DEVELOPMENT OF MEANINGFUL INTERACTION STUDIES FOR COMBINATION THERAPIES

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A common view on polypharmacy

• ‘Polypharmacy is defined as a concurrent use of multiple drugs. It may pose health risks such as adverse drug reactions, drug-drug interactions, medication errors and poor compliance. The number of drugs taken is a predictor of these complications, and a concurrent use of five or more (major polypharmacy) implies a pronounced risk of drug related problems.’

• ‘Polypharmacy was shown to be a statistically significant predictor of hospitalization, nursing home placement, death, hypoglycemia, fractures, impaired mobility, pneumonia, and malnutrition.’


-Frazier SC. Health outcomes and polypharmacy in elderly individuals: an integrated literature review. J Gerontol Nurs. 2005 Sep;31(9):4-11.
HARM-study: prospective study of drug-relations in 300000 hospital admissions

- About 6% of acute hospitalizations is drug-related
- Use of 4 medications or more increases risk of drug-related hospitalizations by 2.7

Hospital Admissions Related to Medication (HARM), OMS/NVZA-Report 2006

Increasing need for combination therapies

1. Disease spectrums
   - Psychiatric spectrum disorders
   - Metabolic syndrome
   - Anesthesiology

2. Multifactorial diseases
   - Atherosclerosis
   - Shock

3. Complex pathophysiological cascades
   - Blood pressure control
   - Inflammation

4. Complete inhibition of pathophysiological cascades
   - Cancer
   - HIV
   - Tuberculosis
   - Prevention of tolerance development

5. Pharmacokinetic optimization
   - CYP3A4-substrates
   - pGP-substrates
   - L-aromatic decarboxylase substrates

6. Development of highly selective new drugs
Rational co-therapies:
1- frequent co-morbidities

- Psychiatric spectrum disorders: depression, anxiety, psychosis

Protocolised treatment combinations:
- benzodiazepine + antidepressant
  - anxiety after start antidepressant
  - sleep disturbance
- antipsychotic + antidepressant
  - psychotic depression
  - bipolar disorder
- antiepileptic + antidepressant
  - bipolar disorder
Rational co-therapies: 2- multifactorial diseases

- Atherosclerosis and ‘poly-pill’

standard of care for stroke prevention
- lipid lowering agent
  - statin
- antihypertensive treatment
  - thiazide diuretic
  - ACE inhibitor
- platelet aggregation inhibitors
  - dipyradimol
  - aspirin
Rational co-therapies: 2- multifactorial diseases

- Circulatory shock
Rational co-therapies:
3- complex pathophysiological cascades

- Hypertension and anti-hypertensive therapy

Rational antihypertensive combinations
- prevention of stroke
  - thiazide diuretic
  - ACE inhibitor
- prevention of diabetic nephropathy
  - ACE-inhibitor
  - angiotensin II inhibitor
Rational co-therapies: 4- complete cascade inhibition

- Cell growth cycle and chemotherapy

<table>
<thead>
<tr>
<th>Combination therapy</th>
<th>Drugs</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAC</td>
<td>taxotere, doxorubicine, cyclophosphamide</td>
<td>breast</td>
</tr>
<tr>
<td>CMF</td>
<td>cyclophosphamide, methotrexate, 5-flourouracil</td>
<td>breast</td>
</tr>
<tr>
<td>CDE</td>
<td>cyclophosphamide, doxorubicin, etoposide</td>
<td>lung (sc)</td>
</tr>
<tr>
<td>EP</td>
<td>cisplatin, etoposide</td>
<td>lung</td>
</tr>
<tr>
<td>TP</td>
<td>paclitaxel, cisplatin</td>
<td>ovary</td>
</tr>
<tr>
<td>TC</td>
<td>paclitaxel, carboplatin</td>
<td>ovary</td>
</tr>
<tr>
<td>BEP</td>
<td>bleomycin, etoposide, cisplatin</td>
<td>germ cells</td>
</tr>
<tr>
<td>CHOP</td>
<td>cyclophosphamide, doxorubicin, vincristine, prednisone</td>
<td>Non-Hodgkin's</td>
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<tr>
<td>MOPP</td>
<td>chloromethin, vincristine, procarbazine, prednisone</td>
<td>Hodgkin's</td>
</tr>
<tr>
<td>FOLFOX</td>
<td>5-fluorouracil, leucovorin, oxaliplatin</td>
<td>colon</td>
</tr>
</tbody>
</table>
Rational co-therapies: 4- complete cascade inhibition

- Viral reproduction and anti-HIV-therapy

Highly Active Antiretroviral Therapy
- two nucleoside reverse transcriptase inhibitors (NRTIs)
- one NRTI + one non-nucleoside reverse transcriptase inhibitor
- one NRTI + one protease inhibitor
- (integrase inhibitor)
Rational co-therapies: 5- pharmacokinetic optimisation

- Elevated action-site concentrations

Highly Active Antiretroviral Therapy
- NRTIs are CYP3A4-inhibitors and substrates
- ritonavir used to increase lopinavir levels

Carbidopa comedication
- levodopa for Parkinson
- (5-hydroxytryptamine for depression)

Valproate for epilepsy in brain tumors?
- valproate is pGP-inhibitor
- chemotherapy is often pGP-substrate
- valproate increases brain penetration
Practical reasons for ‘rational’ co-treatment

- augmentation of treatment efficacy
  - all of previously mentioned combinations
- treatment of pathophysiologically distinct but frequent co-morbidities
  - elderly, immunocompromised, severely ill, etc.
- treatment of drug-induced adverse events
  - neuroleptics + anticholinergics for drug-induced EPS, etc
- acute pretreatment during chronic treatment with delayed onset of action
  - benzodiazepines + SSRIs for anxiety disorder
- acute ‘exacerbation’ treatment during chronic preventive treatment
  - ‘mood stabilizer’ + antidepressant for bipolar disorder
• Polypharmacy is a useful and necessary part of medical care
• Polypharmacy increases the risk of adverse events
• Drug combinations and doses are determined by pharmacokinetic and pharmacodynamic interactions
• Rational development of polypharmacy is needed
  • to develop treatments of complex disorders
  • to improve treatment efficacy
  • to reduce side effects
• Rational polytherapy:
  • combinations of several ‘single-target’ drugs
  • design of ‘promiscuous’ drugs
Rationally designed promiscuous drugs vs combinations of single-target drugs

**single-target drug combinations**

**pros**
- flexibility
  - individual dose optimisation
  - individual target optimisation

**cons**
- more difficult to develop
  - complex dose ranging
  - exclusion criteria
  - intellectual properties
  - marketing issues
- higher chance of pharmacokinetic interactions
- higher chance of adverse events
  - added population variability

**design promiscuous drug**

**pros**
- simplicity

**cons**
- more difficult to design
  - one drug, different pharmacophores
  - larger drugs, more complex PK/BBB
  - overlapping/integrated pharmacophores
- higher chance of interaction with ‘promiscuous targets’
  - PXR/CYP3A4-system
  - hERG-channels
- lower chance of adverse events
  - higher than for selective agents
Requirements for development of meaningful combination therapies

• good understanding of pathophysiological cascade
• drugs with different (key) mechanisms of action that should preferably
  • each be selective (not broad)
  • in combination be additive (not same)
  • not be opposing
  • not be complicated by active metabolites
  • not be complicated by widely disparate, non-linear or interacting pharmacokinetics
• good surrogate markers for disease process
Strategies for development of meaningful combination therapies

1. pathophysiological research
2. preclinical models
   - pathway analyses and (mathematical) disease
   - isobolographs and ‘surface-response’-modeling
   - PK/PD-interaction modeling
     ‘physiological response’, ‘mechanism-based’, nonlinear mixture amount
3. early experimental studies in humans
   - interaction studies
     - CNS-pharmacodynamics/tolerability
     - biomarker identification
   - human disease models
Early clinical development of meaningful combination therapies:
1- pathophysiological research

- Pathophysiology of RA
  - lymphocyte proliferation
  - prostaglandin synthesis
  - TNF-α production/activity

- Proven additive effects of MTX + TNF-α-blocker in early rheumatoid arthritis

- PREMIER-study
Early clinical development of meaningful combination therapies:
1- pathophysiological research

- Pathophysiology of DM2:
  1. delay carbohydrate absorption
  2. increase insulin secretion
  3. improve insulin action
  4. modulate glucose supply
  5. reduce hepatic glucose production

- Proven improvements of glycaemic control
  - sulfonylurea\(^1\) + thiazolidinedione\(^2\)
  - sulfonylurea\(^1\) + metformin\(^4\)
  - thiazolidinedione\(^2\) + metformin\(^4\)
  - sulfonylurea\(^1\) + thiazolidinedione\(^2\) + metformin\(^4\)

Early clinical development of meaningful combination therapies: 2- preclinical models

- discovery of meaningful target combinations
  - pathway analyses:
    - genomics
    - metabolomics
    - proteomics

- biomarker identification
Early clinical development of meaningful combination therapies: 2- preclinical models

- mathematical disease modeling
- modeling of viral replication

- Lithwin S. Mathematical and statistical models for research. A model of liver recovery from infection. www.fccc.edu/research/reports/current/litwin.html
Early clinical development of meaningful combination therapies: 2- preclinical models

- PK/PD-modeling of drug combinations
  - isobolographic analyses

Early clinical development of meaningful combination therapies: 2- preclinical models

- PK/PD-modeling of drug combinations
  - isobolographic analyses

Early clinical development of meaningful combination therapies:
2- preclinical models

- PK/PD-modeling of drug combinations
  - surface response modeling

- Sebel LE, Richardson JE, Singh SP, Bell SV, Jenkins A. Additive effects of sevoflurane and propofol on gamma-aminobutyric acid receptor function. Anesthesiology 2006;104:1176-83
Strategies for development of meaningful combination therapies

1. pathophysiology
2. preclinical models
   • pathway analyses
   • isobolographic analyses
   • ‘surface-response’-modeling
   • nonlinear mixture amount model
   • ‘physiological response modeling
3. early experimental studies in humans
   • interaction studies
     • biomarkers
     • *ex vivo* interaction studies
     • define/compare CNS-pharmacodynamics/tolerability
   • human disease models
Early clinical development of meaningful combination therapies:
3-pathway analysis and biomarker validation

- muscle biopsies for bioinformatics
Early clinical development of meaningful combination therapies: 3-pathway analysis and biomarker validation

- cerebrospinal fluid analysis

www.altcorp.com/affinitylabeling/proteomics.htm
Early clinical development of meaningful combination therapies:
3- early experimental studies in humans

- Ex vivo interaction on platelet aggregation
  - High-dose paracetamol increases NSAID-induced platelet inhibition

Early clinical development of meaningful combination therapies:
3- early experimental studies in humans

- Whole-Blood T-Lymphocyte Proliferation Assay
  - *ex vivo* synergistic effects of prednisolone-tamoxifen combination

IC\textsubscript{50} isobolographs for cell proliferation

Early clinical development of meaningful combination therapies:
3- early experimental studies in humans

- infra-additive effects of two μ-opioids...
  - self-titrated tramadol and morphine on postoperative pain intensity

Early clinical development of meaningful combination therapies:
3- early experimental studies in humans

...and of morphine with a monoamine reuptake inhibitor
- self-titrated nefopam and morphine on postoperative pain intensity

![ED$_{50}$ isobolograph for adequate pain inhibition](image)

Early clinical development of meaningful combination therapies: 3- early experimental studies in humans

- synergistic effects of propofol and opioid
  - ‘no response to intubation’ or ‘unconsciousness’

Early clinical development of meaningful combination therapies: 3- early experimental studies in humans

- additive effects of propofol and sevoflurane
  - ‘no response to skin incision’

Potential problems with interaction studies and some directions for solutions

• Concentration-dependent interactions
  • additive effects at a certain level, no interactions at some and even antagonism at other levels
  • how to study each potential combination?
  • build preclinical model and validate with few dose combinations using quantitative (population-based) models

• Disparate effects on different disease processes
  • additive effects on certain disease aspects, no effects on some and even exacerbation on others
  • many complex diseases have ranges of signs/symptoms
  • use combinations of meaningful biomarkers (and single-target drugs)

• (Supra)-additive co-medication may reduce safety window
  • analyse parameters of efficacy and safety
  data-intensive studies
Pharmacodynamic interaction studies: partial GABA-agonist behaving as a full agonist in combination with alcohol

Pharmacodynamic interaction studies: more complete anticoagulation?

- coumarin
  - vitamin K antagonist
  - inhibition Factors V, VII, IX, X
- thrombin inhibitor
  - inhibition Factor II
Pharmacodynamic interaction studies: (supra)additive effect of vitK+factorIIa-inhibitor

Pharmacokinetic interaction studies:
QTc-prolongation of cisapride+clarithromycin

Summary and Conclusions

- Polypharmacy is both reality and future of drug development, but is undervalued in early phases.
- ‘Design promiscuous drugs’ vs ‘single-target’ combination therapy.
- Development of rational polytherapy requires:
  - Pathophysiological research!
  - Preclinical interaction/disease modeling
  - Good biomarkers
  - Dedicated integrated development programs
- Several techniques are available in early human studies:
  - Physiological biomarkers (in addition to safety biomarkers)
  - Isobolograph/surface response modeling
  - (Population) PK/PD-modeling
  - Data-intensive/multiple endpoint phase I/IIa-studies