Medication review in older adults: Importance of time to benefit

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In older patients, clinical pharmacy (CP) interventions have been shown to improve outcome during and after hospital stay.¹⁻⁴ A CP program was subsequently installed at the 80-bed geriatric wards of the University Hospitals of Leuven, a large teaching hospital in Belgium. Owing to physician support and own research results, definitive

funding was eventually granted in 2018 by the hospital board.⁵⁻⁸

In these older adults, a holistic approach regarding medication reviews is applied by the CP team.⁹ This approach entails evaluating the benefits of drug therapies while assessing patient preferences and treatment goals, including quality-of-life. Importantly, the time to benefit (TTB) of drug therapies is also determined and compared with life expectancy.^{10,11} TTB can be defined as the time point at which patients are expected to derive a benefit from a treatment. If life expectancy is expected to be shorter than TTB, the individual is unlikely to benefit from that therapy.^{9,12}

Published data on the application of TTB are scarce. Therefore, we provide here a step-based approach to support the use of TTB as part of a medication review.

Step 1: Patient selection. TTB should be determined for each prescribed drug in all patients receiving a comprehensive geriatric assessment (CGA).¹³ These assessments will mostly concern very old inpatients with complex medical concerns. By extension, TTB should be estimated, perhaps annually, in all patients systematically receiving a medication review.

TTB should also be estimated in patients with an increased pretest probability of a reduced life expectancy. Such patients might include those in whom the health care professional (HCP) suspects that life expectancy is limited due to the presence of specific conditions. For example, a late diagnosis of small-cell lung carcinoma, end-stage heart failure (HF), conservatively treated ST-elevation myocardial infarction, or severe aortic stenosis (without surgery); these diagnoses are correlated with mortality rates up to 50% within 1 year.¹⁴⁻¹⁸

Step 2: Estimating life expectancy. Beside ascertaining the presence of life-limiting conditions, the following actions can be taken to estimate the life expectancy for individual patients.^{12,14}

First, we suggest consulting regional or national life tables to acquire a notion of local estimates. For example, an 85-year-old Belgian man had a median survival of 5.7 years in 2016.¹⁹ As Lee et al.¹² have indicated in their seminal paper, U.S. data can easily be consulted online in actuarial life tables provided by the U.S. Social Security Administration. Most people admitted to acute geriatric wards will have a shorter lifespan than the median survival for age- and sex-matched persons in the region. Estimates for older inpatients might be estimated by using the quartile estimates, if available.

Second, validated risk scores, such as those available on ePrognosis.com, can be applied.¹² Several prognostic indices have been developed, of which the one by Walter et al.²⁰ is most applicable to older inpatients. Those authors derived a predictive model by using a training sample of 1,495 older inpatients. Subsequently, the model was validated using 2 samples (with 1,427 and 840 patients) also consisting of older inpatients.^{20,21} The index of Walter et al. has been shown to have good predictive ability for 1-year mortality after hospital stay, with a C-statistic of 0.79.²⁰

Third, there is some evidence concerning the “surprise question.”^{9,14,22} This involves asking whether the HCP would be surprised if the patient under consideration died within a year. A negative answer has a reasonable predictive value, and although the answer depends on the clinical setting and the experience and training of the HCP, it is better than relying solely on guessing. In a meta-analysis by White et al.,²³ which was based on a sample of 24 investigations, the pooled accuracy of a negative response to the surprise question was 74.8% (95% confidence interval [CI], 68.6–80.5%), although a high degree of heterogeneity was noted.

Step 3: Estimating TTB. There are several options for estimating TTB. A distinction can be made between therapeutic (including symptomatic) and preventive therapies. Therapeutic treatments will reach a measurable effect within a limited time horizon (hours to days or weeks). This concerns therapies such as anticoagulants for symptomatic pulmonary embolism, carbamazepine for trigeminal neuralgia, or opioids for refractory or severe pain. Importantly, a prompt effect does not obviate the need for evaluating the treatment's appropriateness. Although hypnotic drugs might rapidly reduce insomnia, they should not be used as first-line therapy because of the net clinical harm associated with their use.²⁴

Conversely, the effect of a preventive therapy will usually not be realized quickly. Most preventive therapies need an extended time to exert a measurable clinical benefit, while at the same time exposing patients to immediate risks, such as adverse reactions, costs, and inconvenience.¹² The clinical relevance of preventive benefits should be discussed between the HCP and patient.¹⁰ Patient preferences should actively be elicited in such discussions, as recommended in guidelines of the American Society of Geriatrics on caring for older adults with multiple morbidities.²⁵

Because of the statistical uncertainty inherent to the different approaches described below, clinicians should refrain from overinterpreting post hoc observations. Most randomized clinical trials are not designed or powered to show an effect at intermediate time points; this is especially true for the subset of older adults. Importantly, performing multiple tests on the same dataset increases the chance of finding false positive result.^{26,27} Hence, the TTB data described below should be considered as approximations that should be used prudently.

Study duration. The first, and also the easiest, option is to evaluate study duration or the follow-up time. The total study duration can be regarded as the longest possible TTB in a positive trial, while the median or mean follow-up

duration is the de facto TTB for the average study participant.¹² Both are conservative approximations and will probably overestimate the actual TTB, which will most likely be reached before the end of follow-up for trial participants in a positive trial. In the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) study, enalapril was shown to be an effective treatment to reduce all-cause mortality in severe systolic HF.²⁸ The average study follow-up was 188 days, and the primary endpoint was ascertained at 6 months, both of which support the drug's use in very old adults with a limited life expectancy.

In this regard, TTB and number needed to treat (NNT) are related probabilistic metrics, since NNT is normally interpreted in terms of the median follow-up time. NNT can be calculated manually as the reciprocal of the absolute risk reduction.²⁹ In CONSENSUS, 5.7 patients (95% CI, 3.4–16.3) had to be treated with enalapril, compared with placebo, to observe 1 fewer death within 6 months.^{28,29} TTB and NNT should both be interpreted with caution, as the majority of clinical practice guidelines provide recommendations that are based on randomized clinical trials that are seldom applicable to very old adults.³⁰ Investigations have generally excluded older adults with complex medical problems.³¹

Primary outcomes that are assessed at intermediate time points in landmark analyses of RCTs can also be of interest. For example, in a post hoc analysis of PARADIGM HF, valsartan-sacubitril was significantly associated with fewer 30-day all-cause admissions than enalapril (odds ratio [OR], 0.74; 95% CI, 0.56–0.97).³²

Kaplan-Meier plots. In trials using survival analysis for assessing the primary outcome of time to event, Kaplan-Meier (KM) plots can be used to visually assess the point of divergence. That point might indicate the time at which the intervention improved outcomes compared with the control treatment. KM plots are informative and useful for evaluating differences over the total study duration.³³

In the CONSENSUS study with enalapril in severe HF, a rapid divergence can be observed.²⁸ However, this observation is visual only and does not allow for interpreting the size of the effect or its statistical significance. Inferring significant differences is normally done by using the nonparametric log rank test or semiparametric Cox proportional hazard regression analysis.³³ Both of these tests use the entirety of the trial data and contrast with visual assessment of the KM plot, which carries an inherent risk of false positives.^{26,27,33} It is furthermore relevant to acknowledge that data become less reliable toward the tail end of the KM plot.³³

Visual assessment of divergence in KM plots might seem attractive, but from a statistical viewpoint, caution is needed in applying that assessment in determining TTB.³⁴

Complex appraisals of TTB. Three advanced approaches are discussed below to provide an overview of the currently available options. They all concern defining a time point at which a predefined threshold is exceeded.

First, statistical process control—a graphical method to determine TTB—can be applied. This involves plotting an outcome variable (eg absolute risk reduction) as a function of time. Then a baseline curve, including a CI, is defined; this marks a time period during which the trial is “in control.” The time point at which the numerical outcome consistently exceeds the upper limit of the 99.7% CI is considered to be the TTB.³⁵ This approach has been used by Van de Glind et al.³⁶ to assess TTB for alendronate in postmenopausal women with osteoporosis.

Second, Braithwaite et al.^{37,38} developed a method in which cumulative benefits and harms for a certain intervention are estimated over multiple time points and plotted in a bar chart. The “payoff time” is the point at which the benefits first exceed the harm. To the best of our knowledge, this methodology is the only one that explicitly considers the harm of an intervention.

Third, Lee et al.³⁹ and afterwards Tang et al.⁴⁰ determined a pooled TTB by applying a complex parametric

meta-analytic approach previously described by Ouwens et al.⁴¹

These approaches, although informative, are not readily useable in clinical practice and assume an advanced understanding of statistics. They furthermore suppose the availability of data on multiple time points to reliably infer duration, which is not always the case. These data can, however, be retrieved manually by using specific software, as proposed by Messori et al.⁴²

We expect that the demand for these approaches will only increase, given the overall ageing of the population.⁴³ The single most preferable approach however would still be that TTB becomes a standard part of statistical reporting of controlled investigations, which furthermore should be enriched by including substantial subsets of older adults.¹²

Step 4: Medication review. Our CP team has incorporated steps 2 and 3 into the medication review process, which is provided as part of the CGA (step 1). Currently, a full-time equivalent hospital pharmacist provides medication reviews for geriatric inpatients prior to discharge.

First, an up-to-date medication list is compiled upon admission. Previous drug-related problems and patient preferences are also assessed. This is mostly performed in collaboration with nurses and prescribers. Patient preferences are predominantly elicited as part of the CGA.

Second, a medication review is performed by the multidisciplinary care team, in which TTB and life expectancy are important decision modifiers, as are therapy appropriateness and the size of the expected benefits and harms.^{14,44,45} This process is standardized by applying an internally developed tool, which includes all of these criteria and is based on a validated screening tool for inappropriate drug therapies in older adults.⁵ The actual review takes, on average, 30 minutes per patient.

Third, a consensus concerning a pharmaceutical care plan is reached by the care team as part of the CGA. All therapy changes, including the reasons for changes, are then documented and adopted into the discharge letter.

Fourth, a patient-friendly medication list is provided upon discharge, with additional copies for the community pharmacist, the primary care provider, and nursing home.

Importantly, the CP team can provide this service because of the presence of a multidisciplinary care team, which allows pharmacists to focus on the actual medication review.

Conclusion

Providing a therapy without a timely benefit can expose patients to harm. TTB and life expectancy should systematically be ascertained in older adults when developing a pharmaceutical care plan.

Disclosures

The authors have declared no potential conflicts of interest.

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