Investigation into the dosage form attributes of currently UK licensed cardiovascular and Parkinson's disease drug products

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Abstract

Globally, there is a continuous rise in the older population (over 65 years), particularly in developed countries. As many diseases are age-related, older adults represent a highly heterogeneous cohort. This presents a major challenge for both the pharmaceutical industry and healthcare professionals. The purpose of this research was to attract attention towards the appropriateness of geriatric formulations by investigating the dosage form attributes of currently UK licensed cardiovascular and Parkinson's disease drug products. Medication available in the UK for cardiovascular disorders and Parkinson's disease were screened and the available formulations, packaging and patient information leaflets of these medicines were analysed, with the goal of raising awareness of the need to cater for elderly patients with increasing difficulty in managing their medication. It emerged that although cardiovascular disorders and Parkinson's disease are more prevalent in older people, many treatment options have not been optimised for this cohort. In particular, older patient centred dosage forms, specific dosing requirements, excipients, patient-friendly packaging and easy-to-follow patient information were highlighted as areas to be considered in order to optimise health outcomes in the ageing population.

Keywords

Older people, dosage form, cardiovascular disease, Parkinson's disease, polypharmacy, excipient

Older people, defined as individuals over 65 years old, represent approximately 17.2% of the total community population in the United Kingdom (UK) and this is expected to increase to 22.4% by 2032 (AgeUK, 2014). Similarly, older people constitute around 17% of the total community population in Europe and this is predicted to increase to 30% in 2050 (European Medicines Agency, 2013). According the Age UK 2014 report on later life, cardiovascular disease (CVD) is the greatest causes of death in the UK in people over 65 years (AgeUK, 2014). Parkinson's disease (PD) is another fatal disease that is prevalent in the older population, with almost two thirds of all PD cases reported in those over 70 years old (Meara, 2000). Therefore, in the present study, pharmaceutical products listed in the British National Formulary (BNF) for CVD and PD were screened in order to determine the suitability of the formulations and associated information for older people. It has been previously reported that up to 50% of patients do not use their medication as prescribed (National Collaborating Centre for Primary Care, 2009). By screening the available information on formulations from two areas of particular importance in prescribing for older patients, this research aims to assess the appropriateness of dosage forms with respect to the older population.

All products listed in the Cardiovascular System and Parkinsonism and Related Disorders sections of the BNF (Joint Formulary Committee, 2013) were included for analysis. The available data were then compiled from relevant UK reference sources - the BNF, Summary of Products Characteristics (SmPC) and Patient Information Leaflets (PILS) (Joint Formulary Committee, 2013). In the BNF, 262 products were listed under cardiovascular system and 41 products were listed under Parkinsonism and related disorders. The SmPCs as well as relevant PILs were screened and aspects considered significant in the optimisation of formulations for CVDs (Table 1) and PD (Table 2) in elderly patients were identified for analysis.

The classification of dosage forms for CVD and PD drug products are presented in Table 3. Of the listed cardiovascular drug products, 48% specified general posology adjustment guidelines based on both renal and hepatic function (Fig.1). Posology adjustments of the cardiovascular formulations were mainly based on renal and hepatic impairment. Renal and hepatic functions are often reduced in older patients, affecting drug metabolism and clearance (Mangoni and Jackson, 2004). However, there are other age-related changes that can influence the pharmacokinetic and pharmacodynamic parameters of medication. For example, older patients are often more sensitive to cardiovascular drugs such as digoxin and warfarin, both of which have a narrow therapeutic index, due to a reduction in apparent volume of distribution of these agents. This considerably increases serum concentration and therefore, toxicology and adverse effects. On the contrary, the efficacy of adrenoceptor blocking agents declines with age and careful dose titration is required. However, these factors were considered for less than half of the available cardiovascular dosage forms, with 30 providing neither specific adjustments for older patients nor any information regarding posology adjustments. This suggests that more academic and industrial efforts are required to optimise the efficacy of medicines for the older population (Ford, 2000; Mangoni and Jackson, 2004). Clinical trials often exclude older patients based on age, concomitant conditions, polypharmacy, frailty or the higher costs associated with recruiting and maintaining elderly during clinical trials. However, the extrapolation of clinical findings to include patients outside the tested age range does not offer a true representation of these groups. Clinical studies for older patients are required to maintain the safety of elderly participants and to obtain valid professional data regarding those patients that can be used by healthcare professionals (Cherubini et al., 2010; ICH Steering Committee, 2010).

Of the listed CVD products, 40% specified dose recommendations that were adjusted for older patients, taking into account factors such as comorbidity, polypharmacy, increased vulnerability to adverse effects and other age-related physiological changes that can impact the pharmacodynamic profile and tolerability of the patient. The prevalence of modified

release formulations, fixed-dose combinations (FDCs) and “risky” excipients (for example propylene glycol or sodium) are also shown in Fig. 1. Polypharmacy is common in older patients. While multi-drug prescribing is often necessary in the treatment of age-related conditions including CVD, it can significantly increase the complexity of dosing regimens and contribute to non-compliance (Hilmer et al., 2007). FDCs allow multiple drugs to be delivered in a single entity. Increasing the number of licensed FDCs would be beneficial in reducing the number of medications required in conditions such as CVD, when the level of concomitant prescribing is high (Bangalore et al., 2007; Martial et al., 2013). Modified release formulations offer a prolonged action in the body, which in turn may reduce the frequency of dose administration, particularly in drugs with short biological half-lives. Reducing the complexity of drug regimens by minimising dose frequency has been shown to reduce the incidence of forgotten dose and increases compliance (Collett and Moreton, 2007).

Three types of packaging were identified for PD medication. The majority of formulations (64%) were packaged in a glass bottle with either a screw, tamper evident or child resistant closure, with 46% packed in blisters and 6% packaged in a container with a snap-lid. Packaging is an essential tool in the preservation of safety, stability and identity of pharmaceutical preparations. It can also affect the ability or willingness of a patient to take their medication and can therefore, influence compliance (Murdan, 2013). Previous research has demonstrated that many elderly people have difficulty opening medication containers (Atkin et al., 1994; Philbert et al., 2014). In a recently published survey investigating medicine packaging in older people, Philbert et al. (2014) found that one in four individuals over 65 experienced difficulties opening their medication packaging. These issues are compounded by age-related conditions such as PD and rheumatic disorders, which cause dexterity difficulties. There is strong correlation between Parkinsonism and a reduced ability to handle different types of pharmaceutical packaging, in particular snap-lids,

followed by screw-cap bottles and, to a lesser extent, blister packs (Beckman et al., 2005). Therefore, it appears to be a serious oversight that some PD medication is packaged in these formats.

PILs were available for 39 of the 41 screened preparations; the availability of elderly-specific information is shown in Fig. 2. This information was limited for PD medication, with less than 13% containing pictograms to assist in portraying information (Fig. 2). Whilst patient-specific information may be explained by the prescriber or pharmacist, inclusion of standard information in the PILs may eliminate confusion, particularly as older patients are more likely to have cognitive impairment, anxiety and poor vision, all of which will make it more difficult to remember oral instructions and read written medication labels (Weinman, 1990).

The majority of cardiovascular formulations were formulated as solid oral dosage forms, which is supported by previous research that found between 65% and 70% of available drugs are formulated as solid oral dosage forms (Schiele et al., 2013). Oral dosage forms, particularly solid formulations, tend to have higher stability, are easier to manufacture and handle, cheaper compared to other dosage forms and more palatable. However, in elderly patients, such dosage forms are not always suitable. The prevalence of dysphagia increases with age and CVDs such as hypertension and hypercholesterolemia increase the risk of stroke, which may further exacerbate swallowing difficulties. This may make it difficult for patients to take the medication required to control their condition, such as warfarin and aspirin, which are only available as solid oral dosage forms (Schiele et al., 2013). In addition, complications associated with PD include dysphagia and motor disorders, which can reduce the success of therapy and outweigh the convenience of oral drug delivery (Meara, 2000; Monteiro et al., 2014). In the present study, many of the tablets for PD were available only as a coated formulation to be swallowed whole. Challenges associated with swallowing such a tablet whole may result in the incorrect modification of these dosage

forms by patients and subsequent reduced efficacy and safety issues (Schiele et al., 2013). There are several alternative drug delivery systems that can minimise swallowing difficulties. These include sublingual or buccal tablets, soluble film strips, orodispersible tablets, crushable tablets and capsules that can be opened and mixed with soft food (Breitkreutz and Boos, 2007; Dey and Maiti, 2010).

In the present study, nearly half of the screened CVD formulations contained sodium. In some cases, the amount of sodium in effervescent, dispersible and soluble tablets prescribed for cardiovascular disorders was found to be higher than the recommended UK daily sodium intake of 2.4 g (104 mmol) for adults. High sodium consumption increases water retention by disturbing the electrolyte balance in the body, increasing the risk of many cardiovascular conditions such as hypertension, stroke and heart failure, especially in older patients (George et al., 2013). Further, compounds such as sodium bicarbonate, which acts as an alkalinising agent in some formulations, can aggravate cardiovascular events including chronic heart failure in the elderly population (Turner et al., 2013). Therefore, it is important that pharmaceutical manufacturers consider this when developing formulations and that prescribers, pharmacists and patients are aware of the potential toxicity of excipients in dosage forms and select appropriate dosage forms accordingly. To facilitate this, the sodium content in pharmaceutical products should be clearly labelled, as is the case in the food industry (George et al., 2013; Tuleu and Wright, 2013).

This study highlights the paucity of formulations specifically designed for the elderly population, even in conditions such as CVD and PD, which are more prevalent in older people. Specific age related limitations including comorbidity, polypharmacy, dysphagia, impaired manual dexterity and visual and cognitive impairments need to be considered in relation to their impact on the complexity of the drug regimen, compliance, type of the dosage forms, posology adjustment, packaging and the layout of patient information. The

development of novel fixed-dose combinations and modified release formulations will assist in the simplification of medication regimens and improve patient compliance.

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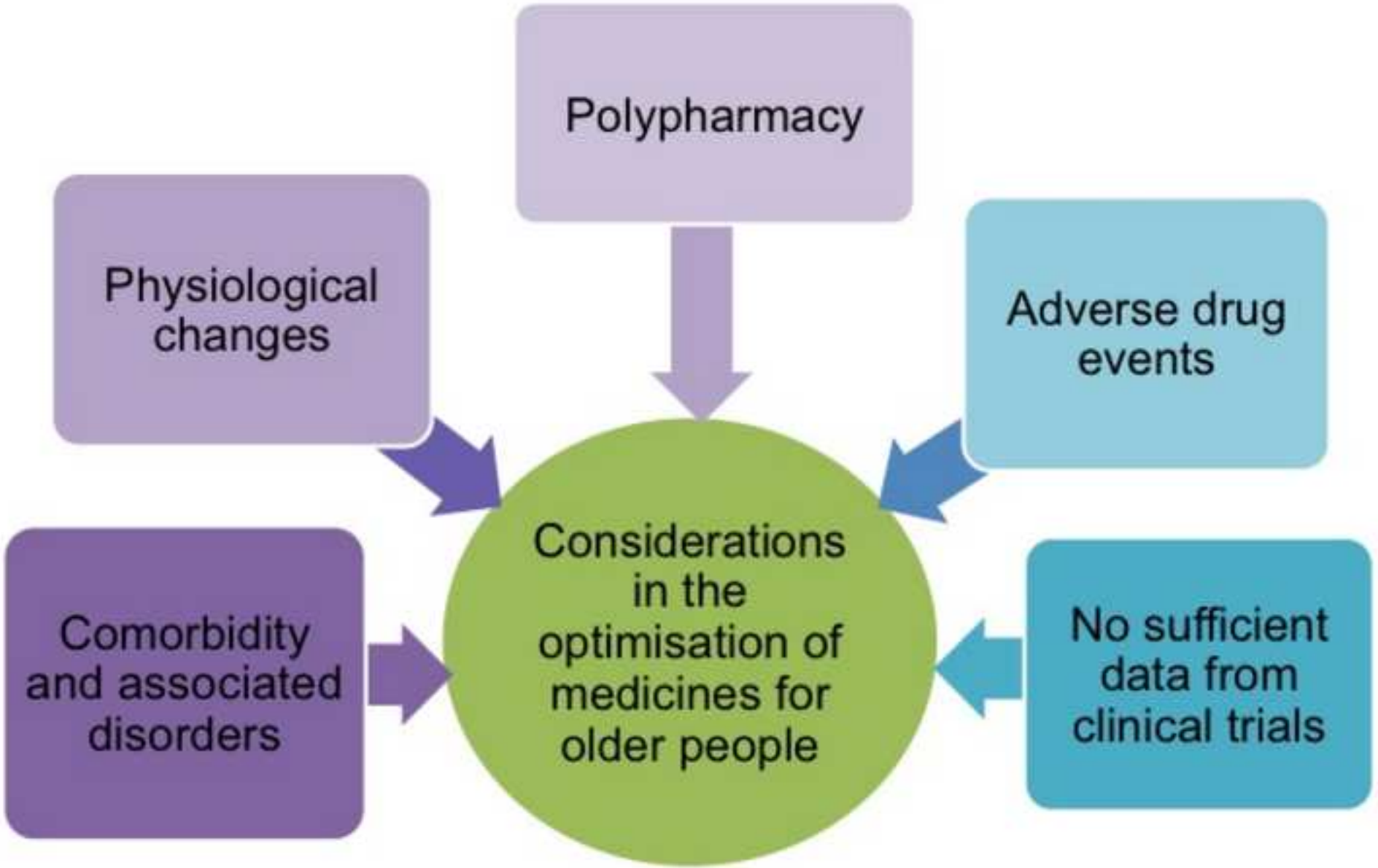
Graphical Abstract (for review)



Table(s)

Table 1. Pharmaceutical formulation aspects considered significant in the screening of dosage forms with respect to elderly patients receiving medication for cardiovascular disorders.

BNF classification
Therapeutic indication(s)
Active pharmaceutical ingredient(s)
Available dosage forms
Therapy type (mono or fixed dose combinations (FDCs))
Dose frequency (mono- or multi- dose)
Potential “risky excipients” (propylene glycol, sodium)
Tablet scoring/ability to be halved
Drug release profile (immediate/modified release)
Coating type
Age range
Minimum age
Elderly-specific section
Packaging type
Storage conditions
Name of marketing authorisation holder
Information source and additional comments

Table 2. Pharmaceutical formulation aspects considered significant in the screening of dosage forms with respect to elderly patients receiving medication for Parkinson's disease.

BNF classification
Therapeutic indication(s)
Active pharmaceutical ingredient(s)
Available dosage forms
Method of administration
Therapy type (mono or fixed dose combinations (FDCs))
Drug release (immediate/modified release)
Packaging
Elderly-specific section
Definition of elderly
Pictogram
Specific warnings for elderly

Table 3. Classification of screened dosage forms and route of administration for cardiovascular disorders (CVD) and Parkinson's disease (PD). Observations are reported as number of drug products (n) and percentage of oral, sublingual, parenteral, topical or other formulations (%).

Route of administration	CVD (n = 262)	PD (n = 41)
Oral, *n* (%)	198 (76)	33 (80)
Tablets, *n*	150	20
Chewable tablets, *n*	1	-
Dispersible tablets, *n*	1	1
Orally disintegrating tablet	-	1
Capsules, *n*	30	5
Liquid, *n*	13	6
Sachet/powder, *n*	3	-
Sublingual, *n* (%)	3 (1.1)	-
Tablet	1	-
Spray	2	-
Parenteral, *n* (%)	58 (22)	7 (17)
IV injection, *n*	17	-
IV infusion, *n*	14	-
IV injection or infusion, *n*	17	-
IV/SC injection or infusion, *n*	1	-
IV/IM injection, *n*	-	1
IM injection, *n*	3	3
SC injection, *n*	5	2
Intra-ocular injection, *n*	1	
Topical, *n* (%)	2 (0.76)	1 (2)
Ointment, *n*	1	
Patches, *n*	1	1
Other	1 (0.38)	1 (2)
Pulmonary, *n* (%)	1	-
Intestinal gel, *n* (%)	-	1

IV = intravenous; IM = intramuscular; SC = subcutaneous

Fig. 1 Prevalence of key characteristics for each of the CVD formulations, presented as a percentage of the 262 formulations screened.

Fig. 2 The availability of elderly specific information in the PILs of formulations for Parkinson's disease.

Figure 1
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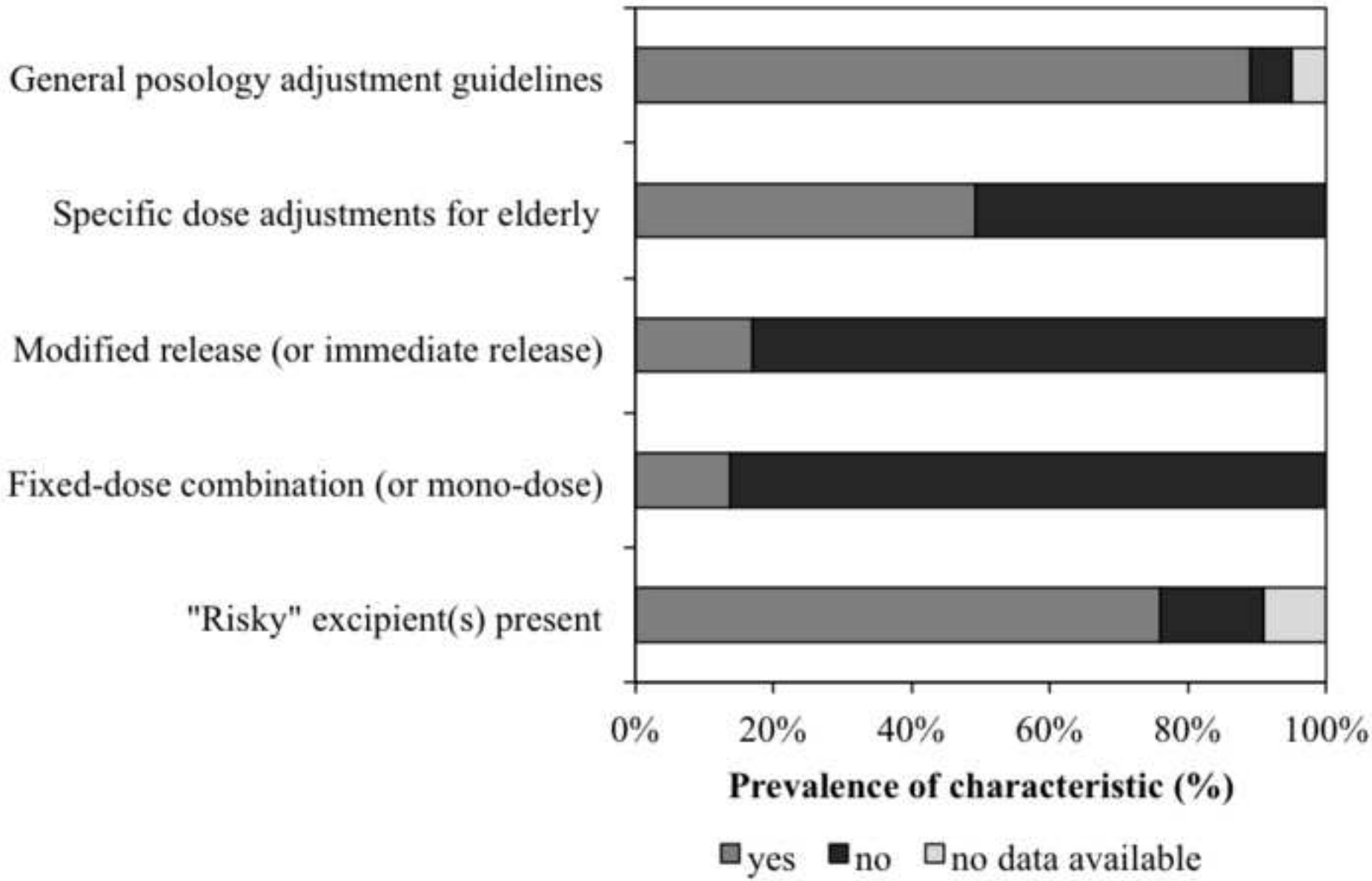

Figure 2
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