university of groningen

Pairwise- and mixed treatment comparison models in multicriteria benefit-risk analysis

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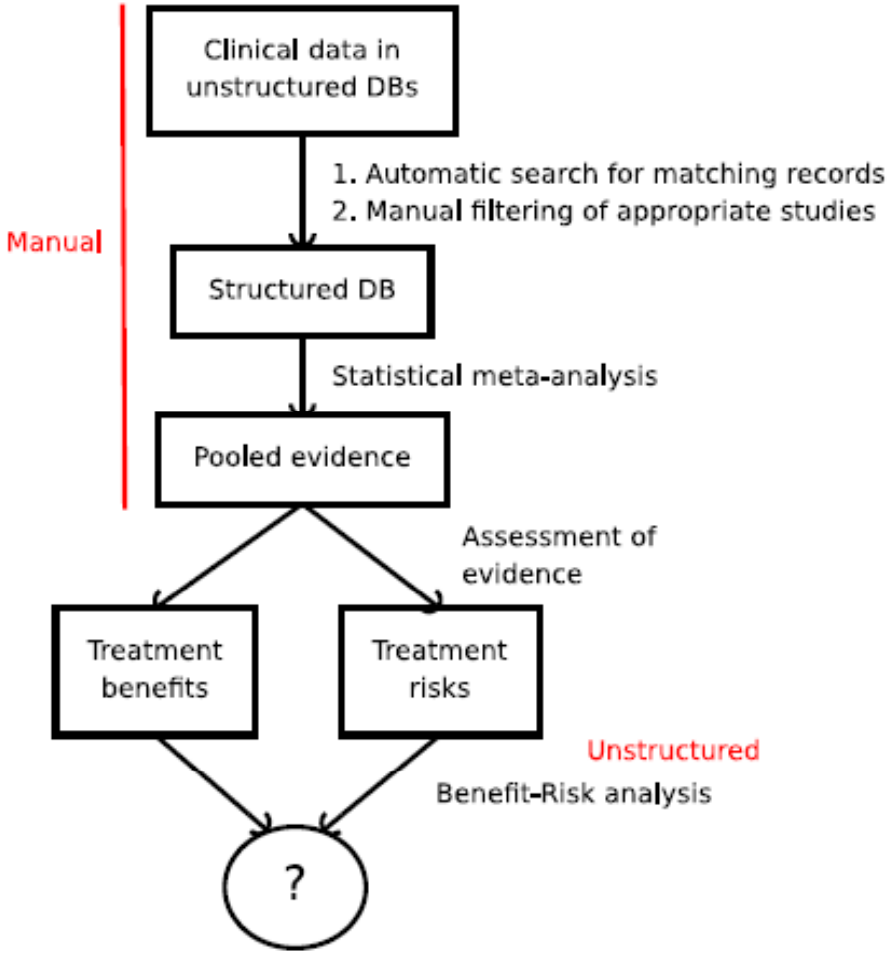
Agenda

- Introduction
- MTC
- SMAA
- Case study
- Results
- Analysis
- Conclusion

Drug Benefit-Risk (BR) analysis

- Drug BR analysis aims to systematically compare benefits and risks of drugs in a therapeutic group, as well as identify the trade-offs between them
- Drug BR analysis should take into account all the relevant evidence
- Drug BR analysis is unstructured and non-transparent



Decision support for BR analysis

- Decision making problem in the contex of drug BR analysis often involve multiple criteria and uncertainties
- Only evidence synthesis is not enough, quantifying the trade-offs between benefits and risks is required

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⇒ Solution: Multi-Criteria Decision Analysis (MCDA)

Decision support for BR analysis

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➡ Solution: Multi-Criteria Decision Analysis (MCDA)

Quantify Uncertainties ✖

Problem + Solution

- Incorporate all available evidence?
- Decision model to treat mutiple criteria and uncertainties?
- Decision making for drug BR analysis requires both?

- Network meta-analysis / Mixed treatment comparison (MTC)!
- Stochastic multicriteria acceptability analysis (SMAA) !

MTC +SMAA = Solution

Meta-analysis

- Meta-analysis is a statistical model for evidence synthesis from multiple trials to obtain overall pooled estimates of effectiveness
- Based on pairwise treatment comparison

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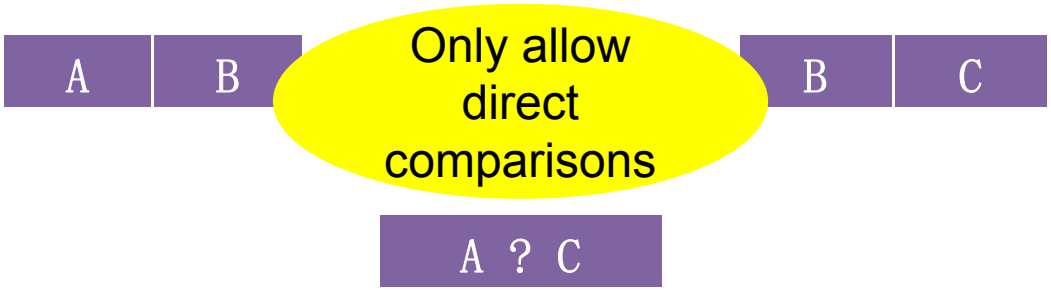


Network meta-analysis

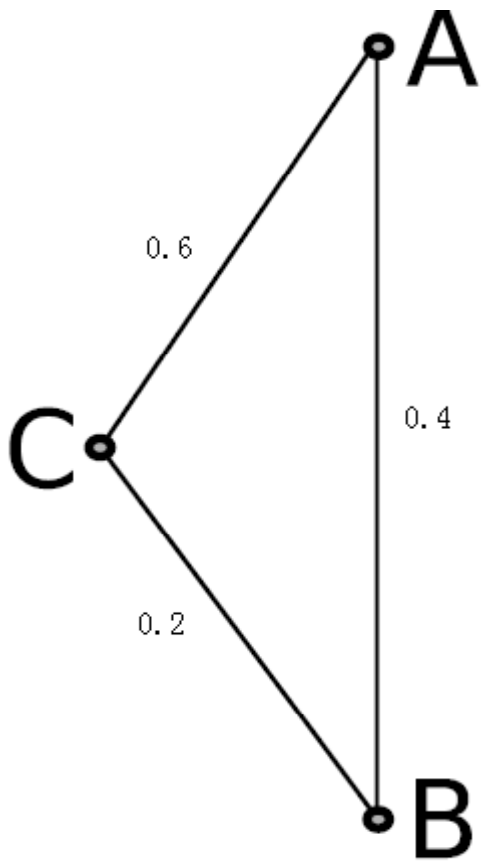
- To overcome the limitation, MTC is developed
- Based on not only pairwise but also mixed treatment comparisons (ABC)
- It allows both direct and indirect comparisons

Indirect comparison

- Consistency and inconsistency models

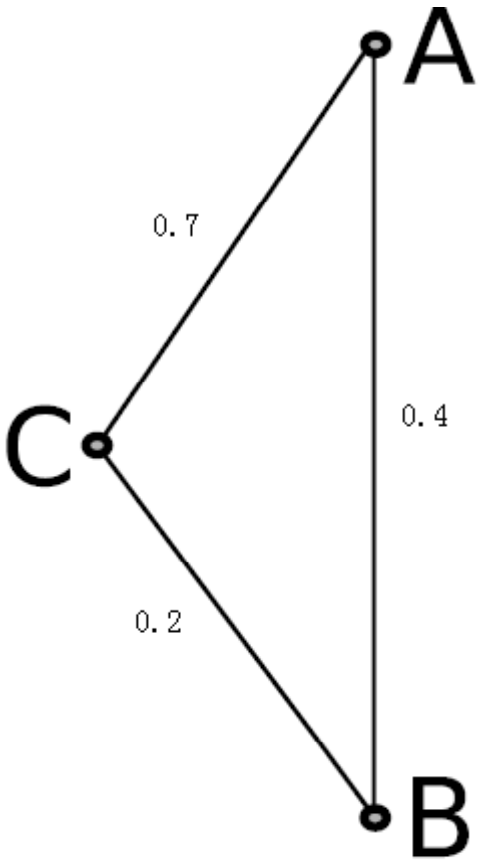
Consistency model

- Consistency model assumes a transitivity among the parameters
- $d_{BC} = d_{AC} - d_{AB}$
- d_{BC} can be estimated from both direct comparison and indirect comparion, and the results are consistent



Inconsistency model

- Treatment effect from direct comparison is inconsistent with it from indirect comparison
- $d_{BC} = d_{AC} - d_{AB} + \Phi$
- Φ represents the inconsistency



Multi-Criteria Decision Aanalysis (MCDA)

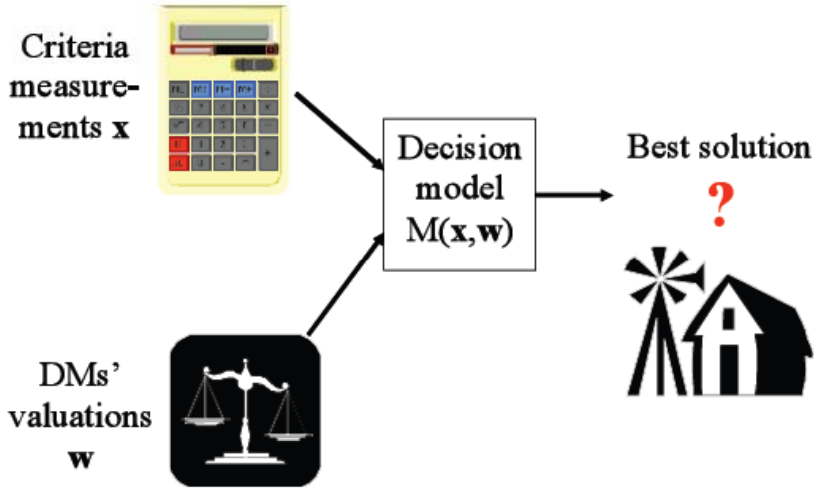
- MCDA is a discipline aiming at supporting decision makers who faced with decisons involving multiple criteria
- Multi-Attribute Utility Theory (MAUT) is a traditional MCDA method
- MAUT makes decision by maximizing the expected utility, and quantifies the relative importance of the criteria by identifying weights
- Weights reflect Decision Makers' (DMs) preference with regard of the importance of various attributes

Stochastic Multicriteria Acceptability Analysis (SMAA)

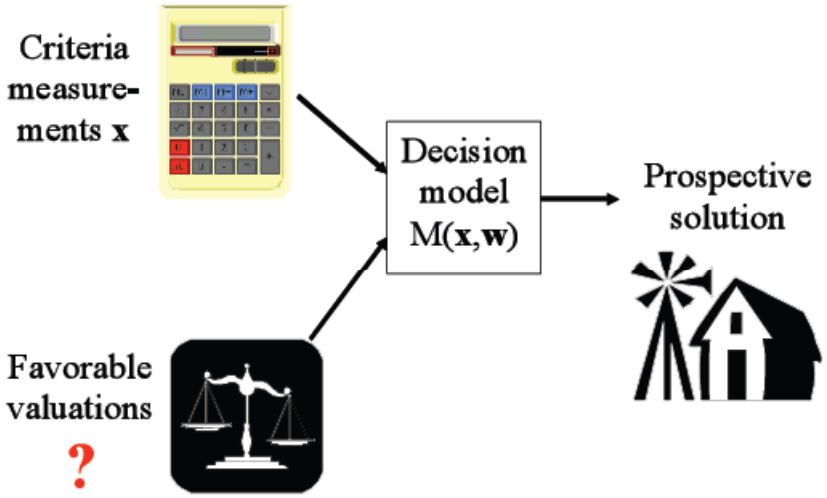
- SMAA (-2) is a MCDA method for ranking a set of alternatives (e.g. treatments) evaluated on basis of a set of criteria (e.g. Benefits and risks)
- SMAA is developed based on MAUT
- SMAA is developed when neither DMs' preference nor criteria mesurements are precisely known
- An inverse approach

Stochastic Multicriteria Acceptability Analysis (SMAA)

normal approach



inverse approach

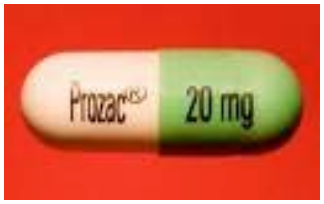


SMAA-2 descriptive indices

- Rank acceptability index - It describes the acceptability of a certain alternative in a certain rank
- Central weight vector - It defines the expected center of gravity of the favourable weight space
- Confidence factor - It is the probability for the alternative to be the preferred one with a chosen central weight vector

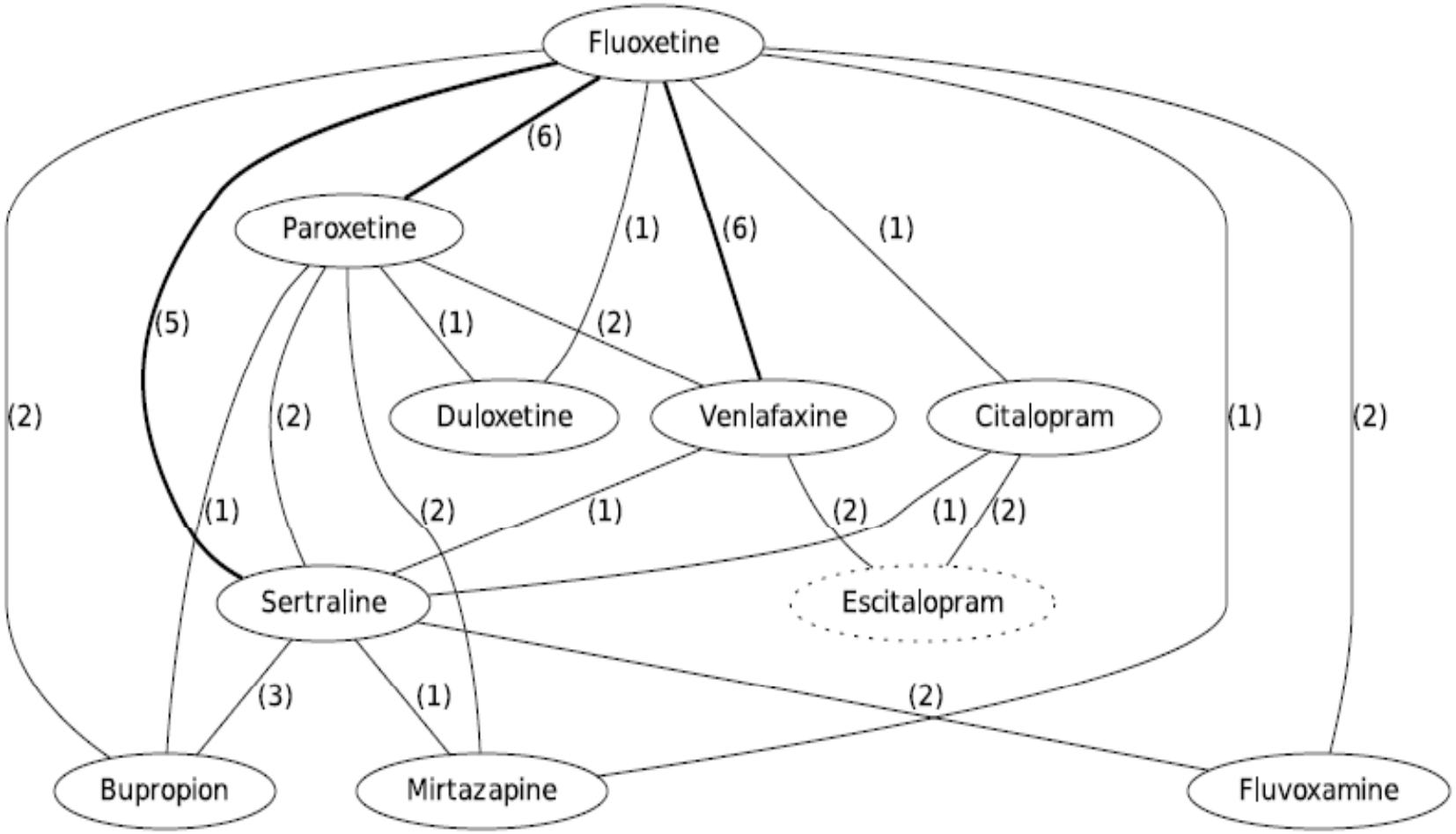
Case study

- Efficacy and safety of second generation antidepressants



- Hansen et al. (Ann Intern Med, 2005) assessed safety and efficacy of four second generation antidepressants and concluded that there are “no significant differences among them”

Case study


Fluoxetine
Paroxetine
Duloxetine
Venlafaxine
Citalopram
Sertraline
Escitalopram
Bupropion
Mirtazapine
Fluvoxamine
(6)
(1)
(6)
(1)
(5)
(1)
(2)
(2)
(2)
(1)
(2)
(1)
(2)
(1)
(2)
(1)
(2)
(3)
(1)
(2)

MA/SMAA

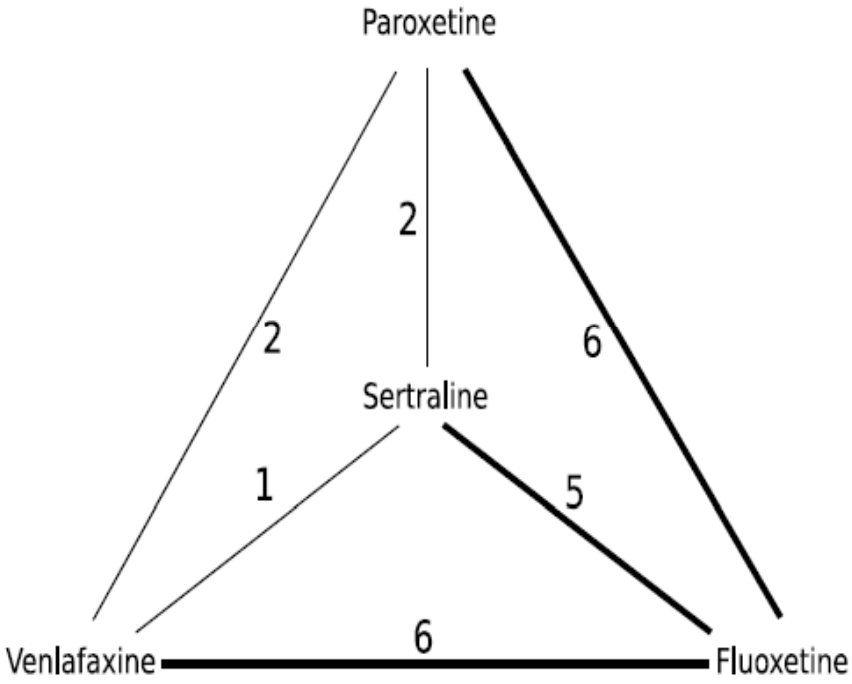
- Tervonen et al. (SOM Research Report, 2010) constructed a SMAA model with the criteria measurements from meta-analysis done by Hansen et al. on four antidepressants
- Drugs: Fluoxetine (baseline), Paroxetine, Sertraline, Venlafaxine
- Scenarios: no preference information, mild depression, severe depression
- Criteria: efficacy - treatment response
  safety - diarrhea, dizziness, headache, insomina, nausea

MA/SMAA

Tervonen et al. concluded that there is trade-offs among those drugs.

Limitation of their method:

- Not all drugs are included
- What if chosen another baseline – results might vary
- Some studies are excluded automatically



MTC/SMAA

Tervonen et al. concluded that there is trade-offs among those drugs.

Limitation of their method:

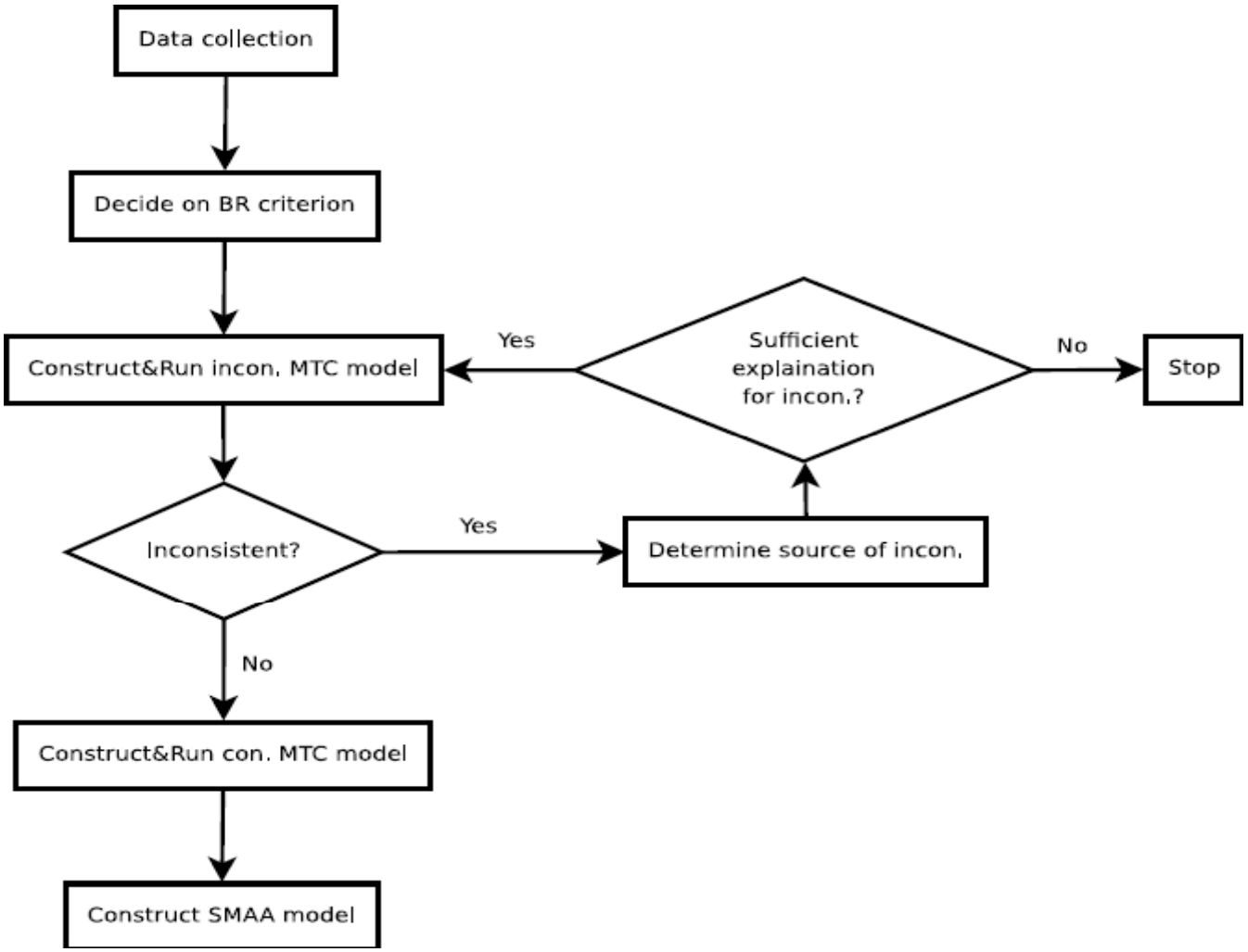
- Not all drugs are included
- What if chosen another baseline – results might vary
- Some studies are excluded automatically

To overcome those limitations MTC/SMAA is proposed in this thesis

Advantages of this method:

- All the drugs are included
- Different baseline does not effect the result
- All the studies are included

MTC/SMAA


Data collection
Decide on BR criterion
Construct&Run incon. MTC model
Yes
Sufficient explaination for incon.?
No
Stop
Inconsistent?
Yes
Determine source of incon.
No
Construct&Run con. MTC model
Construct SMAA model

MTC/SMAA

Implementation:

- MTC model – a Bayesian estimation procedure through JAGS with Markov Chain Monte Carlo simulation, and R is used to transform the results into a comprehensible format
- SMAA model – JSMAA

Results

Name	Measurement unit	Preference direction	Scale range
Efficacy	Relative value compared with Fluoxetine	Ascending	[0.98,1.23]
Diarrhea ADE's	Absolute%	Descending	[-2.24,46.95]
Dizziness ADE's	Absolute%	Descending	[1.69,29.02]
Headache ADE's	Absolute%	Descending	[6.34,33.98]
Insomnia ADE's	Absolute%	Descending	[-0.27,44.94]
Nausea ADE's	Absolute%	Descending	[13.81,40.89]

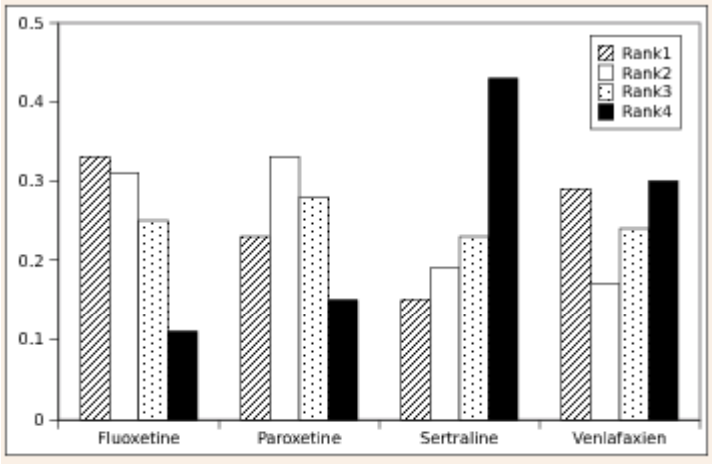
Out of preference

Drug	Confidence factor	Central weight					
		Efficacy	Diarrhea	Dizziness	Headache	Insomnia	Nausea
Fluoxetine	0.49	0.09	0.16	0.2	0.15	0.18	0.22
Paroxetine	0.34	0.16	0.19	0.16	0.17	0.17	0.16
Sertaline	0.23	0.19	0.12	0.23	0.14	0.15	0.17
Venlafaxine	0.52	0.23	0.18	0.11	0.2	0.17	0.12

Results

- Rank acceptability without preference information

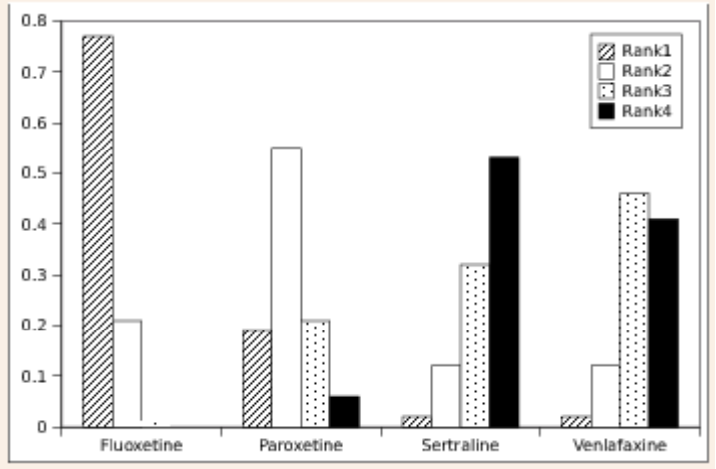
Drug	Rank1	Rank2	Rank3	Rank4
Fluoxetine	0.33	0.31	0.25	0.11
Paroxetine	0.23	0.33	0.28	0.15
Sertraline	0.15	0.19	0.23	0.43
Venlafaxine	0.29	0.17	0.24	0.30



Results

- Rank acceptability in mild depression

Drug	Rank1	Rank2	Rank3	Rank4
Fluoxetine	0.77	0.21	0.01	0
Paroxetine	0.19	0.55	0.21	0.06
Sertraline	0.02	0.12	0.32	0.53
Venlafaxine	0.02	0.12	0.46	0.41

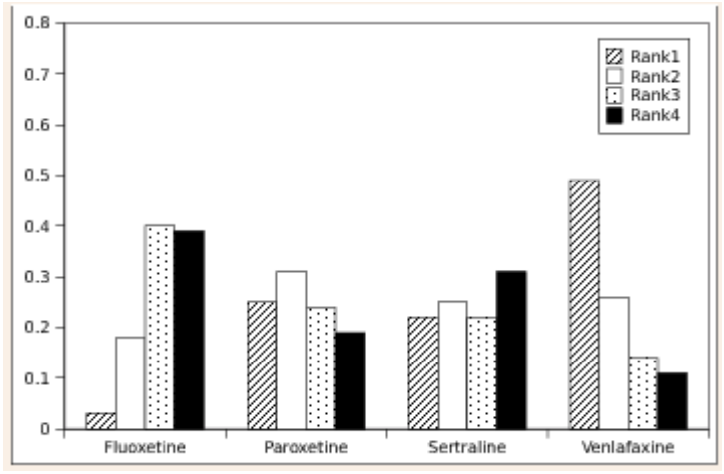


Diarrhea>Nausea>Dizziness>Insomnia>Headache>Efficacy

Results

- Rank acceptability in severe depression

Drug	Rank1	Rank2	Rank3	Rank4
Fluoxetine	0.03	0.18	0.40	0.39
Paroxetine	0.25	0.31	0.24	0.19
Sertraline	0.22	0.25	0.22	0.31
Venlafaxine	0.49	0.26	0.14	0.11



Efficacy>Diarrhea>Nausea>Dizziness>Insomnia>Headache

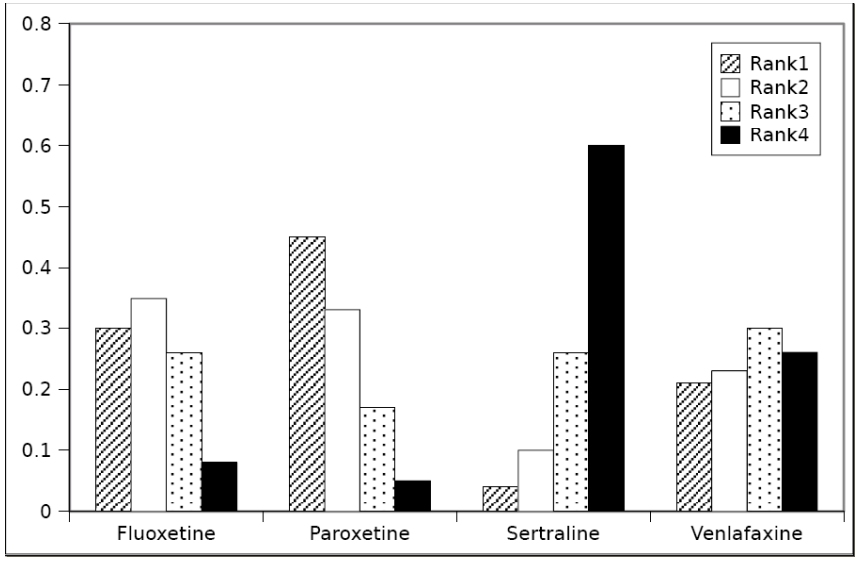
Quantitative analysis

- Compare the results of the MTC/SMAA and MA/SMAA model

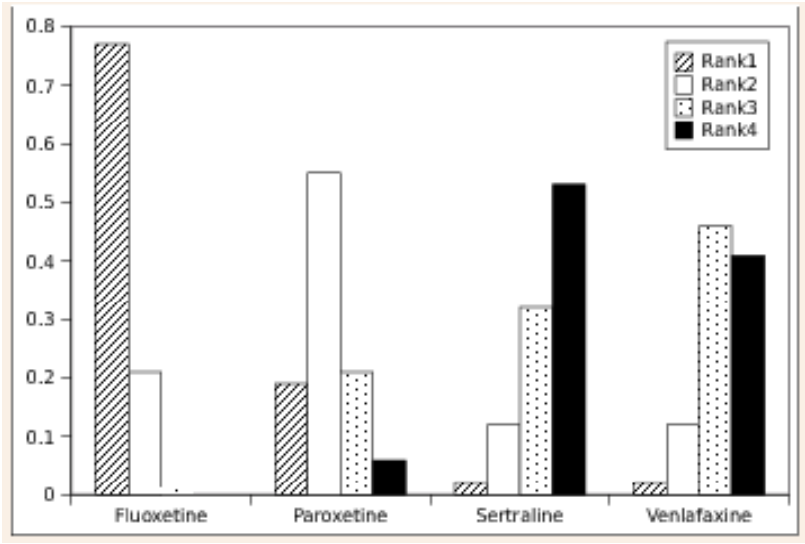
✓ In general, the results are more discriminative

Rank acceptability – mild depression

MA/SMAA



MTC/SMAA



Quantitative analysis

- Compare MTC/SMAA and MA/SMAA quantitatively

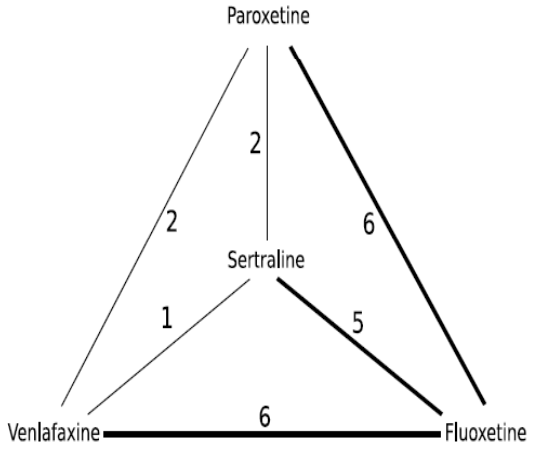
✓ In general, the results are more discriminative

✓ Rank acceptability index

Rank acceptability comparison

RA(MTC/SMAA) – RA(MA/SMAA)

drug	no preference	mild depression	severe depression
Fluoxetine	+1(0.06),-4(0.06)	+1(0.23),-3(0.15),-4(0.06)	+2(0.07),-3(0.13),-4(0.21)
Paroxetine	no significant variation	-1(0.15),+2(0.05),+3(0.07)	-1(0.14),+4(0.08)
Sertraline	-2(0.07),-3(0.07),+4(0.12)	no significant variation	-2(0.05),-3(0.1),+4(0.15)
Venlafaxine	-1(0.09),+3(0.07)	-1(0.12),-2(0.06),+3(0.13)	+1(0.11),-3(0.07)

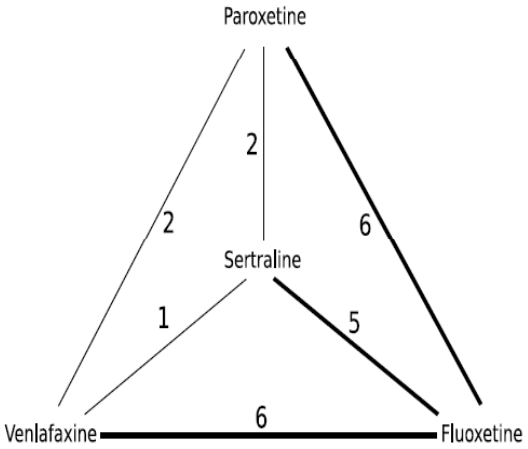


Rank acceptability comparison

RA(MTC/SMAA) RA(MA/SMAA)

The biggest change

drug	no preference	ession	severe depression
Fluoxetine	+1(0.06),-4(0.06)	+1(0.23),-3(0.15),-4(0.06)	+2(0.07),-3(0.13),-4(0.21)
Paroxetine	no significant variation	-1(0.15),+2(0.05),+3(0.07)	-1(0.14),+4(0.08)
Sertraline	-2(0.07),-3(0.07),+4(0.12)	no significant variation	-2(0.05),-3(0.1),+4(0.15)
Venlafaxine	-1(0.09),+3(0.07)	-1(0.12),-2(0.06),+3(0.13)	+1(0.11),-3(0.07)



Diarrhea>Nausea>Dizziness>Insomnia >Headache>Efficacy

Quantitative analysis

- Compare MTC/SMAA and MA/SMAA quantitatively

✓ In general, the results are more discriminative
✓ Rank acceptability index
✓ Central weight vector and confidence factors
- Both models can show clear trade-offs among those chosen drugs

Qualitative analysis

- Any drug can be chosen as the baseline, and the result will not change
- Compare the MA/SMAA and MTC/SMAA method from three perspectives

✓ What is required to implement the method?

Qualitative analysis

- Compare the MA/SMAA and MTC/SMAA method from three perspective

✓ What is required to implement the method?

Data collection, criteria determining, evidence synthesis, SMAA model construction

Only difference is evidence synthesis:

MA/SMAA – Hierachical linear model

MTC/SMAA – Bayesian model

Qualitative analysis

- Compare the MA/SMAA and MTC/SMAA method from three perspective

✓ What is required to implement the method?

✓ What is the difference in the complexity of the method?

Qualitative analysis

- Compare the MA/SMAA and MTC/SMAA method from three perspective

✓ What is required to implement the method?

✓ What is the difference in the complexity of the method?

1. The steps needed to implement the method
2. Model generation
3. The format of the results

Qualitative analysis

- Compare the MA/SMAA and MTC/SMAA method from three perspective

✓ What is required to implement the method?

✓ What is the difference in the complexity of the method?

✓ What is the additional information is required in MTC/SMAA?

Qualitative analysis

- Compare the MA/SMAA and MTC/SMAA method from three perspective

✓ What is required to implement the method?

✓ What is the difference in the complexity of the method?

✓ What is the additional information is required in MTC/SMAA?

1. Inconsistency analysis
2. Transforming the results into meaningful format

Conclusion

- MTC/SMAA model generates more discrimintive results
- Clear trade-offs among drugs are identified with the uncertainties to support BR analysis
- Compared with MA/SMAA, MTC/SMAA has three advantages:

1. Possibility of taking into account all available evidence
2. Possibility to support the decison making without a common comparator
3. Improve the transparency of decison making process

Future work

- Future research could address applicability of the MTC/SMAA method in other therapeutic areas
- Future research should show how to integrate evidence synthesis, decison model generation, and BR analysis into one process

Thank you!