Complexity in clinical pharmacy practice - consequences for research and evaluation

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Translation to humans
Phase 1 / 2 studies

Bench: Basic Science
Bed: Clinical Research

Clinical Practice

Based on Westfall, 2007 (JAMA)
Translation to humans
*Phase 1 / 2 studies*

Translation to patients
*Meta-analyses Guidelines*

Translation to practice
*Dissemination Implementation*

Bench: Basic Science

Bed: Clinical Research

Practice Based Research

Clinical Practice

Based on Westfall, 2007 (JAMA)
Example 1

• Is a Multidisciplinary Multistep Medication Review (3MR) effective to reduce a patient’s Drug Burden Index (DBI)?

• Innovation: targeting medication reviews to high risk patients with a high load of using anticholinergic and sedative medication

$$\text{DBI} = \sum \frac{D}{D+\delta}$$

D: daily dose of the medication
\(\delta\): minimum recommended daily dose

Hilmer, 2009

• RCT in 15 community pharmacies in the Netherlands

Results

• N=157 patients, mean age 76 years, 70% female

Primary outcome: % patients having a decrease in DBI ≥ 0.5

<table>
<thead>
<tr>
<th></th>
<th>Intervention</th>
<th>Control</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>14.7%</td>
<td>15.9%</td>
<td>0.91 [0.38-2.18]</td>
<td>0.8</td>
</tr>
<tr>
<td>(n=157)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Per protocol</td>
<td>15.2%</td>
<td>16.8%</td>
<td>0.88 [0.35-2.24]</td>
<td>0.8</td>
</tr>
<tr>
<td>(n=136)</td>
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</table>
What did we learn from the trial?

- Multidisciplinary multistep medication reviews not effective in reducing the Drug Burden Index (DBI)
- DBI a good tool to identify vulnerable high risk patients
- The future of medication reviews in primary care?
  - Develop target criteria
  - Use a tailored approach
Key elements of the development and evaluation of complex interventions

Craig et al 2008

To reduce the high DBI

• Pharmacists screen for patients with a DBI >2 who have recently a new anticholinergic/sedative medications
• Review the medication to reduce DBI
• Currently piloting feasibility/effects of this approach in 50 community pharmacies
Example 3
Find selection criteria for patients in need of a medication reviews (ESOM study)

• Develop a screening algorithm for patients ≥ 65 years with ≥ 5 chronic medications which can be used in community pharmacies

• Mixed methods
  – Experts to develop algorithm
  – Pilot to test feasibility possible effects of the algorithm in 5 community pharmacies
Preliminary results

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of medication</td>
<td>1</td>
</tr>
<tr>
<td>Number of prescribers</td>
<td>3</td>
</tr>
<tr>
<td>Does not collect own medication</td>
<td>4</td>
</tr>
<tr>
<td>A severe fall in the last 12 months</td>
<td>7</td>
</tr>
</tbody>
</table>

Screening

Low complexity: Pharmacy consultation

High complexity: multidisciplinary approach (pharmacist and physician)

Example 4
Finally, a success story of medication reviews in nursing home residents!

To examine whether multidisciplinary medication reviews

- increase successful discontinuation of inappropriate medication,
- improve prescribing in other respects,
- and improve clinical outcomes in nursing home residents.
Study design

- Cluster randomised controlled trial
- Inclusion criteria:
  - Wards: long stay wards
  - Patients: life expectancy of >4 months
- Inclusion of 426 patients

Intervention:
Multidisciplinary Multistep Medication Review

- Assessing Patient Perspective and Medical Information
- Analysis (electronic decision support and clinical knowledge)
- Meeting of physician & pharmacist: pharmacotherapeutic actions
- Execution & evaluation of pharmacotherapeutic Actions
Primary outcome

% residents ≥1 inappropriate medication(s) successfully discontinued

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Intervention</th>
<th>OR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary analysis</td>
<td>29.5%</td>
<td>39.1%</td>
<td>1.57 [1.03-2.39]</td>
</tr>
<tr>
<td>Secondary analysis</td>
<td>34.6%</td>
<td>44.0%</td>
<td>1.54 [0.99-2.42]</td>
</tr>
</tbody>
</table>

Adjusted for sex, age, marital status, length of stay in nursing home, Charlson's comorbidity index, and dementia diagnosis

Secondary outcomes – no differences between intervention and control groups

Pharmacological outcomes:
- initiation ≥1 under prescribed medications
- dose adjustments
- safer alternatives
- mean Drug Burden Index

Clinical outcomes
- fall incidents
- outpatient clinic visits
- visits elderly care physicians
- paramedic consultations
- cognitive function (SIB-sf, MMSE)
- Neuropsychiatric symptoms (NPI-NH)
- Quality of life (EQ-5D-3L, DQI)
Number successfully discontinued drugs

<table>
<thead>
<tr>
<th>Category</th>
<th>Control</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>A0: Stomatological preparations, drugs for acid related disorders, drugs for functional gastrointestinal disorders, drugs for constipation</td>
<td>15</td>
<td>19</td>
</tr>
<tr>
<td>A1: Drugs used in diabetes, vitamins, mineral supplements</td>
<td>8</td>
<td>14</td>
</tr>
<tr>
<td>B0: Antithrombotic agents antianemic preparations</td>
<td>9</td>
<td>24</td>
</tr>
<tr>
<td>C0: Cardiac therapy, antihypertensives, diuretics, beta blocking agents, calcium channel blockers, agents acting on the renin-angiotensin system</td>
<td>16</td>
<td>19</td>
</tr>
<tr>
<td>C1: Lipid modifying agents</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>G0: sex hormones and modulators of the genital system, urologicals</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>H0: Corticosteroids for systemic use</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>J0: Antibacterials for systemic use</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>L0: Immunosuppressants</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>M0: antiinflammatory and antirheumatic producs, muscle relaxants, drugs for treatment of bone disease, other drugs musculoskeletal treatments</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>N0: Anesthetics, analgesics, antiepileptics, anti-parkinson drugs</td>
<td>24</td>
<td>48</td>
</tr>
<tr>
<td>N0: Anesthetics, analgesics, antiepileptics, anti-parkinson drugs psycholeptics, psychoanaleptics</td>
<td>24</td>
<td>48</td>
</tr>
<tr>
<td>R0: drugs for obstructive airway disease, cough/cold, systemic antihistamines</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>S0: ophthalmologicals</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>V0: Other therapeutic drugs</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>93</td>
<td>162</td>
</tr>
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</table>

The multidisciplinary medication review is effective in discontinuing inappropriate medication in frail nursing home residents without a decline in their wellbeing.

More results of the DimNHR study: Annals of Internal Medicine – published online today!!
Qualitative study alongside the RCT: 35 interviews

Controversies on each others role: having access to the medical history

Pharmacist R: “having the medical history on paper is of utmost importance”

Physician I: “[reading on medical history] will take him hours, ...physician knows this already, we can always explain this drug is for this disease”

Physician Z: “And they should not sit on our chairs in my opinion ... we just expect them to judge whether combinations of medications we prescribe are possible”
### Physician – pharmacist relationship

<table>
<thead>
<tr>
<th>Pharmacist R: “There are different physicians, and different kinds of discussions. For some physicians you notice that they literally adjust the drug prescriptions behind their computer and you see that they follow your advice, whereas other physicians nod a few times and make notes on a bloc note”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physician R: “There has to be a kind of relationship with the physician.”</td>
</tr>
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</table>

### Dissemination/wider implementation

- Dissemination of the toolbox containing materials for the intervention
- Implementation in national guidelines focusing on nursing home residents
Useful resources

- Formal process evaluation – guideline Moore, 2015, BMJ
- Know the guidelines on design/reporting of studies: www.equator-network.org
- Guidelines for systematic reviews on complex interventions published in Journal of Clinical Epidemiology (2017)
- Learn from implementation science for the dissemination phase (Curran, 2017; Shoemaker, 2017; Research in Social and Administrative Pharmacy)

Final remarks

- Most clinical pharmacy services are complex interventions
- Build up your intervention stepwise
- Collect information alongside the trial: process measures/qualitative data
- Consider wider context for implementation/up-scaling of interventions in other settings/countries
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