The SENATOR project: developing and trialling a novel software engine to optimise medications and non-pharmacological therapy in older people with multimorbidity and polypharmacy

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Abstract

Optimisation of drug and non-drug therapy in older people with multiple co-morbidities is a frequently encountered and highly challenging problem in most fields of medicine. The relative undersupply of clinicians with special interest and expertise in this area means most clinicians may need better guidance or tools to aid management. However, the utility of guidelines and existing tools is limited by the complexity and heterogeneity of this patient population. The SENATOR consortium ambitiously set out to develop and test a novel software engine that would give non-expert clinicians bespoke recommendations on evidence-based pharmacological and non-pharmacological therapy, based on each patient's unique characteristics. The SENATOR software incorporates validated tools, such as the START/STOPP criteria, but is also developing new tools such as the Optimisation of Non-drug Therapy in Older People (ONTOP) for its inclusion. Here, we briefly describe the aims, first steps, challenges and progress so far in the development and testing of the SENATOR software.

Introduction

Older people have the highest prevalence rates of polypharmacy, inappropriate prescribing and adverse drug reactions (ADRs) with associated high levels of morbidity [Permpongkosol 2011; Scott & Jayathissa 2010]. Studies from several European countries consistently show about 6% of all hospital admissions in adults can be directly attributed to ADRs [Pirmohamed 2004; Franceschi et al 2008; Hamilton et al 2011]. Another large study in the Netherlands calculated that €94M (0.5%) of the country's total hospital budget was spent on medication-related admissions [Leendertse et al 2011]. The cost for the UK was estimated around €706M in 2004 [Pirmohamed et al] and €434M in Germany in 2006 [Rottenkolber et al 2011]. There is wide agreement that the best strategy to prevent ADR-related morbidity is to focus on high-risk groups such as older people with polypharmacy [Leendertse et al 2011; Dequito et al 2011]. Demand for geriatricians and other specialists in this field far outweigh supply, so the prospect of easy-to-use software to guide clinicians has tremendous potential to improve patient care. However, a major challenge is that any software solutions would need to safely handle the complexity that characterises this patient group. A recent review concluded that there are no validated, reliable, widely-used prevention strategies in older people [Petrovic et al 2012]. Although there are a number of well known existing tools such as the STOPP-START criteria [O'Mahony et al 2015] and Beers criteria [AGS Beers Criteria Update Expert Panel, 2015], they are usually limited to use in research and are not easily applied in routine clinical practice due to the volume of information and multiple rules that apply [Caslake et al 2013]. Some interventions provide a structured format for the review of prescribed medication, but either rely on the clinician's considerable specialist clinical pharmacology knowledge in older people or involve applying one of the above tools (e.g. the systematic tool to reduce inappropriate prescribing (STRIP)) [Keijsers et al 2015]. A number of Computerised Provider Order Entry (CPOE) systems are in use for electronic prescribing, but none are specially designed for older people and, though partly effective, they rely mostly on warning clinicians only about drug-drug interactions [Schiff et al 2015]. Moreover, another potentially important strategy to avoid ADRs involves maximising use of

evidence-based non-pharmacological therapies but none of the above tools address this. Therefore, there was a clear need to develop and validate a new and more sophisticated tool that could address this important gap. Here, we describe the efforts made to date by our group to develop and test a new software engine for the optimisation of medical and non-drug therapy in older people with multi-morbidity and polypharmacy (SENATOR).

Establishing the SENATOR consortium

The SENATOR consortium is an international collaboration funded under the European Union FP7 programme (www.senator-project.eu). This followed a call for investigator-driven projects to address management of elderly individuals with multiple diseases. It is led by Prof Denis O'Mahony in University College Cork and includes collaborators from 12 European organisations with a wide range of expertise including geriatric medicine, clinical pharmacology, software design and project management.

SENATOR software

The SENATOR software incorporates a number of individually validated tools to provide clinicians with evidence-based recommendations. Key components include the START-STOPP2 criteria [O'Mahony et al 2015] and databases of licensed indications for medications and drug-drug interactions (from the British National Formulary and a licensed CPOE product called SafeScript). The risk of death in the next year is calculated using CIRS-G (Cumulative Illness Rating Scale for Geriatrics) [Miller et al 1992]. Another novel component is a tool that predicts the risk of an ADR, since this may influence the extent of de-prescribing. Since the best current tools, such as GerontoNet [Onder et al 2010], have only moderate ability to predict ADRs in older people [Petrovic et al 2012], the study team plan to create, test and validate its own bespoke tool from the extensive

clinical data that was being collected for the study. This will only be incorporated into the final product if it is superior to GerontoNet when validated. Provided the software is given enough information on the patient's medical history and usual medications, it can make recommendations on inappropriate prescribing. This includes addressing under-prescribing of evidence-based treatments and recommendations for medication withdrawal to combat polypharmacy. To help keep prescribing costs down, SENATOR has information on drug availability, pricing and policies for each participating centre, and can make recommendations on the most cost effective option. The latter involved a significant amount of original development work as this information is not easily available. The SENATOR software's output is in the form of easy to follow bullet-point recommendations. They will still require clinicians to make their own, final judgment in conjunction with the patient themselves, as there are a number of factors that the software cannot easily take into account. In particular, there is no way of taking into account patient preference, or the result of any previous attempts at medical optimisation.

Non-drug therapies

One of the most exciting and innovative aspects of the SENATOR project is the development of individually tailored advice on appropriate non-pharmacological therapies. This aspect has required considerable original research and development as there are no existing compendia of non-pharmacological therapies, along with their evidence-based indications. This is in stark contrast to pharmacological therapies, where regularly updated tomes, such as the British National Formulary, provide clinicians with all the information they need for safe prescribing in an easily accessible format. It is therefore perhaps unsurprising that non-drug therapies are currently under-utilised [Chen et al, 2014; Naci and Ionnadis, 2013].

The SENATOR project developed a bespoke methodology to gather the best available evidence called ONTOP (Optimal Non-drug Therapy for Older Persons) [for a detailed description see Abraha et al 2015]. Initially, common geriatric conditions that may respond to non-drug therapy were selected for inclusion by panel discussion involving all the principal SENATOR investigators (authors). For each one, an international panel of 13 experts were asked to list and rate the clinical importance of all available outcome measures with the aim of identifying critically important outcome measures using a Delphi technique. For example, for the management of pressure ulcers, rates of complete wound healing was rated as a critically important outcome measure, whereas length of hospital stay was not. The next stage involved a 'systematic review of systematic reviews' of each condition, without specifying any individual interventions. This was important to avoid missing any little-known interventions. Reports were included if they assessed any non-drug therapy using systematic review methodology. From included reviews, all relevant primary studies were identified for inclusion in the final analysis. Usual inclusion criteria included: mean study population age over 65 years, randomised controlled trial design and outcomes measures that included at least one rated as critically important by the Delphi panel. This allowed the team to generate specific questions using PICO (Population, Intervention, Comparator, Outcomes) methodology to evaluate the evidence-base of each intervention for each condition, and in specific patient groups. Meta-analyses were used where appropriate. Finally, results of each meta-analysis and systematic review are evaluated for quality using the GRADE methodology [Guyatt et al, 2011]. Bullet-form recommendations for inclusion in the SENATOR software are written where there is at least moderate evidence of effect. These recommendations can potentially be individualised for patients by the software (e.g. a recommendation for group exercise therapy may only be triggered where incontinence is listed as a problem, and the patient is female).

The initial SENATOR trial includes a 'proof of concept' study testing the feasibility of making computer-generated recommendations on non-pharmacological therapy. Initially, the trial will evaluate whether clinical teams follow advice on the prevention of delirium using non-drug

techniques. The final SENATOR software will include recommendations on the non-drug treatment and/or prevention of ten common geriatric conditions and some of the ONTOP reviews are already available (see Table 1) [Abraha et al, 2015; Abraha et al, 2016; Lozano-Montoya et al 2016; Vélez-Díaz-Pallarés et al 2015; Vélez-Díaz-Pallarés et al 2016, Rimland et al 2016].

Pan-European tool

One of the remits of the project was that any tool that was developed would be suitable for use throughout Europe. This represents a major challenge, as healthcare systems, therapy availability and practices vary widely. Moreover, there are significant language barriers. A major work package was devised to translate and reverse-translate all the SENATOR user interfaces and recommendations from English to Spanish, French, Italian and Icelandic to cover the native language of all the countries that would test the software in a clinical trial.

Testing the software

One of the major goals of SENATOR is to reduce ADR, so the rate of ADR was the obvious primary outcome for a randomised controlled trial. Although SENATOR is designed to be used in any setting, a decision was made to test it in the hospitalised setting first as this allowed more pragmatic recruitment of large numbers of volunteers at high risk of ADR within a short time period. Trials of interventions to reduce ADR pose several challenges. It is impossible to achieve effective and safe blinding of clinicians and patients. There is a risk of contamination of the control group due to clinicians learning from the intervention. Although these risks can be mitigated with a cluster-randomised design, the latter also poses many challenges. The underlying risk of ADR in different ward areas varies widely, so many different clusters would be needed to avoid an inherent bias in one arm just by chance. Moreover, out of hours cross-cover arrangements and the high workplace

mobility of trainee medical staff between control and intervention units would mean the risk of contamination across clusters remained. Additionally, the danger of ascertainment bias is high as ADRs in older people can easily be missed or dismissed.

In an attempt to overcome many of these inherent difficulties, the SENATOR trial was divided into two distinct trial periods. The first was an observational study across hospitals in six different countries. This allowed verification of recruitment rate and baseline ADR rate across each country and within each region in different types of wards. It also allowed the development and testing of the SENATOR software interface, a tool to predict ADR and the feasibility of data collection for all the SENATOR components ahead of the trial in Period 2. The randomised controlled trial (Period 2) will start in 2016 and will be an unblinded controlled trial with randomisation at the level of the patient. Important secondary outcome measures include quality of life, length of stay in hospital, mortality, and healthcare utilisation costs both during the admission and at 3 months follow-up.

Dissemination

The trial protocol is publicly available (https://clinicaltrials.gov/ct2/show/NCT02097654) and all major findings will be presented widely at international conferences and published in major scientific journals. Results of the main trial should become available late in 2018. If successful, SENATOR will be an extremely useful adjunct to any clinician working with older people.

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Table 1: Planned list of conditions that the SENATOR software will advise on Optimal Non-drug Therapy for Older People (ONTOP)

Condition
Delirium
Dementia
Falls
Heart failure
Immobility
Orthostatic hypotension
Pressure sores
Stroke
Undernutrition
Urinary incontinence