Invited Editorial

Title:

Global pandemic – the true incidence of adverse drug reactions

Author:

Dr Roy L Soiza MB ChB MRCP(UK)

Consultant Physician, NHS Grampian

Honorary Clinical Reader, Ageing Clinical & Experimental Research (ACER), University of Aberdeen

Address:

Ageing Clinical & Experimental Research (ACER), Room 1:128 Polwarth Building, University of Aberdeen, Aberdeen, AB25 2ZN, United Kingdom

E-mail:

roy.soiza@nhs.net

One in six hospitalised people aged 65 or over will experience a new, significant adverse drug reaction (ADR) during their hospital stay. That is the major conclusion of a comprehensive systematic review and meta-analysis published in today's *Age & Ageing* [1]. The high incidence is unlikely to surprise those who work in the acute care of older people, but arguably this figure only describes the tip of the iceberg. Any estimate of incidence relies crucially on outcome ascertainment, but most healthcare systems (and even scientific studies in this field) do not have a sensitive system to prospectively identify all events for adjudication as a potential ADR. Moreover, most validated systems of ADR ascertainment such as the Naranjo classification [2] or the WHO-UMC system [3] are fallible and none is universally accepted [4]. They lack sensitivity in identifying ADRs in people with multi-morbidity, mostly because they require exclusion of other potential causes before it can be ascertained that an ADR has 'probably' or 'certainly' occurred. For example, using these classification systems may make it falsely appear that people with Crohn's disease are practically immune to all drug-related diarrhoea. Similarly, many drug-related symptoms would be classified as only 'possible' or even 'unlikely' ADRs in frail older people with multi-morbidity, even if they were real. ADR classification systems are based on the outdated 'Ocham's razor' concept, that symptoms are best explained by a single condition or entity to form one correct, unifying diagnosis. In reality, geriatricians will be fully aware that most acute presentations in older people are multi-factorial, with medications frequently playing an important, but not easily quantifiable, part in their aetiology. Therefore, the true incidence of ADRs is likely to be much higher than the 16% reported in the meta-analysis.

Further evidence for the likely under-reporting of ADRs in the published literature lies on closer inspection of the distribution of type of ADRs. Almost all electrolyte imbalances, one of the commonest of all ADRs, were allegedly due to potassium disorders. This is despite clear evidence that hyponatraemia is by far the commonest electrolyte disorder in hospitalised people and that older people are disproportionately affected [5]. This is likely to reflect the same limitations with outcome ascertainment, since hyponatraemia in older people is often multi-factorial [6] but medications play a key role [7]. Presumably, potassium imbalance is more likely to be considered directly linked to medications, but it seems implausible that they are genuinely 10 times more common than sodium disorders, as the new systematic review reports [1].

These limitations are also likely to influence the findings on the drug and drug types that are most frequently linked to ADRs. Some, such as non-steroidal anti-inflammatory medications causing acute kidney injury or gastro-intestinal bleeding may be more likely to be picked up based on notoriety and because it is less likely that patients prescribed these drugs will have any other plausible explanation for their new symptoms. However, some medications, such as anti-depressants, may appear safer than they really are because almost their entire ADR profile could potentially be mis-attributed to the disease they are supposed to treat, or because they are considered risk factors rather than causes of adverse events, such as falls [8]. Although there is always a possibility of 'confounding by indication', this should not be used to dismiss concerns about drug safety and ADRs without objective evidence for such confounding.

Unsurprisingly, given these limitations, the authors found enormous variations in estimates across studies beyond what might be expected from variations in case-mix and setting. The authors correctly point out the true burden of ADRs on older people in hospital is difficult to quantify. Some ADRs are arguably unavoidable when there is a strong indication for the drug and there is no evidence that a different dose, regime or agent would have resulted in a better risk/benefit ratio, and such factors are subjective and difficult to reliably ascertain. Research into avoidable ADRs rarely considered the impact on patient-reported measures such as quality of life, and even clinically important ADR-related outcomes such as length of stay were rarely reported [1]. Such deficiencies in the literature undermine the case for a more radical recalibration of prescribing decisions that is badly needed to stem the tide of polypharmacy and ADRs in older people. It is hard to argue that an internationally accepted 'gold standard' for ADR ascertainment would help more coherently and consistently define the extent of ADR-related morbidity and mortality, but such a standard should also work well in older people with multi-morbidity and polypharmacy, as the group most prone to ADRs.

Beyond higher standards of pharmacovigilance and research to better define the extent of the problem, Jennings and colleagues recommend a greater focus on predicting and preventing ADRs. Lamentably, here again the evidence-base is found wanting. ADRs in frail older people are difficult to predict and none of the ADR-risk tools have sufficient predictive value for clinical use [9]. Perhaps this is unsurprising, as ADRs are a heterogeneous collection of symptoms and risk factors for individual ADRs vary widely. It may be difficult for a single scoring system to accurately simultaneously define the risk of any of diarrhoea or constipation or bleeding or any of the other 20 diverse clinical presentations that together comprised 90% of all ADRs in the present systematic review [1]. Just four different drug classes – diuretics, antibiotics, anti-thrombotic agents and analgesics – accounted for over half of all ADRs. This may well represent an important opportunity

for targeted interventions to reduce incident ADRs in hospital. However, as the authors acknowledge, their results are not entirely consistent with other systematic reviews that looked at ADRs in either other settings or in wider age groups or included ADRs that led to admission. Neither does this 'black-list' correlate particularly well with findings from studies employing other ways to define drug-related health burden, such as measuring the cumulative effects on physical function in community-dwelling older people[10], where anticholinergic and sedative medications seem most dangerous . Nevertheless, the findings of the current systematic review are helpful in focussing on new ADRs occurring in older people in hospital and revealing the high incidence of this problem, even if the evidence base only allows us to see the tip of the iceberg.

References

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