MAIN FINDINGS

This thesis addresses different stages in the process of developing and evaluating deprescribing interventions. Deprescribing interventions usually are complex, involving various stakeholders, such as doctors, pharmacists, patients and patients’ caregivers. The UK Medical Research Council (MRC) has published guidance regarding best practice for developing and evaluating complex healthcare interventions. [1] Thus, we positioned the chapters of this thesis in the context of the MRC guidance (Figure 1).

In the first part of this thesis, two methods for the identification of potentially inappropriate prescribing of specific medications within defined populations were explored. Using a retrospective cohort study we identified high use of preventive medications at the end of life in older nursing home residents. The study also highlights the use of routinely collected data for the identification of potentially inappropriate prescribing (Chapter 2). The study showed that deprescribing remained limited, with little change in medication prescribing throughout the last year of life. Small increases in the prescribing of symptomatic medications indicated some awareness of changed need, but high prescribing of preventive medications suggested treatment goals were not being revised when life expectancy changed. Using a cross-sectional study design in a national population of community-dwelling older persons, we identified individuals with a high anticholinergic/sedative load (Chapter 3). Our results showed that a large proportion of older community-dwelling patients in the Netherlands had a high anticholinergic/sedative medication load. According to their medication use, four distinct subpopulations with high anticholinergic/sedative loads were identified using latent class analysis. Both studies provide evidence for deprescribing opportunities, and therefore are positioned in the development stage of the MRC development and evaluation process.
While it is best practice to evaluate an intervention before implementing it in practice, sometimes interventions are implemented without first evaluating effectiveness. In this case, the effectiveness of the intervention might need to be evaluated in practice, for example in specific circumstances (defined target populations/specific medications). The deprescribing intervention, pharmacist-led medication review as currently performed in the Netherlands, was evaluated in a randomised controlled trial to examine its effectiveness on deprescribing chronically used anticholinergic/sedative medications in older community-dwelling patients with a high anticholinergic/sedative load. The results of this study showed that while vulnerable older people in need of medication optimisation were targeted, pharmacist-led medication reviews were not effective in deprescribing anticholinergic/sedative medications in this population (Chapter 4 and 5). This study showed the need to go back to the development and feasibility/piloting stage in order to target the intervention to this population. The study also suggests the need for de-implementation of ineffective medication review activities in this population.

Based on the results of Chapter 3, 4 and 5, a new deprescribing intervention was developed and its feasibility, acceptability and potential effectiveness were tested in a prospective study (Chapter 6). This study design was more sophisticated than a feasibility/pilot, but not yet a definite effectiveness evaluation (randomised controlled trial) and is therefore positioned between these two stages in the MRC development and evaluation process. The new deprescribing intervention signalled initiation of a new anticholinergic/sedative medication in older people with an already high anticholinergic/sedative load. The results of the study showed that this intervention was feasible, as a considerable number of patients in need of medication optimisation could be identified. Acceptability of the intervention was high both among pharmacists and patients and time investment was reasonable. Also, the intervention was potentially effective, as in one third of patients an increase in anticholinergic/sedative load was prevented.

**WHAT CAN WE LEARN FROM THIS THESIS?**

This thesis shows a robust approach of developing and evaluating deprescribing interventions, by performing a variety of studies investigating different stages in the process. All studies in this thesis focused on older people at high risk for medication related harm. Within each study, specific subpopulations of older people were targeted, such as nursing home residents at the end of life or community-dwelling older patients. Furthermore, different medication groups were studied (preventive medications, anticholinergic/sedative medications) using different study designs (retrospective, cross-sectional, randomised controlled trial, feasibility/acceptability/potential effectiveness study).

This thesis highlights that pharmacist-led medication review as currently conducted in the Netherlands is not a suitable intervention for deprescribing chronically used anticholinergic/sedative medications among older community-dwelling patients. While effectiveness of pharmacist-led medication review for optimising medication was found in other population groups, such as users of cardiovascular medication [2] and nursing home residents, [3] the lack of effectiveness of pharmacist-led medication review in our
population may be due to a number of factors. Firstly, it may be related to differences in patient populations and risk assessment of their medications, e.g. long term risks for cognitive- and physical decline in anticholinergic/sedative medications, [4, 5] which may be difficult to assess, versus measurable hard outcomes, such as blood pressure, for cardiovascular medication. [6] Secondly, differences in the level of collaboration between the pharmacist and physician. Close collaboration of physicians specialised in aged care with pharmacists in nursing homes, might have been accountable for the positive effects of medication review seen in this setting. [3] Several barriers to deprescribing have been identified, including the collaboration between different health care professionals. [7] Based on our findings we would like to add an important barrier/enabler, which is targeting the deprescribing to the right subpopulation.

Considering these barriers, an innovative deprescribing intervention on anticholinergic/sedative medications was developed targeting newly initiated, instead of chronic, anticholinergic/sedative medications. Evaluation of the intervention showed it was a feasible, acceptable and potentially effective approach to reducing anticholinergic/sedative load in older community-dwelling adults. The intervention targeted specific medications rather than all chronic anticholinergic/sedative medications, it was less time consuming than current medication review processes [8, 9] and the newly initiated anticholinergic/sedative medication and other anticholinergic/sedative medications were highlighted for the pharmacist when selecting a patient. Furthermore, guidance on prescribing of relevant anticholinergic/sedative medications was provided, helping the pharmacist to propose evidence-based recommendations for medication optimisation. While showing promise in terms of effectiveness, this study also suggests some refinements of the intervention, such as electronic integration of the intervention, including most updated evidence-based pharmacotherapeutic advice and a more specific focus on relevant medications. Furthermore, a complete overview of a patient’s medication use and a good collaboration with the patient’s GP is needed. [10]

While for anticholinergic/sedative medications we developed and evaluated interventions, it was outside the scope of this thesis to perform this for preventive medications used at the end of life in older nursing home residents. Our study showed prescribing of preventive medication in this population is high, suggesting the potential need for deprescribing. Since the initiation of our study in 2013, several studies have been performed in this area, including an exploration of patients’, relatives’, nurses’ and physicians’ perspective on medication management at the end of life [11] and identification of barriers of physicians to de-prescribe medications at the end of life. [12] An efficacy study on the use of antipsychotics for delirium in palliative care [13] indicates the growing awareness of the need for evidence-base prescribing in individuals at the end of life. A first pragmatic trial showed positive effects of deprescribing statins at the end of life. [14] Suggestions were even made for best choices on study designs for the evaluation of deprescribing in an older population with limited life expectancy. [15] As highlighted already, multidisciplinary medication reviews have been found to be effective to discontinue inappropriate medication in nursing home residents. [3] This body of research is a good basis to develop specific interventions optimising medication use at the end of life in older people, following the MRC development and evaluation process.

**IMPLICATIONS FOR PRACTICE AND FURTHER RESEARCH**

Our studies support the concept of the development and evaluation process of complex healthcare interventions following best practice guidance. [1] Good evidence on real world practice is required before implementing an intervention and scaling up. [16] Interventions that are implemented without evidence-based development and extensive evaluation can lead to ineffective
Deprescribing in older people

General discussion

The MRC framework provides useful guidance in the process of development and evaluation of interventions, but based on this thesis we would suggest an amendment to this process. The MRC process does not include the step from implementation back to evaluation, while this thesis shows that sometimes this step may be needed. Thus we propose the red arrow in Figure 1. If an already implemented intervention is to be used for different medications or population groups, it should be re-evaluated and if not effective, the intervention should not be used for this population. This may lead to de-implementation of the intervention.

Despite the extensive work in this thesis, a number of questions remain. Our study about preventive medication at the end of life raises the question about the timing of deprescribing. At which point do risks outweigh the benefits and when is a patient at his/her end of life? Our study on medication reviews leaves the question which patient population may benefit from medication reviews. What is the best way to identify this patient group? Algorithms seem to be an efficient way to identify target populations for an intervention. Furthermore, how do we know a patient is benefiting from deprescribing? Robust meta-analyses have not been able to show significant effects of medication review on hard outcomes, such as hospitalisation and mortality. Outcome reporting of studies evaluating medication review is heterogeneous. A core set of relevant patient outcomes, like geriatric outcomes (e.g. fall risk, frailty and cognitive function) and adverse events (e.g. side effects, drug-related hospital admission) should be evaluated in real world randomised controlled trials.

Furthermore, cost-effectiveness evaluations should be performed to advise policy makers about potential implementation of interventions. Interprofessional collaboration of healthcare providers, such as pharmacists and general practitioners, but also medical specialists should be improved, as poorly developed interprofessional relationships are an important barrier in the deprescribing process. Improving pharmacists’ communication skills might improve the interprofessional collaboration.

More specific guidelines are needed to help healthcare professionals in the deprescribing process. The underlying pharmacotherapeutic evidence remains weak, although some work has been done, e.g. the study about efficacy of antipsychotics for delirium in palliative care, described above. Deprescribing interventions should be patient-centred and recommendations for deprescribing should be based on shared decision-making with the patient.

More work is needed to understand the patient perspective in this process. This may include helping patients understand the benefits of deprescribing medication and taking away their fears for adverse effects of deprescribing.

CONCLUSIONS

Opportunities for deprescribing exist in older populations, such as the high prescribing of preventive medications at the end of life in older nursing home residents and anticholinergic/sedative medications in older community-dwelling adults. To reduce a high anticholinergic/sedative load in community-dwelling older adults, medication reviews, as currently performed in the Netherlands, are not effective. An innovative deprescribing intervention using information technology to target newly prescribed anticholinergic/sedative medication in this population seems more successful. Future deprescribing strategies should be patient-centred, targeted to the right populations and medications, tailored to patient’s needs, and should have a high degree of interprofessional collaboration.
REFERENCES