



Pharmacotherapy in Older Adults: An Approach towards Individualised Therapeutic Care Concepts

Drug therapy plays a major role in healing or managing acute and chronic diseases to re-establish the health and wellbeing of individuals in our society. This has led to a significant increase in life expectancy over the past century, a fact acknowledged by the European Commission's declaration of the "European year for active ageing and solidarity between generations 2012".

While we all enjoy our expanding lifespan, it has challenging consequences for our healthcare system and the pharmaceutical industry. The key questions will be around how to best design and deliver pharmacotherapy to maintain the health and independence of older adults as long as possible, given our increasingly limited healthcare resources. This article will take a closer look to the future of drug therapy in older adults.

Pharmacotherapy in the Year 2025

Discovering and developing new drug products is a lengthy process that takes an average of 10 to 15 years. This basically means that the products coming out of our discovery pipelines today will not reach the market before 2020. Drug therapy is not only directed towards a specific clinical target of a disease condition, but also towards an individual patient who is suffering from this disease condition, alone or in conjunction with other diseases, and has a set of personal factors in which the drug should exhibit its benefit. While the clinical targets are quite homogeneous within the potential drug responder group, the individual patient is quite the opposite. This is specifically true for the people beyond 65 years of age who differ significantly from each other, and have been described as the most vulnerable patient population.

Within the up-coming four decades, the demographic situation of our society will change considerably due to the aging post-war baby boomer generation, followed by the contraceptive-related drop in birthrates in the late 1960s. This is creating a society in which one-quarter of the

population is 65 years or older, and a significant increase in the number of the people older than 80 years of age. For developed countries, it is expected that in 2050, 343 million of their 1.4 billion people will be over 65 years old, 86 million of whom will be between 80 and 89 years old and 38 million of whom will be over 90 [Stegemann et al. 2010]. With 30-50% of all prescription drugs used by people over 65 years old, the significant increase in older adults will shift the great majority of prescriptions to people in this age group. There is therefore an obvious need to rethink our pharmaceutical product development and design with regard to the future patient population that is at least in its seventh decade of life.

The Older Adult

Aging is a process that starts with birth and continues over the entire lifetime with physiological, biological, physical and social functional changes. The first signs of aging might occur after maturation, but become evident in most people in the post reproductive stage [Smith & Gerstorf 2004; Turnheim 2005]. The aging process goes along with different functional changes that might or might not occur in individuals, and are not a matter of numerical age. Following an incident like acute illness or hospitalization, older adults might develop frailty impacting various organ functions with incremental declines due to additional acute events [Ahmed et al. 2007]. Moreover, older adults are prone to experiencing social issues like increasing loneliness and declining income that affect their wellbeing and potential medication management capabilities. The population of older adults therefore represents the most heterogeneous patient group, that not only varies in their specific medical needs but also regarding their capabilities to manage their drug therapy.

Prescription to Older Adults

Prescribing drug therapies to older adults does not always follow the same decision process that it does for the younger population. First,

it is important to understand that drug therapy normally starts with experiencing symptoms of a disease or other impact on wellbeing, which tends to be less sensitive in older adults as these are often interpreted as normal aging processes that could not be treated, and hence are not reported. Following a careful evaluation of the older patient, physicians need to take into consideration that age-related physiological changes are occurring on various levels and can have an important impact on the pharmacokinetic and pharmacodynamic of a drug compound and therapy chosen. For example, the body water/fat ratio begins shifting in older adults to higher fat and lower water in the body, which could increase the volume of distribution and the half-life of lipophilic drugs. Furthermore, liver mass and the blood flow through the liver and the kidney decline with age, and may reduce the metabolism and elimination of drug compounds leading to an increased exposure. A reduction in plasma albumin and 1-acid glycoprotein has been found in older adults which could lead to a higher concentration of the free drug in the plasma, increasing the drug effect or causing an adverse drug reaction. Overall, older adults have less homeostasis and resources making them more vulnerable to both desired and adverse drug reactions. Another difference between young people and older people is a higher number of chronic diseases and morbidities and their related drug therapies, which makes polypharmacy a common situation in the older adults. Very often, different medical disciplines are involved in prescribing drug therapies to the same patient independently, leading to misinterpretation of symptoms as a new disease rather than an adverse drug reaction caused by other drugs unknown to the physician. Taking into account these various factors, over- and under-prescribing has been identified as a common phenomenon in older patients. As a result, adverse drug reactions occur most frequently and are significantly more severe in older patients compared to the

younger generation. Several strategies have been proposed to improve the prescription regimens to older adults by using lists of inappropriate medicines [Beers 1997] or criteria to start or stop therapies for appropriate prescribing [Gallagher et al. 2008]. It should be pointed out that despite the pure treatments of the medical conditions, most people believe that the patient's health objectives and wishes should be of prime importance.

Older Adults and Medication Management

Following a doctor's visit, patients receive a prescription of one or more drugs and some verbal or written guidance on when and how to take these medicines. It is assumed by all healthcare professionals that the patient will go to the pharmacist to receive the final drug product, take it back home, establish his or her proprietary medication schedule and then take the drugs adherent to the doctor's guidance. Establishing a medication schedule requires that the patient understood the medication and can recall several hours if not days after the visit the different drugs and their application mode, as well as an implementation plan to follow through this medication schedule. Despite the above cognitive tasks involved in medication management, a minimum level of sensory and motor capabilities is required to execute the implementation plan.

In addition, hearing losses in speech identification affect about 60% of people aged 70 years and older [Herbst & Humphrey 1981; Gates et al. 2008] and it is poorly recognised and treated [Hanratty & Lawlor 2000]. Serious visual impairment like macular degeneration, cataract or optic neuropathy is another typical age-related functional limitation in many older adults that makes the reading of the patient information sheet and drug product identification difficult, if not impossible, especially for traditional white tablets or other uncolored oral dosage forms [Klaver et al. 1998; Stegemann 2005].

Accessing the medicines in their primary packaging like vials or blisters is also a prerequisite for following through with a medication schedule. Age-related decline in hand sensitivity

and functioning as well as disease conditions like rheumatoid arthritis can be an unsolicited barrier for the older adults to simply access their required medicines or modify the drug product by tablet-splitting [Atkin et al. 1994].

Finally, once the patient has access to his or her medication, the oral dosage form needs to be swallowed. Swallowing issues are very common in older adults and account for 15% of the asymptomatic patients [Chen et al. 2009], 63% of the patients with reported swallowing issues [Ekberg & Feinberg 1991] and up to 84% of patients with M. Alzheimer [Rofes et al. 2011]. As a result, it has been reported that more than one-third of all tablets are crushed or capsules opened in nursing homes to administer the drugs to the patients [Wright 2002; Morris 2005].

Therefore it should not come as a surprise that compliance rates in older adults remain poor and are caused by a variety of factors [Murray et al. 2004; Vik et al. 2006]. In the future, drug therapy, and especially the drug therapy for older adults, must address compliance and adherence in drug development and design. The WHO report on long-term adherence to drug therapy concluded that "Increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatment" [WHO 2003].

Regulatory Implications of the Aging Population

In 2001 the Food and Drug Administration (FDA) put forward a Guidance to Industry called "Content and format for geriatric labeling" in which the FDA requested clinical data on efficacy, safety and pharmacokinetic/pharmacodynamic of drug products. Research since then, however, showed that older adults are not represented sufficiently in the clinical trials, and sometimes the final user age group is nearly negligible [Cherubini et al. 2010]. In 2008, the International Conference for Harmonization (ICH) adopted its Guideline "E7 (R1): Studies in support of special population: Geriatrics" in which it requires clinical studies in a population that is representative of the target patient population as well as the inclusion of more geriatric patients, the age group between 65 and 74 and the

very elderly aged 75 years and above [ICH 2008; EMEA 2009]. In February 2011, the European Medicines Agency (EMA) released its geriatric medicines strategy and roadmap to 2015 to address the changing demographic situation and the increasingly older patient population [EMA 2011a]. An EMA Geriatric Expert Group (GEG) has recently been installed to help the EMA in developing its geriatric medicines strategy towards better drug product for the older patients [EMA 2011b].

Individualised Medicine

As discussed above, older adults represent the most heterogeneous patient population with several subpopulations having specific medical needs, capabilities and personal health objectives for their late life. Future drug product development will have to focus on the patient, as well as on the disease itself, which might require individualised or 'individualisable' dosage forms. Interestingly, this has already been required by the ICH Quality by Design guideline by specifying that quality of a product should "In all cases, be designed to meet patients' needs and the intended product performance." [ICH 2009]. To design and develop individualised medicines, a series of drug delivery technologies exist which are able to fulfil the needs of the majority of older adult patients [Geriatric Medicine Society 2011].

Individualised medicine does not require a high degree of sophistication; it can be as simple as offering a drug product in more than the standard dose strength or an easily differentiated oral dosage form by using different colours, colour combinations or shapes. More sophisticated approaches could include the development of an oral liquid form, a sprinkle form or a transdermal dosage form to circumvent swallowing issues and limitations.

Finally, reducing the pill burden is another area of consideration for individualised medicines as compliance has been found to decrease as the number of medicines to be taken by a patient increases [Murray 2004]. Reducing the pill burden can be achieved by combination products, sustained release or even dual release formulations that allow a once-daily dosing regimen.

REGULATORY & MARKETPLACE

Conclusion

The demographic change in our population is a worldwide fact that will lead to an increasing number of old and very old adults in our society over the next four decades. Drug therapy will continue to be the major healthcare support for these individuals due to its economic efficiency versus hospitalisation or home care. Older patients differ in a variety of domains from younger patients, and therefore require more age-appropriate medicines. This has recently been recognised by health authorities who have now started the dialogue with different stakeholders to begin developing meaningful guidance. Due to the heterogeneity of the older patient population, patient-centric drug product design will lead to individual medicines that are most appropriate for the patient, ultimately enhancing their therapeutic outcome ■

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