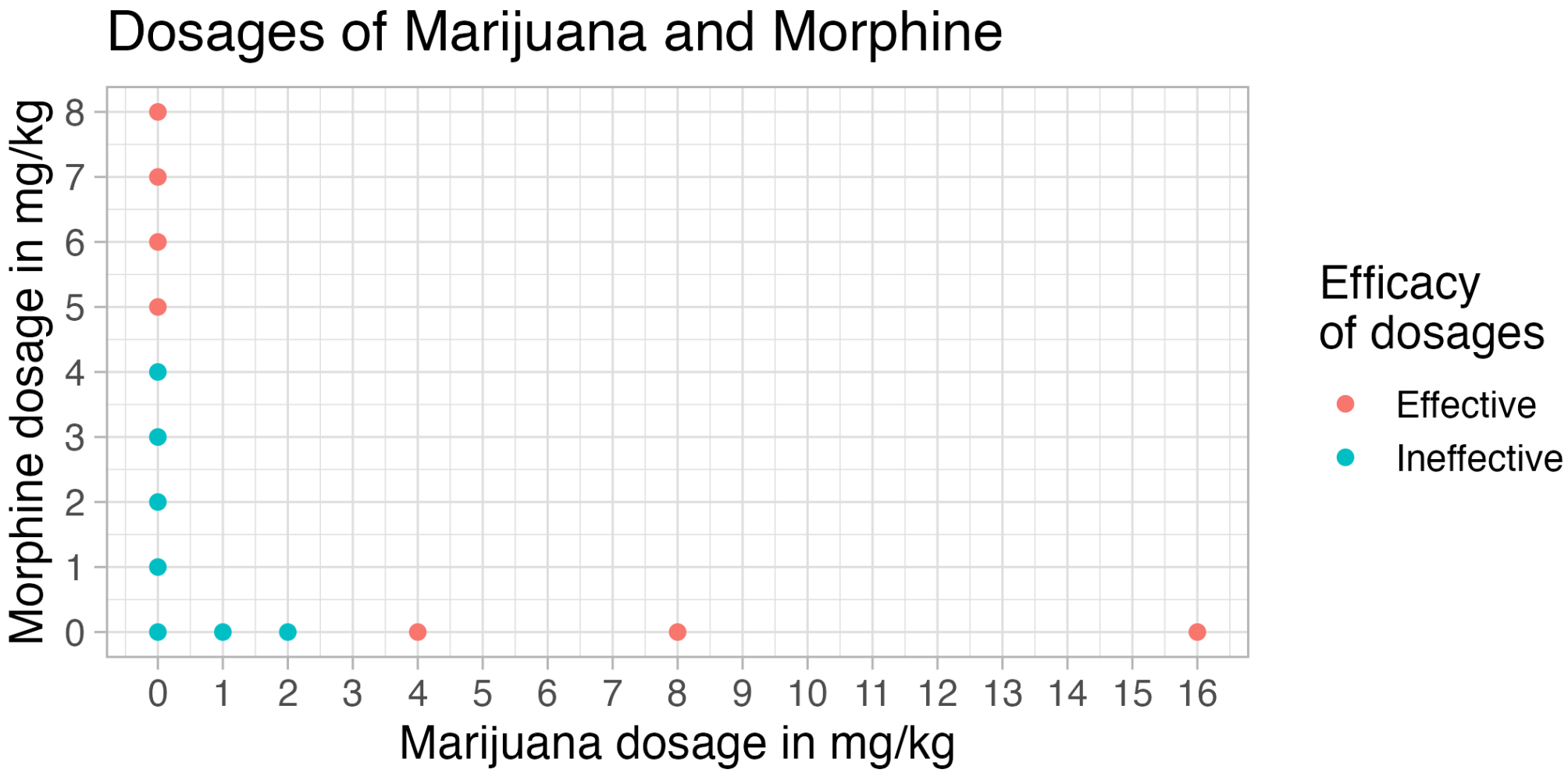
Dosages of Marijuana and Morphine
Morphine dosage in mg/kg
8
7
6
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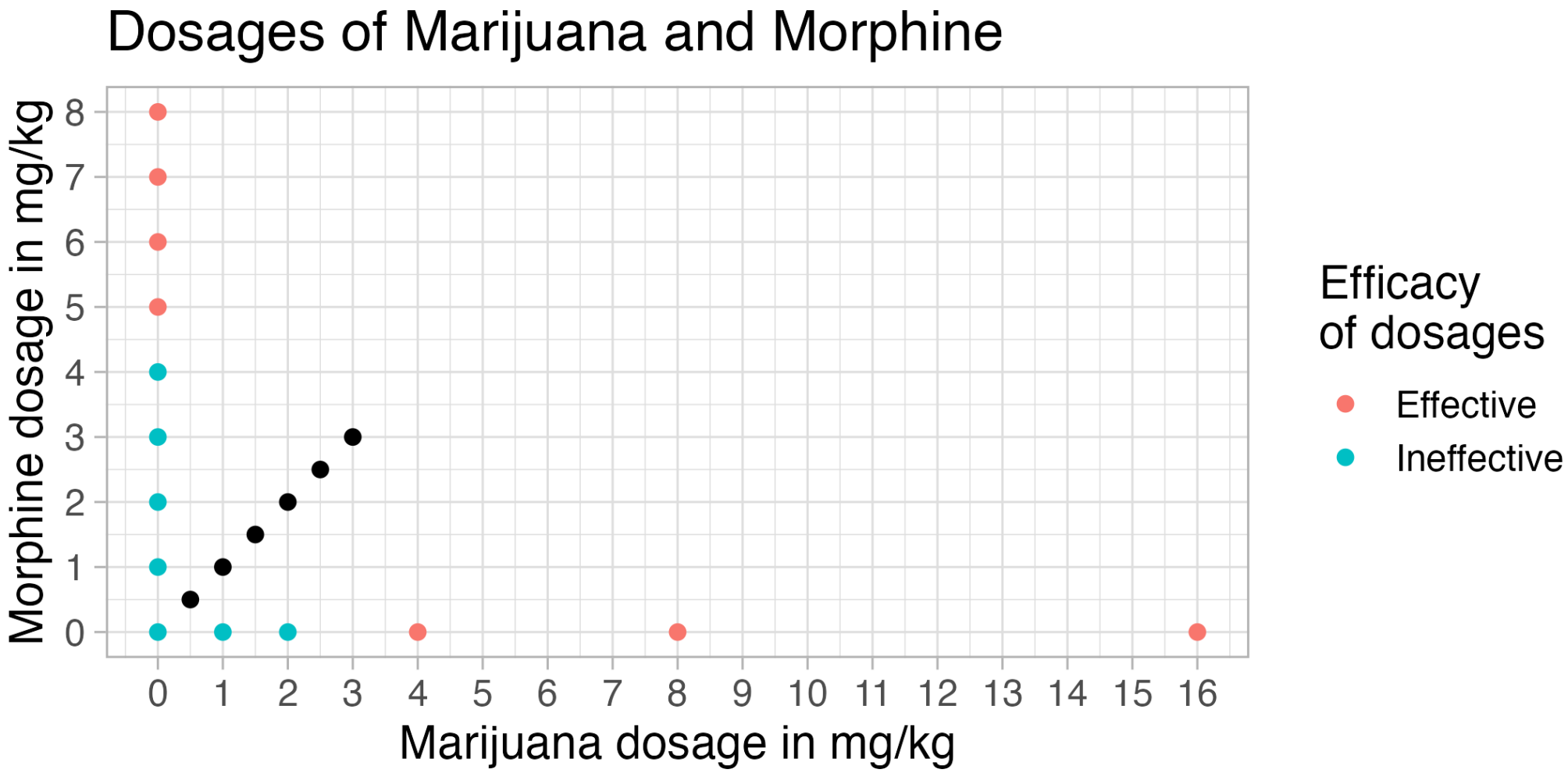
Marijuana dosage in mg/kg
Efficacy of dosages
Effective
Ineffective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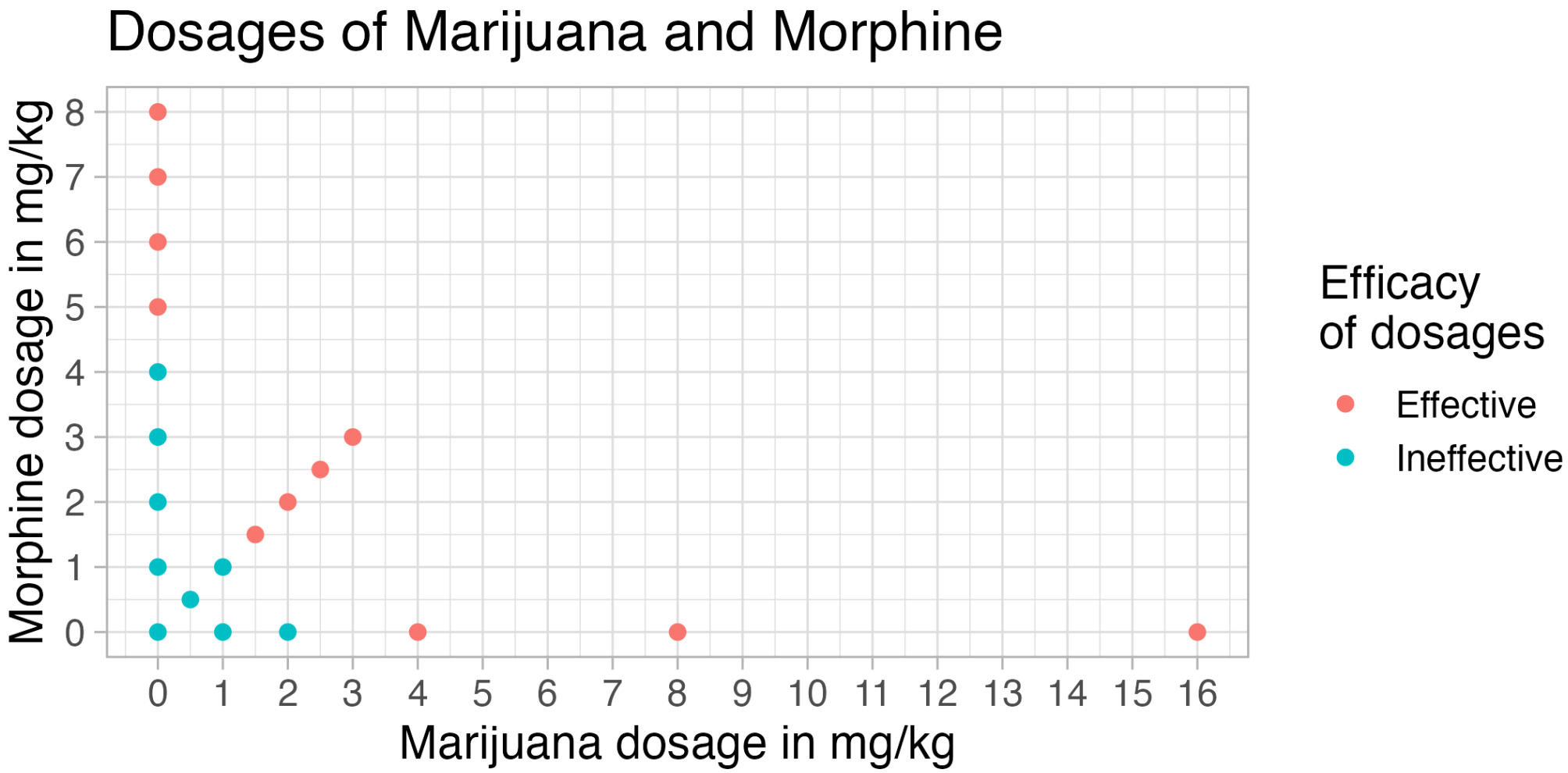
Efficacy of dosages
Effective
Ineffective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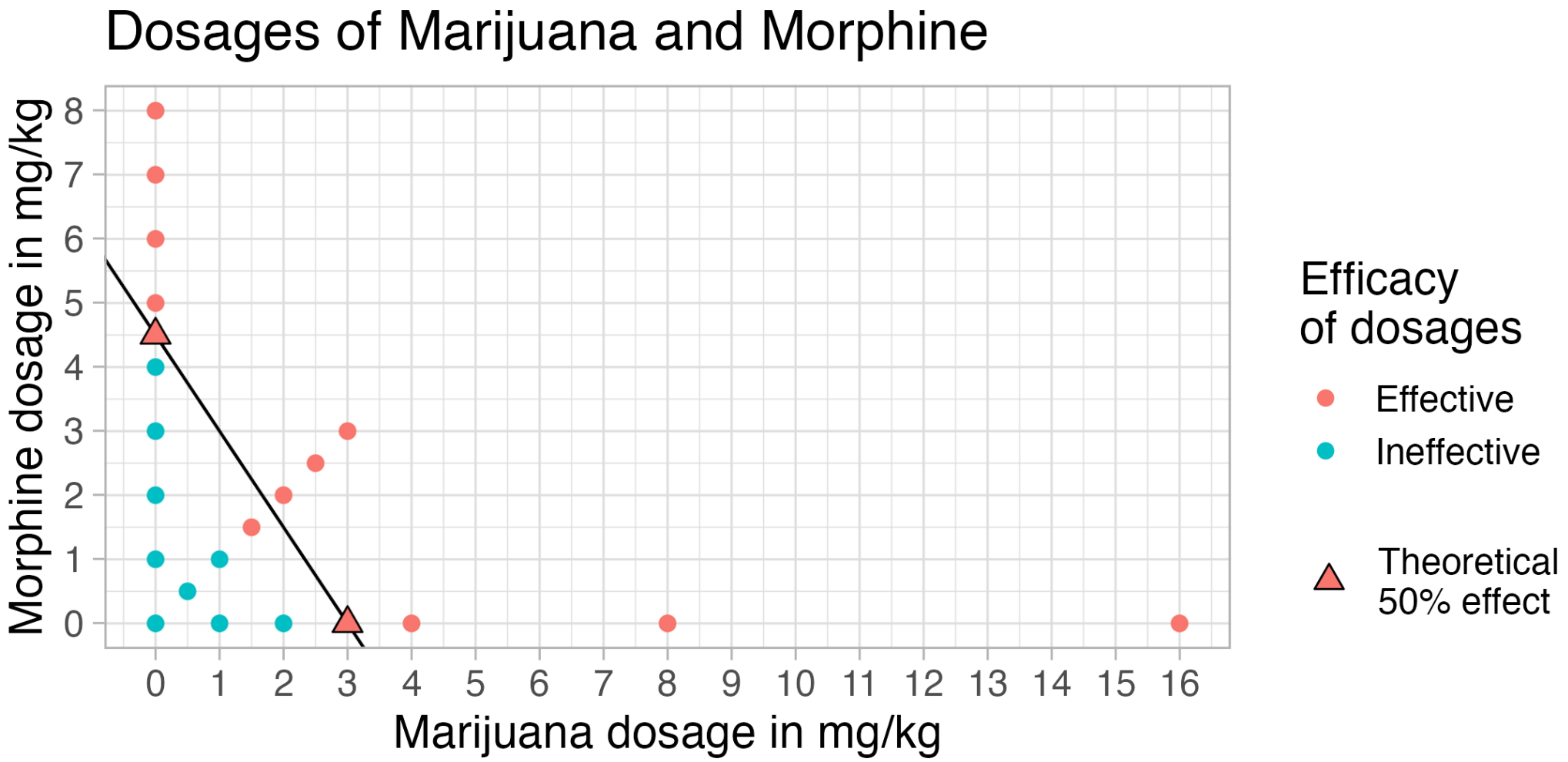
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Efficacy of dosages
Effective
Ineffective
Theoretical 50% effect

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 the isobole have an efficacy greater than 50%.
- And respectively, all points below the isobole have an efficacy lesser than 50%.
- A point below the isobole with an efficacy greater than 50% is a departure from independence indicating synergy.

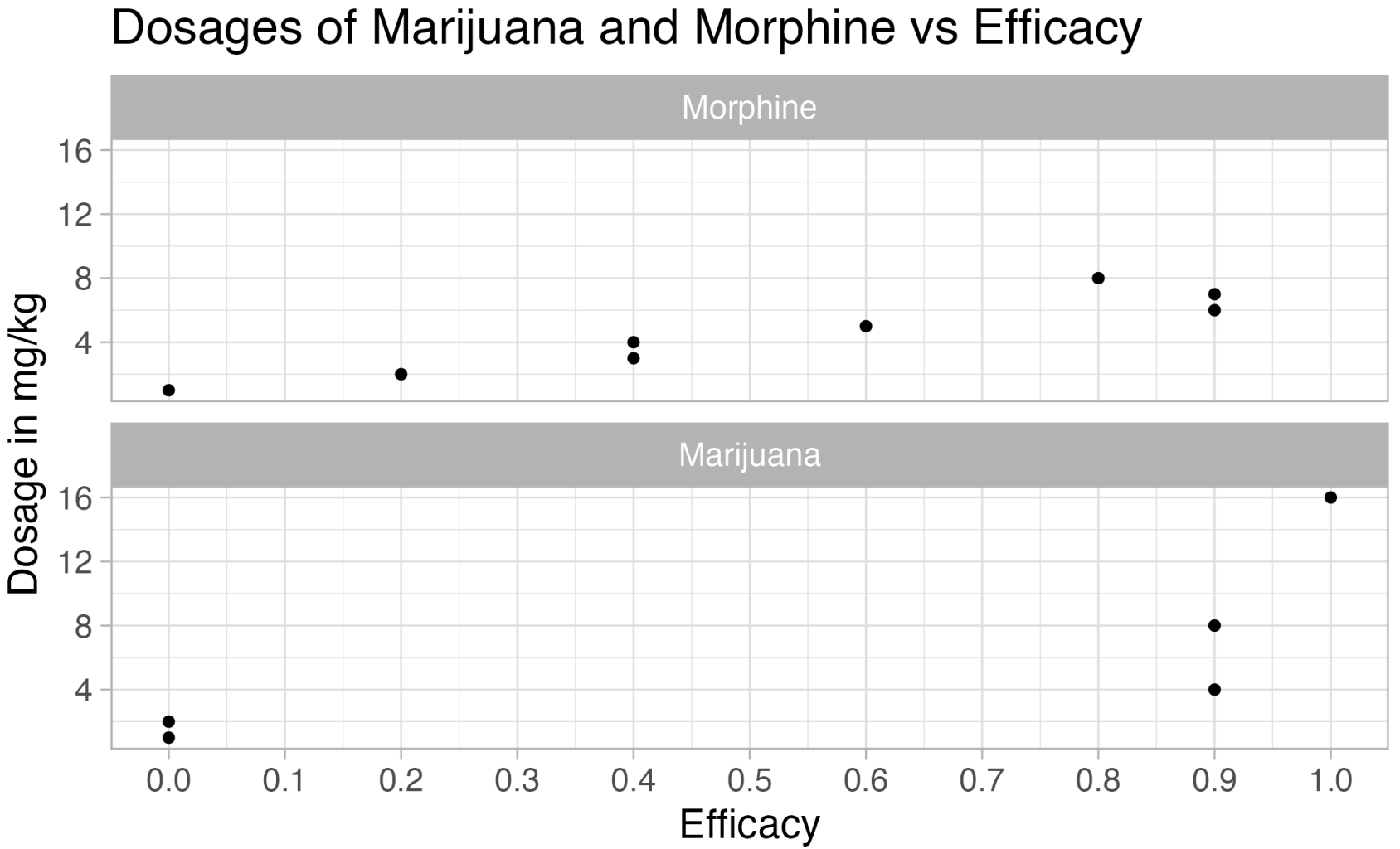
Isobole Conclusion

- ✓ First objective, minimal effective dosage:
  - 5.0 mg/kg for morphine alone;
  - 4.0 mg/kg for marijuana 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.

Isobole Method Assumptions



Isobole Method Assumptions

- 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.

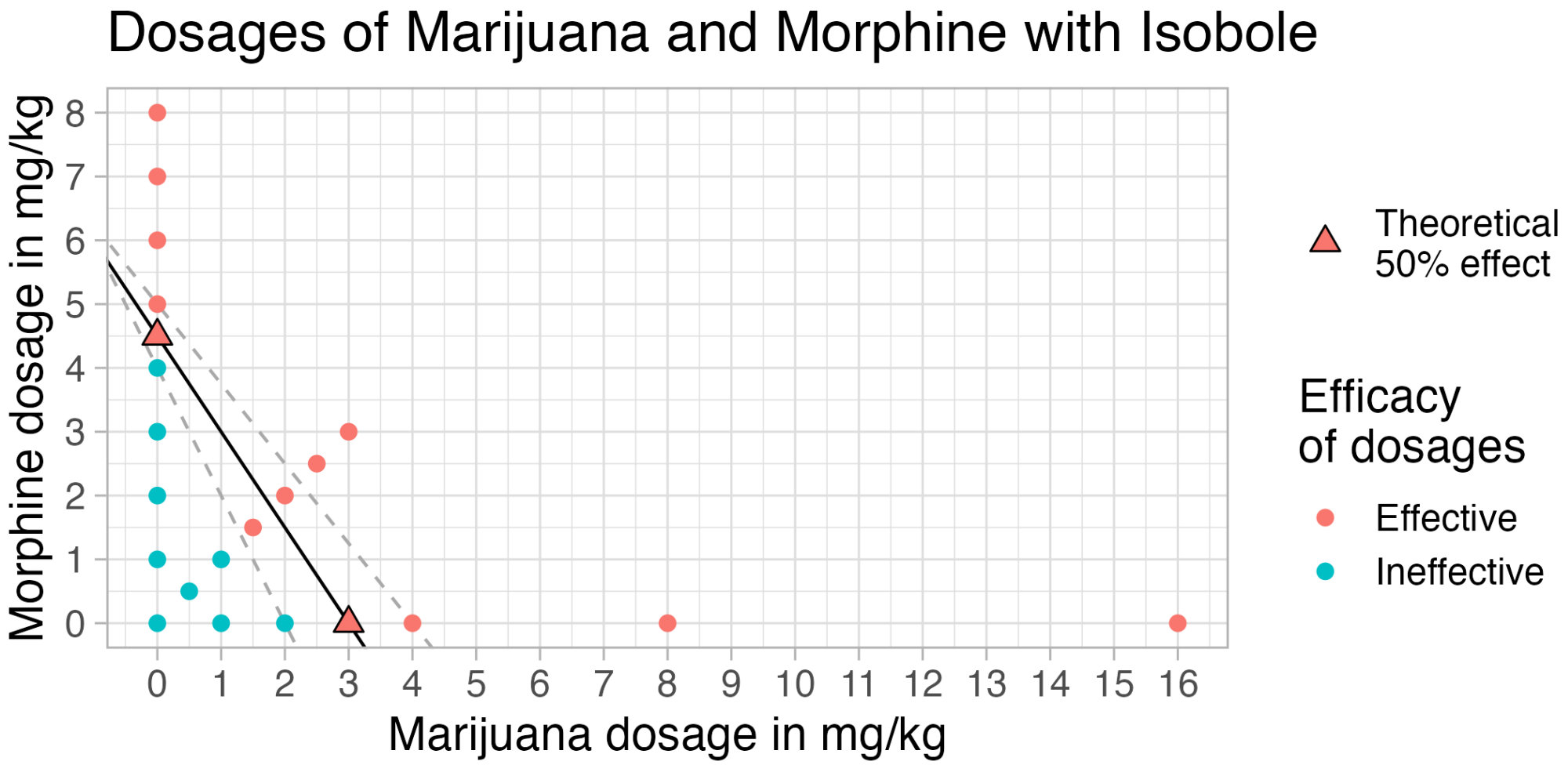
Isobole Method Assumptions

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%.

Isobole Method Assumptions

- 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.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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.

Conclusions

- Minimal effective dosages have been identified, but there could be significative improvement for marijuana.

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

Thank you for your attention!