ネットワークメタアナリシスによる Comparative Effectiveness Research と 高次漸近理論に基づく推測手法

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朝日新聞 DIGITAL

apital ▸医療ニュース ▸ニュース・フォーカス

シリーズ：その他

ジェネリック薬の普及を加速　厚労省、医療費抑制で

水戸部六美　2017年5月20日06時00分

厚生労働省は、後発医薬品（ジェネリック）の普及割合を８０％に引き上げる目標時期について、２０２０年秋に半年前倒しする方針を固めた。薬剤費は増え続けており、価格の安い薬の普及を加速させて社会保障費の抑制をめざす。

２３日に開かれる政府の経済財政諮問会議（議長・安倍晋三首相）で、塩崎恭久厚生労働相が表明する方針だ。後発薬は特許が切れた先発薬と同じ成分で、価格は一般的に先発薬の４～５割程度と安い。普及を早めて薬剤費を抑制させる。前倒しによる具体的な財政効果は試算していない。

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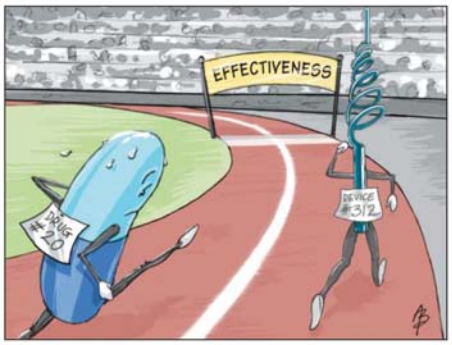
http://www.asahi.com/articles/ASK5M7W4QK5MUBQU019.html

Comparative Effectiveness Research (CER)



Comparative effectiveness research allows investigators to determine the superiority, inferiority, or equivalence of various interventions when pitted against each other.

Mitka, M. (2010). US Government Kicks Off Program for Comparative Effectiveness Researches. JAMA 304: 2230-1.

- The Institute of Medicine committee has defined CER as "the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care. The purpose of CER is to assist consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve health care at both the individual and population levels."

http://www.nap.edu/read/12648/chapter/4

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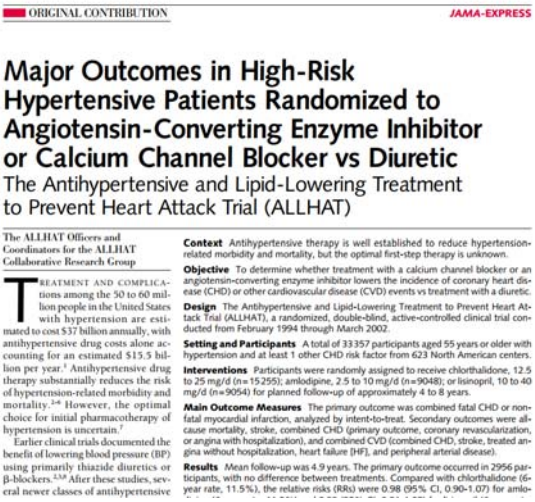

ORIGINAL CONTRIBUTION JAMA-EXPRESS

Major Outcomes in High-Risk Hypertensive Patients Randomized to Angiotensin-Converting Enzyme Inhibitor or Calcium Channel Blocker vs Diuretic

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)

The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group

TREATMENT AND COMPLICATIONS among the 50 to 60 million people in the United States with hypertension are estimated to cost $37 billion annually, with antihypertensive drug costs alone accounting for an estimated $15.5 billion per year.[1] Antihypertensive drug therapy substantially reduces the risk of hypertension-related morbidity and mortality.[2-6] However, the optimal choice for initial pharmacotherapy of hypertension is uncertain.[7]

Earlier clinical trials documented the benefit of lowering blood pressure (BP) using primarily thiazide diuretics or β-blockers.[2,3,8] After these studies, several newer classes of antihypertensive

Context Antihypertensive therapy is well established to reduce hypertension-related morbidity and mortality, but the optimal first-step therapy is unknown.

Objective To determine whether treatment with a calcium channel blocker or an angiotensin-converting enzyme inhibitor lowers the incidence of coronary heart disease (CHD) or other cardiovascular disease (CVD) events vs treatment with a diuretic.

Design The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), a randomized, double-blind, active-controlled clinical trial conducted from February 1994 through March 2002.

Setting and Participants A total of 33357 participants aged 55 years or older with hypertension and at least 1 other CHD risk factor from 623 North American centers.

Interventions Participants were randomly assigned to receive chlorthalidone, 12.5 to 25 mg/d (n=15255); amlodipine, 2.5 to 10 mg/d (n=9048); or lisinopril, 10 to 40 mg/d (n=9054) for planned follow-up of approximately 4 to 8 years.

Main Outcome Measures The primary outcome was combined fatal CHD or nonfatal myocardial infarction, analyzed by intent-to-treat. Secondary outcomes were all-cause mortality, stroke, combined CHD (primary outcome, coronary revascularization, or angina with hospitalization), and combined CVD (combined CHD, stroke, treated angina without hospitalization, heart failure [HF], and peripheral arterial disease).

Results Mean follow-up was 4.9 years. The primary outcome occurred in 2956 participants, with no difference between treatments. Compared with chlorthalidone (6-year rate, 11.5%), the relative risks (RRs) were 0.98 (95% CI, 0.90-1.07) for amlo-

JAMA 2002, 288: 2981-2196.

- ALLHAT試験：1990年代、米国で行われた、降圧薬のComparative Effectivenessを比較した臨床試験
- 利尿剤、β-blocker、ACE阻害薬、Ca拮抗薬の4薬剤を比較した試験
- 当初、計画段階で見積もられたサンプルサイズは、4万人！（多重性も考慮しなくてはならない）
- Head-to-headの比較試験で、Comparative Effectivenessの検証的なエビデンスを得るためには、膨大なサンプルサイズ、費用、時間がかかる！

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Network Meta-Analysis (NMA)

- 有効性についてのエビデンスが確立された複数の治療法のComparative Effectivenessを評価するために新たに開発されたエビデンス統合のための方法論
- 過去に行われた臨床試験の結果を統合し、利用可能な複数の治療法の有効性・安全性を、系統的に比較するためのメタアナリシスの方法論
- Multiple treatment comparison meta-analysis, Mixed-treatment comparisonなどともいわれる

Caldwell et al. (2005), Salanti (2012)

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- 双極性障害の維持治療における17種類の薬物療法の有効性・許容性を比較したネットワークメタアナリシス
- 九州大学，統計数理研究所，京都大学，Oxford大学，Ioannina大学，München工科大学の研究者による国際共同研究
- ベイズ流階層モデル，MCMCを用いた高度な統計解析を行っており、生物統計専門家として、野間，田中司朗先生（京都大学），Georgia Salanti先生（Ioannina大学）が参加している
- 2015年度 日本うつ病学会 下田光造賞，2015年度 総合病院精神医学会 国際論文賞 受賞

Miura, Noma, Furukawa et al. (2014). *Lancet Psychiatry* **1**: 351-9.

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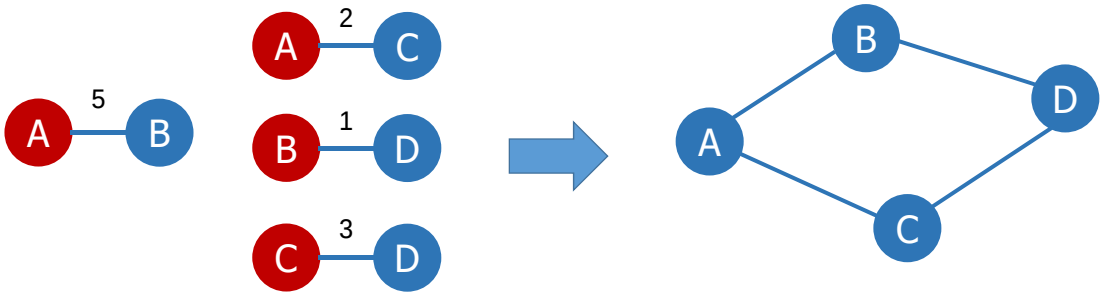
‘Network’ Meta-Analysis



赤：当該試験のActive Treatment
数字：試験数

※ 個々の臨床試験では、ほとんどが2つの治療の対比較で、多くても3-4ほどの比較が行われるのみ

直接比較のエビデンスのパスをつなげて、治療のネットワークを作り、対象となる治療（A-D）間の治療効果の比較を行う

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- 12種類の新世代抗うつ薬の有効性・許容性を比較したネットワークメタアナリシス
- 1991年から2007年に実施された、12種類の新世代抗うつ薬のいずれかを比較したランダム化臨床試験（117試験，25,298 人）の結果を統合解析
- 精神医学領域で初めて行われた、最大規模のネットワークメタアナリシス
- 有効性に関するアウトカムは、割りつけられた治療への反応（=0,1）
- 効果の指標には、Odds Ratio (OR) を採用

8

Cipriani, Furukawa, Salanti *et al*. (2009). *Lancet* **373**: 746-58.

Network for the 12 antidepressants

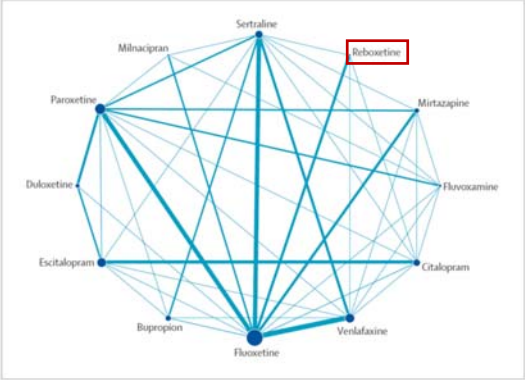

Figure 2: **Network of eligible comparisons for the multiple-treatment meta-analysis for efficacy (response rate)** The width of the lines is proportional to the number of trials comparing each pair of treatments, and the size of each node is proportional to the number of randomised participants (sample size). The network of eligible comparisons for acceptability (dropout rate) analysis is similar.

Cipriani, Furukawa, Salanti et al. (2009)

- 直接比較をした試験が１つもないパスでも、間接比較のエビデンスによって、ネットワーク上のその他のすべての治療と有効性を比較することができる
- Reboxetineは、ネットワーク上で、直接比較のパスは、Sertraline, Fluoxetine, Venlafaxine, Citalopramの4薬剤しかないが…

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Reboxetine vs.

	OR (95%CI)
Bupropion	0.63 (0.46, 0.83)
Citalopram	0.61 (0.47, 0.80)
Duloxetine	0.68 (0.50, 0.95)
Escitalopram	0.51 (0.39, 0.68)
Fluoxetine	0.68 (0.53, 0.86)
Fluvoxamine	0.69 (0.50, 0.97)
Milnacipran	0.67 (0.46, 0.97)
Mirtazapine	0.49 (0.36, 0.66)
Paroxetine	0.67 (0.50, 0.86)
Sertraline	0.54 (0.41, 0.71)

他の11薬剤すべてに有意に劣るという結果に

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対比較オッズ比の推定値，信頼区間

Efficacy (response rate) (95% CI) | Comparison | Acceptability (dropout rate) (95% CI)

BUP	1·00 (0·78-1·28)	0·75 (0·55-1·01)	1·06 (0·86-1·32)	0·89 (0·74-1·08)	0·73 (0·53-1·00)	0·87 (0·58-1·24)	0·87 (0·66-1·14)	0·81 (0·65-1·00)	0·62 (0·45-0·86)	1·01 (0·82-1·27)	0·84 (0·68-1·02)
0·98 (0·78-1·23)	CIT	0·75 (0·55-1·02)	1·07 (0·86-1·31)	0·90 (0·73-1·09)	0·73 (0·54-0·99)	0·87 (0·60-1·24)	0·87 (0·66-1·15)	0·81 (0·65-1·01)	0·62 (0·45-0·84)	1·02 (0·81-1·28)	0·84 (0·67-1·06)
1·09 (0·83-1·43)	1·12 (0·87-1·44)	DUL	1·43 (1·09-1·85)	1·19 (0·91-1·57)	0·98 (0·67-1·41)	1·16 (0·77-1·73)	1·16 (0·83-1·61)	1·08 (0·84-1·40)	0·83 (0·57-1·22)	1·36 (1·01-1·83)	1·12 (0·84-1·50)
0·82 (0·67-1·01)	0·84 (0·70-1·01)	0·75 (0·60-0·93)	ESC	0·84 (0·70-1·01)	0·69 (0·50-0·94)	0·81 (0·55-1·15)	0·81 (0·62-1·07)	0·76 (0·62-0·93)	0·58 (0·43-0·81)	0·95 (0·77-1·19)	0·78 (0·64-0·97)
1·08 (0·90-1·29)	1·10 (0·93-1·31)	0·99 (0·79-1·24)	1·32 (1·12-1·55)	FLU	0·82 (0·62-1·07)	0·97 (0·69-1·32)	0·97 (0·77-1·21)	0·91 (0·79-1·05)	0·70 (0·53-0·92)	1·14 (0·96-1·36)	0·94 (0·81-1·09)
1·10 (0·83-1·47)	1·13 (0·86-1·47)	1·01 (0·74-1·38)	1·35 (1·02-1·76)	1·02 (0·81-1·30)	FVX	1·18 (0·76-1·75)	1·18 (0·87-1·61)	1·10 (0·84-1·47)	0·85 (0·57-1·26)	1·38 (1·03-1·89)	1·14 (0·86-1·54)
1·07 (0·77-1·48)	1·09 (0·78-1·50)	0·97 (0·69-1·38)	1·30 (0·95-1·78)	0·99 (0·74-1·31)	0·97 (0·68-1·37)	MIL	0·99 (0·69-1·53)	0·94 (0·68-1·31)	0·72 (0·48-1·10)	1·17 (0·84-1·72)	0·97 (0·69-1·40)
0·79 (0·72-1·00)	0·80 (0·63-1·01)	0·72 (0·54-0·94)	0·96 (0·76-1·19)	0·73 (0·60-0·88)	0·71 (0·55-0·92)	0·74 (0·53-1·01)	MIR	0·93 (0·75-1·17)	0·72 (0·51-1·03)	1·17 (0·91-1·51)	0·97 (0·76-1·23)
1·06 (0·87-1·30)	1·08 (0·90-1·30)	0·97 (0·78-1·20)	1·30 (1·10-1·53)	0·98 (0·86-1·12)	0·96 (0·76-1·23)	1·00 (0·74-1·33)	1·35 (1·11-1·64)	PAR	0·77 (0·56-1·05)	1·25 (1·04-1·52)	1·03 (0·86-1·24)
1·60 (1·20-2·16)	1·63 (1·25-2·14)	1·46 (1·05-2·02)	1·95 (1·47-2·59)	1·48 (1·16-1·90)	1·45 (1·03-2·02)	1·50 (1·03-2·18)	2·03 (1·52-2·78)	1·50 (1·16-1·98)	REB	1·63 (1·19-2·24)	1·34 (0·99-1·83)
0·87 (0·72-1·05)	0·88 (0·72-1·07)	0·79 (0·62-1·01)	1·06 (0·88-1·27)	0·80 (0·69-0·93)	0·79 (0·61-1·01)	0·81 (0·60-1·11)	1·10 (0·90-1·36)	0·82 (0·69-0·96)	0·54 (0·41-0·71)	SER	0·82 (0·67-1·00)
0·85 (0·70-1·01)	0·86 (0·71-1·05)	0·77 (0·60-0·99)	1·03 (0·86-1·24)	0·78 (0·68-0·90)	0·77 (0·59-0·99)	0·79 (0·58-1·08)	1·08 (0·82-1·33)	0·79 (0·67-0·94)	0·53 (0·40-0·69)	0·98 (0·82-1·16)	VEN

12薬剤すべてを比較した効果の指標の推定値・信頼区間を得ることができる

Cipriani et al. (2009)

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三竦み（さんすくみ）

- 蜘蛆食蛇、蛇食蛙、蛙食蜘蛆、互相食也

《「関尹子」三極から》蛇はなめくじをおそれ、なめくじは蛙（かえる）をおそれ、蛙は蛇をおそれること。転じて、三者が互いに牽制し合って、それぞれが自由に動けない状態。

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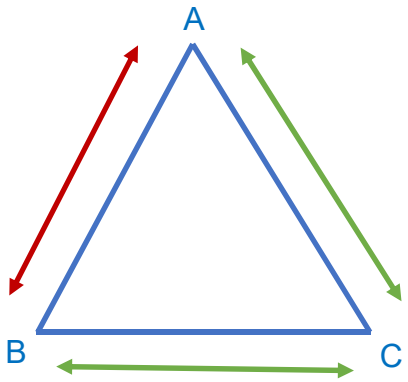
ネットワーク上の比較の妥当性



- NMAにおいて、直接比較・間接比較のエビデンスを統合して、治療間の妥当な比較を行うためには、直接比較・間接比較のパスにおける治療間の差が一致していなくてはならない
  - 直接比較：A vs B
  - 間接比較：B vs C, C vs A
- 2つのパスにおけるA-B間の差が一致しなくては、NMAにおける治療の比較の妥当性は失われてしまう！！

Salanti (2012), Dias et al. (2013)

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Inconsistency

- Consistency: ネットワーク上の直接・間接エビデンスによる治療間のEffect Sizeの差が一致（consistent）すること
  - ネットワーク上の任意の治療のペアにおいて、直接・間接エビデンスによるEffect Sizeの差が互いに一致して整合すること
  - より概念的には、Transitivityと言われることも
- Inconsistency: Lack of consistency
  - ネットワーク上の治療の比較の妥当性が、前提として成り立たないということに！！

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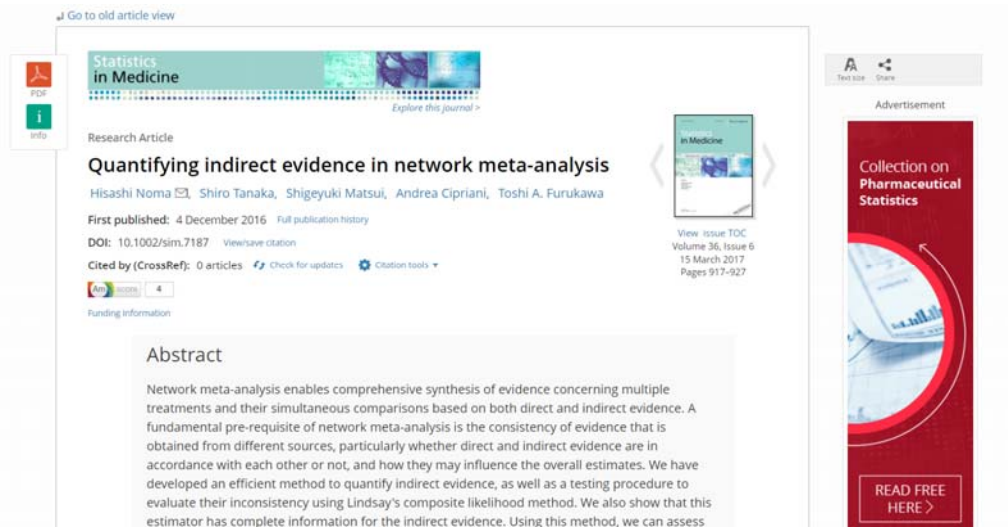

http://onlinelibrary.wiley.com/doi/10.1002/sim.7187/abstract

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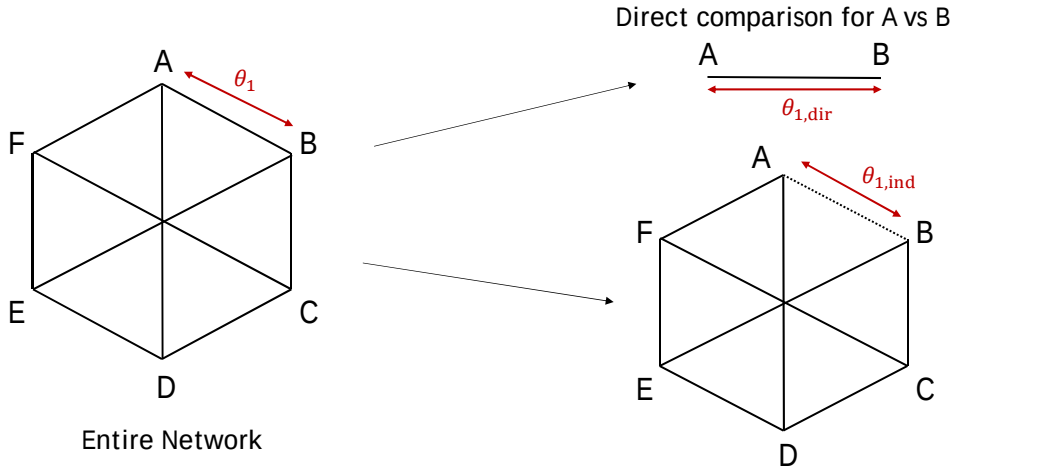
Inconsistency on the Network



NMA for 12 New Generation Antidepressants

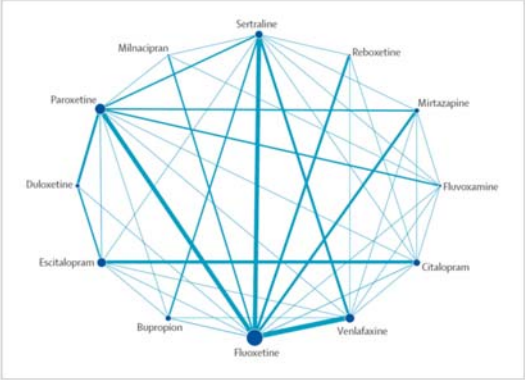
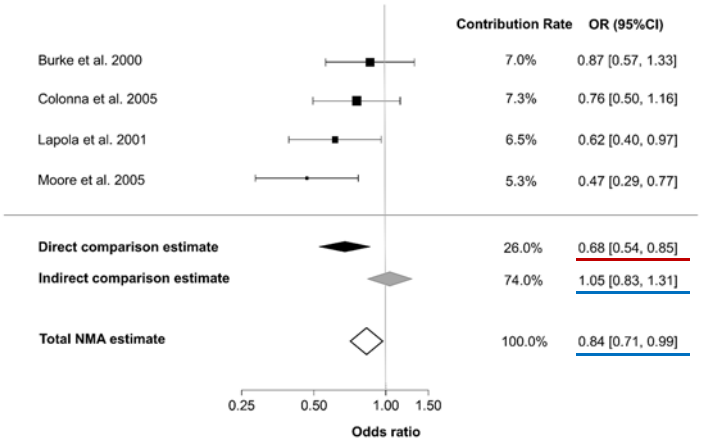


Figure 2: **Network of eligible comparisons for the multiple-treatment meta-analysis for efficacy (response rate)** The width of the lines is proportional to the number of trials comparing each pair of treatments, and the size of each node is proportional to the number of randomised participants (sample size). The network of eligible comparisons for acceptability (dropout rate) analysis is similar.

- Review for 117 RCTs (25,298 patients) from 1991 to 2007, which compared 12 antidepressants for the acute treatment of unipolar major depression.
- The outcome was response to the allocated treatment (binary).
- The comparative efficacy for the 12 antidepressants was evaluated by NMA.

Cipriani, Furukawa, Salanti et al. (2009) 17

Escitalopram vs. Citalopram



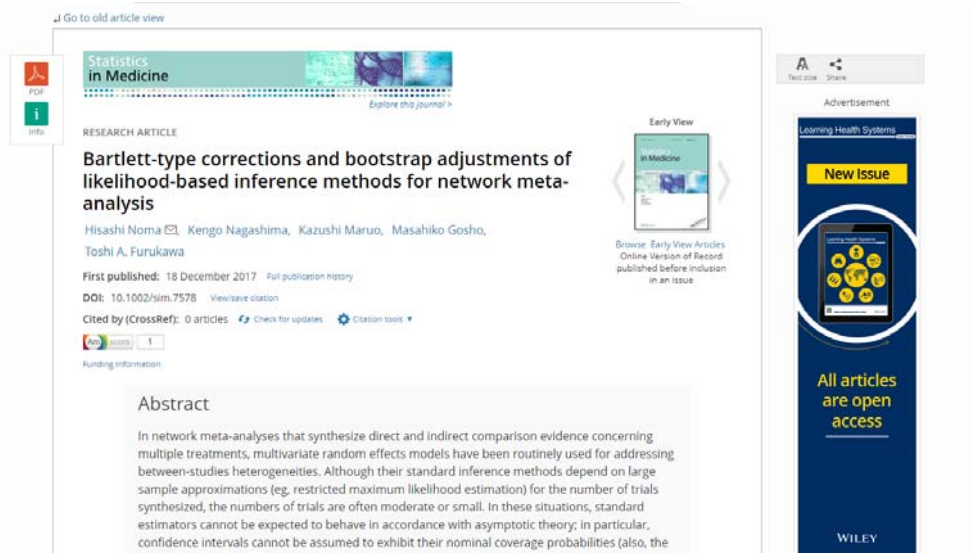
P=0.009

Noma et al. (2017) Industrial sponsorship bias?? 18

Validity of Statistical Inference on NMA

- 実際のネットワークメタアナリシスは、疾患・薬剤などによっては、比較的少数の試験による小規模なネットワークでの統合解析を行うことも多い
- 副次的に、サブグループ解析を行う際には、数試験程度の小規模なネットワークで解析を行うことも多い
- 大標本理論に基づく最尤法などの推測手法の妥当性は、試験数が十分に大きい条件下でなくては成り立たない
- 高次漸近理論を用いた手法により、より正確な統計的推測手法を開発

Noma (2011), Noma et al. (2017) 19



http://onlinelibrary.wiley.com/doi/10.1002/sim.7578/abstract 20

Multivariate Random-Effects Model

- Suppose Y_{ir} is the estimated treatment effect for the rth outcome in the ith trial ($i = 1, 2, \ldots, N$; $r = 1,2, \ldots, p$), which is defined as a contrast to a common baseline treatment (e.g., placebo).
  - $Y_{ir} \sim N(\mu_{ir}, s_{ir}^2)$, $\mu_{ir} \sim N(\theta_r, \tau_r^2)$
- s_{ir}^2 is within-study variance (ordinarily, fixed to a valid estimate).
- θ_r is corresponding to the average treatment effect, and τ_r^2 is across-studies variance.

White (2011), White et al. (2012) 21

Matrix Notation

- $Y_i = (Y_{i1}, Y_{i2}, \ldots, Y_{ip})$, $(i = 1,2, \ldots, N)$
- $Y_i \sim N(\mu_i, S_i)$, $\mu_i \sim N(\theta, \Sigma)$
- $\theta = \begin{pmatrix} \theta_1 \\ \theta_2 \\ \ldots \\ \theta_p \end{pmatrix}, S_i = \begin{pmatrix} s_{i1}^2 & \rho_{i12} s_{i1} s_{i2} & \cdots & \rho_{i1p} s_{i1} s_{ip} \\ \rho_{i12} s_{i1} s_{i2} & s_{i2}^2 & \ldots & \rho_{i2p} s_{i2} s_{ip} \\ \vdots & \vdots & \ddots & \vdots \\ \rho_{i1p} s_{i1} s_{ip} & \rho_{i2p} s_{i2} s_{ip} & \cdots & s_{ip}^2 \end{pmatrix}$
- $\Sigma = \begin{pmatrix} \tau_1^2 & \kappa_{12} \tau_1 \tau_2 & \cdots & \kappa_{1p} \tau_1 \tau_p \\ \kappa_{12} \tau_1 \tau_2 & \tau_2^2 & \ldots & \kappa_{2p} \tau_2 \tau_p \\ \vdots & \vdots & \ddots & \vdots \\ \kappa_{1p} \tau_1 \tau_p & \kappa_{2p} \tau_2 \tau_p & \cdots & \tau_p^2 \end{pmatrix}$

White (2011), White et al. (2012) 22

対数尤度関数

- Parameter vector：$\eta = (\theta_1, \dots, \theta_p, \tau_1, \dots, \tau_p, \kappa_{12}, \dots, \kappa_{(p-1)p})$

$$\ell(\eta) = \sum_{i=1}^{N} \log p(y_{i1}, \dots, y_{ip} | \eta)$$

$$= -\frac{1}{2} \sum_{i=1}^{N} \{\log|\Sigma + S_i| + (y_i - \theta) W_i (y_i - \theta)^T + p_i \log 2\pi\}$$

  - where $W_i = (\Sigma + S_i)^{-1}$

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Conventional ML-based Inference Methods

- Likelihood Ratio Statistic
  - $T(\mu_1^{null}) = -2\{\ell(\mu_1^{null}, \tilde{\boldsymbol{\mu}}_c, \tilde{\boldsymbol{\eta}}) - \ell(\hat{\mu}_1, \hat{\boldsymbol{\mu}}_c, \hat{\boldsymbol{\eta}})\}$
- Efficient Score Statistic
  - $S(\mu_1^{null}) = U_{\mu_1}(\mu_1^{null}, \tilde{\boldsymbol{\mu}}_c, \tilde{\boldsymbol{\eta}})^2 / J_{\mu_1}(\mu_1^{null}, \tilde{\boldsymbol{\mu}}_c, \tilde{\boldsymbol{\eta}})$
- Jackson et al. (2011) などの著名な文献では、多変量変量効果モデルのもとでは、複雑な計算が必要になり実践的ではないなどと予想がされていたが、Noma et al. (2017) では、単純な代数演算で実行できる計算式を与えている

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Bartlett-type Correction for LR Statistic

- 尤度比統計量，スコア統計量のカイ二乗近似の精度を上げるための高次漸近論に基づく補正方法
- Bartlett Correction
  - $T^*(\mu_1^{null}) = T(\mu_1^{null})/\hat{\xi}$
  - $\hat{\xi} = \hat{\mathrm{E}}[T(\mu_1^{null})]$
- 1次モーメントを合わせるための修正を行うだけの方法であるが、カイ二乗近似の精度は $O(N^{-1})$ から $O(N^{-2})$ まで改善される

Barndorff-Nielsen and Hall (1988), Cordeiro and Cribari-Neto (2014) 25

Efficient Numerical Bartlett-type Corrections

- 従来のBartlett補正は、尤度比統計量の真の分布の1次モーメントを解析的な型で与えて、補正項として用いている
- ネットワークメタアナリシスで用いられる多変量変量効果モデルなどの複雑なモデルでは、この補正項の計算は、解析手順として困難
- Noma et al. (2017) は、ブートストラップ法を用いて、この補正項を求めることを提案し、同様に、スコア統計量などの他の有効な検定方式全般で、これが正確な補正方法になることを示した

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Algorithm 1. Bartlett Correction for $T\left(\mu_1^{null}\right)$

- 1. For the multivariate random effects model (*), compute the CML estimates $\{\widetilde{\boldsymbol{\mu}}_c, \widetilde{\boldsymbol{\eta}}\}$ of $\{\boldsymbol{\mu}_c, \boldsymbol{\eta}\}$ under $\mu_1 = \mu_1^{null}$.
- 2. Resample $\boldsymbol{Y}_1^{(b)}, \boldsymbol{Y}_2^{(b)}, \ldots, \boldsymbol{Y}_N^{(b)}$ from the estimated null distribution of (*) with the parameters substituted with $\{\mu_1^{null}, \widetilde{\boldsymbol{\mu}}_c, \widetilde{\boldsymbol{\eta}}\}$ via parametric bootstrap, B times (b = 1,2,…,B).
- 3. Compute the ML estimates $\{\hat{\mu}_1^{(b)}, \widehat{\boldsymbol{\mu}}_c^{(b)}, \widehat{\boldsymbol{\eta}}^{(b)}\}$ and the CML estimates $\{\widetilde{\boldsymbol{\mu}}_c^{(b)}, \widetilde{\boldsymbol{\eta}}^{(b)}\}$ for the bth bootstrap sample $\boldsymbol{Y}_1^{(b)}, \boldsymbol{Y}_2^{(b)}, \ldots, \boldsymbol{Y}_N^{(b)}$. Also, replicate it for all B bootstrap samples (b = 1,2,…,B).

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(Continued) Algorithm 1

- 4. Compute the likelihood ratio statistics for all B bootstrap estimates,
$$T^{(b)}(\mu_1^{null}) = -2\{\ell\left(\mu_1^{null}, \widetilde{\boldsymbol{\mu}}_c^{(b)}, \widetilde{\boldsymbol{\eta}}^{(b)}\right) - \ell\left(\hat{\mu}_1^{(b)}, \widehat{\boldsymbol{\mu}}_c^{(b)}, \widehat{\boldsymbol{\eta}}^{(b)}\right)\}$$
and calculate a bootstrap estimate of ξ,
$$\hat{\xi}_{bs} = \frac{1}{B}\sum_{b=1}^{B} T^{(b)}(\mu_1^{null}).$$
- 5. We can obtain the corrected likelihood ratio statistic,
$$T_{bs}^{*}\left(\mu_1^{null}\right) = T\left(\mu_1^{null}\right)/\hat{\xi}_{bs}.$$

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Algorithm 2. Bartlett Correction for $S\left(\mu_1^{null}\right)$

- 1. Conduct processes 1–3 of Algorithm 1.
- 2. Compute the efficient score statistics for all *B* bootstrap estimates,

$$S^{(b)}(\mu_1^{null}) = U_{\mu_1}\left(\mu_1^{null}, \widetilde{\boldsymbol{\mu}}_c^{(b)}, \widetilde{\boldsymbol{\eta}}^{(b)}\right)^2 / J_{\mu_1}\left(\mu_1^{null}, \widetilde{\boldsymbol{\mu}}_c^{(b)}, \widetilde{\boldsymbol{\eta}}^{(b)}\right)$$

and calculate a bootstrap estimate of $\psi = \mathrm{E}[S\left(\mu_1^{null}\right)]$,

$$\hat{\psi}_{bs} = \frac{1}{B}\sum_{b=1}^{B} S^{(b)}(\mu_1^{null}).$$

- 3. We can obtain the corrected efficient score statistic,

$$S_{bs}^{*}\left(\mu_1^{null}\right) = S\left(\mu_1^{null}\right)/\hat{\psi}_{bs}.$$

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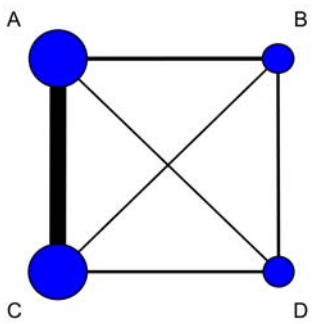
Simulation Studies



Design	$N = 24$	$N = 16$	$N = 8$
A vs. B	3	2	1
A vs. C	14	8	4
A vs. D	1	1	—
B vs. C	1	1	—
B vs. D	1	1	—
C vs. D	2	1	1
A vs. C vs. D	1	1	1
B vs. C vs. D	1	1	1

Noma et al. (2017)

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Simulation Results (N=24)

N	τ	param.	ML	REML	LR	LR-BTC	ES	ES-BTC
24	0.05	μ_1	94.6%	95.2%	95.4%	96.0%	95.8%	95.3%
24	0.05	μ_2	95.1%	95.6%	95.2%	96.8%	95.4%	95.8%
24	0.05	μ_3	95.8%	96.5%	95.4%	94.6%	95.8%	95.8%
24	0.10	μ_1	93.9%	94.8%	94.2%	95.8%	94.9%	94.6%
24	0.10	μ_2	94.8%	95.5%	95.3%	95.6%	95.8%	95.0%
24	0.10	μ_3	94.2%	95.6%	95.2%	93.8%	96.4%	94.9%
24	0.20	μ_1	91.3%	93.0%	92.2%	94.7%	93.6%	94.5%
24	0.20	μ_2	92.0%	93.6%	94.4%	95.1%	95.3%	94.5%
24	0.20	μ_3	92.1%	93.5%	93.3%	94.3%	94.0%	95.0%
24	0.30	μ_1	91.6%	93.3%	93.0%	95.2%	94.2%	94.6%
24	0.30	μ_2	92.1%	94.1%	92.4%	94.2%	94.1%	94.6%
24	0.30	μ_3	91.6%	93.8%	93.5%	94.8%	94.8%	94.9%
24	0.60	μ_1	91.8%	93.4%	93.8%	95.5%	94.9%	96.0%
24	0.60	μ_2	92.7%	94.1%	92.0%	94.1%	93.3%	95.3%
24	0.60	μ_3	92.4%	94.0%	92.8%	95.2%	94.6%	96.2%

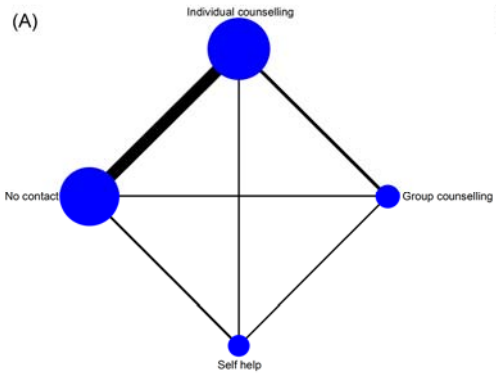
Simulation Results (N=16)

N	τ	param.	ML	REML	LR	LR-BTC	ES	ES-BTC
16	0.05	μ_1	94.6%	95.7%	95.1%	94.8%	95.4%	95.9%
16	0.05	μ_2	95.4%	95.8%	95.2%	95.2%	96.1%	95.8%
16	0.05	μ_3	94.4%	95.2%	95.7%	95.3%	96.7%	95.1%
16	0.10	μ_1	93.2%	94.5%	95.8%	95.6%	96.1%	95.2%
16	0.10	μ_2	93.6%	94.8%	95.1%	95.2%	96.2%	94.8%
16	0.10	μ_3	93.6%	94.4%	95.2%	95.6%	96.1%	95.0%
16	0.20	μ_1	91.4%	93.4%	93.2%	93.9%	94.9%	94.3%
16	0.20	μ_2	92.3%	94.4%	92.1%	94.2%	93.2%	94.7%
16	0.20	μ_3	90.8%	93.3%	92.2%	94.2%	93.9%	94.4%
16	0.30	μ_1	91.0%	93.9%	91.7%	94.2%	93.8%	94.6%
16	0.30	μ_2	89.1%	92.7%	91.8%	94.2%	94.4%	95.4%
16	0.30	μ_3	90.5%	93.0%	92.2%	95.3%	93.7%	93.9%
16	0.60	μ_1	90.6%	93.2%	92.9%	95.2%	94.8%	94.2%
16	0.60	μ_2	91.4%	94.1%	92.2%	94.9%	94.1%	94.7%
16	0.60	μ_3	90.9%	93.3%	93.0%	95.5%	94.7%	95.5%

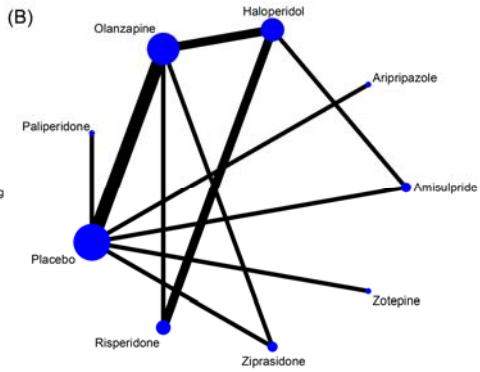
Simulation Results (N=8)

N	τ	param.	ML	REML	LR	LR-BTC	ES	ES-BTC
8	0.05	μ_1	95.5%	96.2%	95.0%	96.5%	95.7%	95.8%
8	0.05	μ_2	94.8%	95.4%	95.5%	94.9%	96.2%	96.4%
8	0.05	μ_3	94.7%	95.8%	94.4%	95.2%	95.4%	96.1%
8	0.10	μ_1	93.3%	94.6%	94.2%	93.8%	95.8%	95.2%
8	0.10	μ_2	93.3%	94.4%	94.5%	95.4%	96.2%	95.4%
8	0.10	μ_3	93.2%	94.7%	94.8%	94.8%	96.4%	95.2%
8	0.20	μ_1	89.3%	92.1%	90.2%	93.6%	92.4%	94.7%
8	0.20	μ_2	89.2%	92.8%	90.5%	93.5%	93.0%	94.4%
8	0.20	μ_3	90.0%	92.6%	92.3%	93.1%	94.3%	95.2%
8	0.30	μ_1	86.8%	91.7%	89.6%	93.1%	93.6%	95.1%
8	0.30	μ_2	85.6%	91.0%	90.2%	93.4%	93.5%	94.6%
8	0.30	μ_3	85.5%	91.2%	89.7%	92.6%	92.6%	94.6%
8	0.60	μ_1	83.7%	89.6%	87.7%	94.4%	92.4%	95.6%
8	0.60	μ_2	83.7%	89.8%	89.7%	94.6%	93.2%	95.5%
8	0.60	μ_3	84.2%	90.3%	88.6%	94.1%	93.0%	95.2%

Applications to Real Data



禁煙治療のネットワークメタアナリシス
（N=24; Hasselblad, 1998）



統合失調症のネットワークメタアナリシス
（N=15; Ades, 2010）

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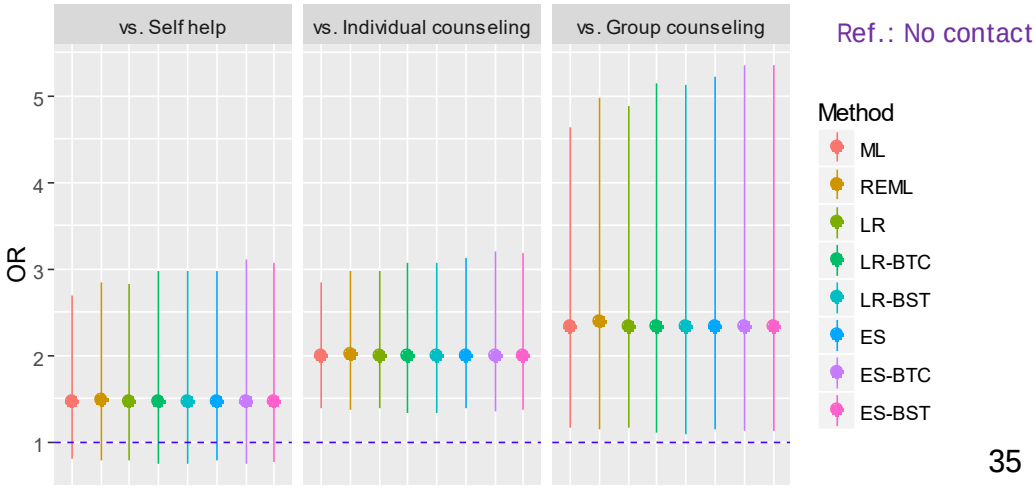
禁煙治療のネットワークメタアナリシス



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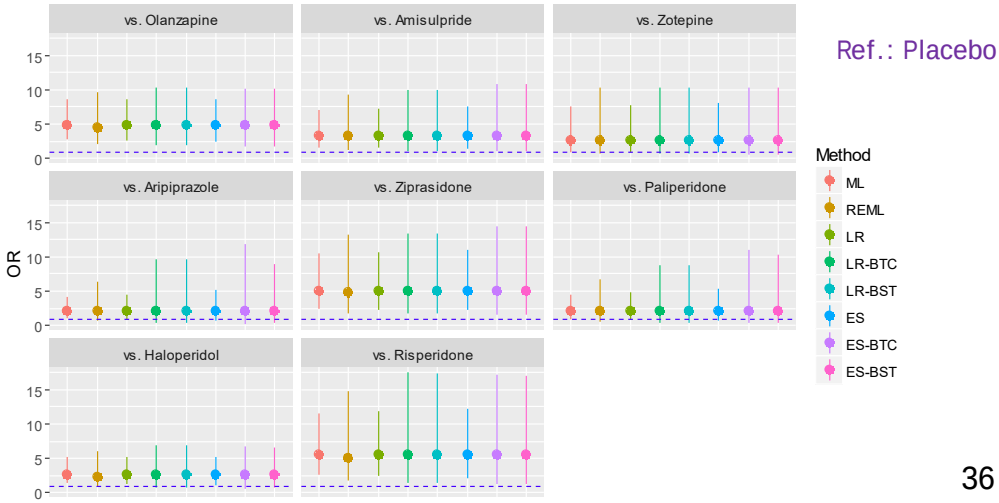
統合失調症のネットワークメタアナリシス



Ref.: Placebo

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Concluding Remarks

- 世界的な問題となりつつある、超高齢社会の医療と社会保障の問題に、ネットワークメタアナリシスは、新しい有用なデータサイエンスの方法論として、大きな注目を受けている
- 21世紀の今日、持続可能な社会の問題解決のため、データサイエンスと、その方法論に求められる役割は、ますます大きくなるものと思われる

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