Scoping on anti-dementia drugs

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1 Second draft of the PICO-question

Population: Patients with Alzheimer's disease of intermediate severity (mini-mental score: 10-19 (inclusive))

Intervention: Medical combination therapy (cholinesterase inhibitor and memantine)

Comparator 1: cholinesterase inhibitor (the same as for the intervention)

Comparator 2: memantine

Outcomes (clinical):

1. Delay in nursing home placement (critical)
2. Cognition (critical), questionnaires considered:
   I. ADAS-Cog,
   II. Mini-Mental Score,
   III. then either Severe Impairment Battery, Revised Wechsler Memory Scale, Fuld Object-Memory Test, Benton Visual Retention Test, Trail Making Test, Alzheimer's disease Cooperative Study-Clinical Global Impression of Change, Ten-Point Clock Drawing Test, Mental Function Impairment
3. Activities of daily living (critical), questionnaires considered:
   I. Any of the following: Progressive Deterioration Scale, Alzheimer's Disease Cooperative Study activities of daily living inventory, Caregiver Activity Survey, Nurses' Observation Scale for Geriatric Patients, Functional Independence Measure (FIM)
4. Global impression (critical), questionnaires considered:
   I. Any of the following: Clinician's Interview-Based Impression of Change, Clinical Global Impression of Change, (Global Deterioration Scale (GDS), assesses changes of stage and is hence is less sensitive))
5. Behaviour (critical), questionnaires considered:
   I. Neuropsychiatric Instrument,
   II. Behavioural Pathology in Alzheimer's disease,
   III. Cohen-Mansfield Agitation Inventory (CMAI))
6. Withdrawal (important)
7. Side effects (important)
8. Care Giver Burden or distress (important), questionnaires considered:
   I. Any of the following: Neuropsychiatric Inventory of Caregiver Distress Scale (NPI-D), Resource Utilization in Dementia (RUD), Disability for Dementia (DAD))

9. General quality of life (important), questionnaires considered:
    I. SF-36
    II. Euroqol

Will not be assessed as part of the systematic review:

10. Depression (not so important)
11. Survival (not so important)

Assessed for two time points: Follow-up of ≤ 6 months and ≥ 1 year

Outcomes (cost-effectiveness):

1. Delay in nursing home placement
2. Quality adjusted life years (QALY)
3. Direct costs (including inpatient, outpatient, and treatment costs)
4. Indirect costs (in particular costs related to productivity loss)
5. Incremental cost-effectiveness ratio (cost per quality-adjusted life year gained)

Details regarding the inclusion criteria for the:

Population: In the included studies Alzheimer's disease should have been diagnosed based on pre-defined criteria (DMS-III, DSM-IIIR, DSM-IV, DSM-V, ICD-10, AA-NiA, NINCDS-ARDA).

Intervention/Comparator: Cholinesterase inhibitors are being dosed as high as possible with regard to side effects (mostly gastro-intestinal like nausea and vomiting and diarrhoea). The dosages for intervention and comparator should be comparable.

Outcomes (clinical):

The tools to measure the relevant outcomes have been listed without ranking if no specific preferences could be established. If different tools are used to measure the same outcome in one study then the tool most frequently used in the included studies will be used. For some outcomes certain tools were judged to be more suitable than others: in this case the tools were numbered with higher numbers corresponding to a decreasing preference.

3 Reasons for the Scope

Dementia corresponds to a serious neurocognitive disorder that manifests itself with a marked decline of cognitive function compared to an earlier level in one or more domains (disturbance in attention, executive functions, learning and memory, speech, perceptual-motor ability and social cognition)[1,2] The limitations are great enough to limit independence.[1]

The WHO considers dementia as a priority in public health.[3] Alzheimer's disease plays a large role in Switzerland. It has been estimated that about 110'000 people living in Switzerland in 2011 suffered from dementia. According to forecasts of the Swiss Federal Office of Public Health (SFOPH) 300'000 affected patients are expected for 2060.[4] Alzheimer's disease – either on its own or in combination with other diseases – is one of the most frequent causes for dementia. Cholinesterase inhibitors are being given for mild to moderate dementia (mini-mental score of a max. 30 to 10), while memantine is being given for moderate to severe dementia. In theory both substances can be given in dementia of intermediate severity (mini-mental score 19-10) but in contrast to the practice in most other European countries the Swiss mandatory basic health insurance only covers either cholinesterase inhibitors or memantine but not the combination therapy. In clinical practice both substances are being given in combination most of the time with the more expensive drug being reimbursed by the insurance and the cheaper one being paid by the patient. The rationale is that the clinicians believe that the combination therapy is well tolerated, that cholinesterase inhibitors may even have less side-effects in combination with memantine than given alone and that it improves the symptoms and delays nursing home placement. An application to the SFOPH for coverage of the combination therapy was rejected a few years ago though.

In the US both substances are being prescribed and covered. Recently the FDA has approved Namzaric® a fixed combination of memantine and donezepil for the treatment of Alzheimer's disease. But for Switzerland no date for the introduction on the market is known. In Switzerland the patents for memantine, donepezil and galantamine have expired and for rivastigmine it will expire soon. The costs of treatment are being estimated to lie between 3(-4) CHF per day for memantine and about 2 CHF per day for cholinesterase inhibitors.

4 Systematic review on effectiveness

Several systematic reviews on the treatment of Alzheimer's disease with memantine, cholinesterase inhibitors or their combination have been published recently.[5-14]

The review of Matsunaga et al. from 2015 (literature search till October 2014) included 7 RCTs on combination therapy in Alzheimer's disease.[11] In the meta-analysis by Atri et al. the cumulative benefit of the combination therapy of memantine and donepezil (a cholinesterase inhibitor) in intermediate and severe Alzheimer's disease was assessed based on the pooled area under the curve of 4 studies.[5] The authors of both reviews drew the conclusion that combination therapy is helpful in intermediate to severe Alzheimer's disease. The review of reviews by Buckley et al. from 2015 investigated anti-dementia drugs in general and included both randomised controlled trials as well as observational studies respectively systematic reviews of such studies if available. The included evidence syntheses didn't show a statistically significant improvement of cognitive function for the combination of memantine and cholinesterase inhibitors. This assessment is based though on an evidence synthesis by NICE from 2011. Buckley et al. were also critical regarding the use of cholinesterase inhibitors and came to the conclusion that they could be harmful in frail, elderly

patients due to their clinically significant side effects.[8] In the context of a systematic review for the SMB the evidence will be re-assessed based on RCTs and evaluated against the background of existing reviews. As the data are up-to-date the systematic review is unlikely to identify new evidence.

5 Cost-effectiveness analysis

5.1 Description and rationale

As a part of the scoping process we have performed a first unsystematic literature search to identify available economic evaluation studies with regards to the above-defined PICO question. There were few international studies available measuring cost per QALY regarding the combination of memantine and cholinesterase inhibitors compared to monotherapy (memantine or cholinesterase inhibitors). For instance, a recent study by Thibault et al.[15] showed that adding memantine to cholinesterase inhibitors was cost-effective compared to cholinesterase inhibitors alone. Another study from US by Weycker et al.[16] showed that in patients with moderate to severe Alzheimer disease already treated with donepezil, the addition of memantine resulted in improved clinical outcomes and reduced total costs. Similarly, the study by Touchon et al.[17] based on a French cost-effectiveness analysis showed that the combination of memantine and cholinesterase inhibitors was cost saving compared with cholinesterase inhibitors alone. This was mainly due to lower costs and increased quality-adjusted life years (QALYs) from the societal and healthcare perspective.

In Switzerland a study by Pfeil et al.[18] examined the budget impact and cost-effectiveness (cost per QALY gained) of combination therapy (cholinesterase inhibitors and memantine) compared to monotherapy (weighted average of cholinesterase inhibitors and memantine as observed in a large health insurance claims database) from the perspective of the Swiss health system. This study showed that combination therapy was cost saving compared to monotherapy.[18]

Available national and international health economic literature has been pre-checked for content and relevance. Based on this information we propose to: a) update the published Swiss cost-effectiveness article by Pfeil et al.[18], with current (off-patent) prices of interventions, and the newest available data on disease costs, b) undertake a systematic review of the economic literature to understand the impact of combination therapy compared to monotherapy, c) compare a) and b), and d) undertake a budget impact analysis from the perspective of the Swiss health system.

5.2 Update of the current Swiss cost-effectiveness model

The aim is to update the published Swiss cost-effectiveness model by Pfeil et al.[18], with the newest (off-patent) prices of interventions, and the newest available data on cost of disease. This will enable us to understand the current situation on the cost-effectiveness of combination therapy compared to monotherapy in Alzheimer's disease patients, and whether there has been a change in the evidence base between 2011 and 2015, from the perspective of the Swiss healthcare system.

5.3 Systematic review of the health economic evaluations

5.3.1 Search strategy

The aim of the literature search will be to identify international literature on the costs and cost-effectiveness of combined therapy of cholinesterase inhibitors and memantine compared with monotherapy (cholinesterase inhibitors or memantine) for patients with Alzheimer disease. The quality of the identified economic studies will be critically assessed. As one tool, the "Consolidated health economic evaluation reporting standards" (CHEERS) checklist will be used. Transferability of international results to Switzerland and validation of the results will be critically assessed. Data on the Swiss cost-effectiveness model[18] together with relevant international cost-effectiveness studies will be extracted. Given that there is only one study from Switzerland that we are aware of, the review of the cost-effectiveness studies will mainly be based on the international literature. Based on what we will extract from the literature in terms of costs and cost per QALY, an adaptation to the Swiss health system setting will take place. In order to perform the adaptation we will take into account aspects such as purchasing power parity and health care expenses per capita. The Swiss cost-effectiveness model by Pfeil et al. will be compared with the international literature. In addition, difficulty of quality of life measurement in patients with dementia will be considered/discussed.

5.4 Budget impact analyses

The expenditure of combination therapy versus monotherapy with regards to Alzheimer disease and its impact on the Swiss healthcare system will be investigated. Swiss epidemiological data concerning disease prevalence will be combined with the estimated cost difference between the intervention and comparator strategies to derive the yearly budget impact. The article by Pfeil et al.[18] will be used as a reference point for budget impact analyses.

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