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Safety of coprescribing NSAIDs with multiple antihypertensive agents

Triple therapy is associated with higher rates of hospitalisation with AKI, but questions remain

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Current guidelines by the National Institute for Health and Clinical Excellence (NICE) recommend treatment with angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) for conditions such as hypertension,[1] chronic heart failure,[2] and proteinuric chronic kidney disease.[3] In England, the prescription of these drugs has increased by 15.8% over the past four years.[4] Because ACE inhibitors and ARBs are often coprescribed with non-steroidal anti-inflammatory drugs (NSAIDs) and diuretics, particularly in older people,[5] we need to know more about the safety of such combinations.

In a linked paper, Lapi and colleagues used a large database that was representative of UK primary care to examine data on 487 372 patients taking antihypertensive drugs.[6] They used a nested case-control design to examine whether adding an NSAID to an ACE inhibitor, ARB, or diuretic in double or triple therapy combinations increased the risk of subsequent hospital admission with acute kidney injury (AKI). Acute kidney injury is seen in more than 20% of hospital inpatients and is associated with around half of all potentially preventable deaths in hospital.[7 8] Although recent observational evidence suggests a link between this condition and use of diuretics, NSAIDs, ACE inhibitors, and ARBs,[9] such studies are confounded by indication. Patients who are prescribed a combination of these agents are usually at high risk of acute kidney injury, which makes it difficult to establish a causal association.

The jury is still out on whether double drug combinations are indeed safe

The authors of the current study used a strict case definition of acute kidney injury: cases were defined using the first diagnostic code and those in which acute kidney injury was just a secondary problem were excluded. They excluded people with chronic kidney disease and adjusted for other comorbidities in the analysis. Chronic kidney disease is associated with an increased risk of acute kidney injury and well informed patients may avoid taking NSAIDs, which could introduce confounding by contraindication.[10]

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Acute kidney injury is associated with half of preventable deaths in hospital

Adjusted analyses found a 31% higher risk of acute kidney injury (relative risk 1.31, 95% confidence interval 1.12 to 1.53) for a triple drug combination (adding an NSAID to an ACE inhibitor or ARB plus diuretic) but no clear evidence of an increased risk of acute kidney injury for double drug combinations (NSAID added to either a diuretic, ACE inhibitor, or ARB). These results remained consistent after several sensitivity analyses.

So can clinicians be confident that NSAIDs in double combination with an ACE inhibitor, ARB, or diuretic are not associated with acute kidney injury? Defining safety as the absence of adverse events provides us with the difficult statistical challenge of excluding the presence of associations. To make sure that a particular drug combination is safe, an extremely large dataset of a representative patient population must be randomised to a given drug combination versus a single drug class, with frequent follow-up to detect adverse events.

In the current study, confidence intervals for estimates of risk for double drug combinations were wide, so the evidence of safety is not strong. Indeed, there was a suggestion of an early increase in risk for a diuretic-NSAID combination. Secondly, this analysis could not adjust for over-the-counter NSAID use or tell us about instances when primary care doctors detected increases in serum creatinine and stopped drugs before patients needed hospital admission. Thirdly, drug associated acute kidney injury is often a complication of other illnesses.[11] Lastly, defining acute kidney injury in patients with chronic kidney disease is complex, but it is important to understand how acute kidney injury can be prevented in this high risk group.[10] Therefore, Lapi and colleagues' study probably underestimates the true burden of drug associated acute kidney injury. The jury is still out on whether double drug combinations are indeed safe.

The implications of the current analysis are nevertheless important: clinicians must advise patients who are prescribed diuretics, ACE inhibitors, or ARBs of the risks associated with NSAID use and they must also be vigilant for signs of drug associated acute kidney injury in all patients. Importantly, current NICE quality standards for people with chronic kidney disease advise a drug review and renal function check during acute illness.[12]

Lapi and colleagues' paper highlights how observational data can improve our understanding of the risk to benefit ratio of drugs in routine use in the general population (as opposed to the defined populations where initial clinical trials were undertaken). Work still needs to be done to understand whether drug associated acute kidney injury is preventable, and what role intercurrent illness plays. The role of prescribed drugs in increasing the severity or duration of hospital admission may be as important as single organ complications in the elderly population with multiple comorbidities to whom these drugs are mainly prescribed. The current study is an important step in the right direction, but a longer road of discovery is ahead.

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Advice to patients invited to participate in a clinical trial[17]
Agree to participate in a clinical trial only if: (1) the study protocol has been registered and made publicly available; (2) the protocol refers to systematic reviews of existing evidence showing that the trial is justified; and (3) you receive a written assurance that the full study results will be published and sent to all participants who indicate that they wish to receive them.

All trials must be registered and the results published

Academics and non-commercial funders are just as guilty as industry

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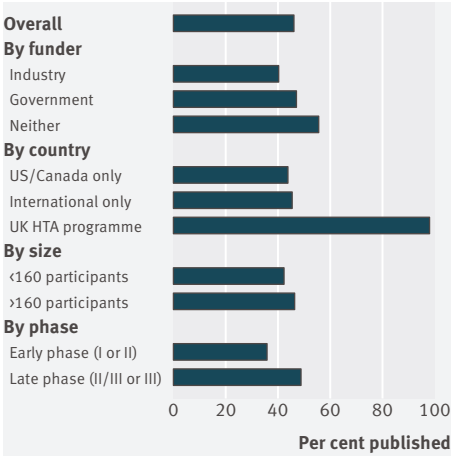
Biased under-reporting of research has been documented for well over two decades and the evidence for it is now overwhelming.[1-4] Under-reporting is research misconduct and has serious consequences.[5 6] It leads to overestimates of the benefits of treatments and underestimates of harms, puts patients at risk and wastes healthcare resources.[7]

Much of the criticism has focused on commercially funded trials, and justifiably so. There is consistent evidence of under-reporting and manipulation of the scientific literature by the drug and devices industries,[4] and industry sponsors most of the world's clinical trials. But under-reporting is not confined to commercially sponsored trials. Indeed, early examples of failure to publish negative results came from academia.[5 8]

Nor has academia been any better than industry at cleaning up its act in the intervening decades. Because of trial registration, we can now estimate the magnitude of and describe under-reporting of clinical trials. Only around half of all registered trials have published at least some of their results, and this level of under-reporting affects most types of trial (see figure).[9]

Participants in clinical trials assume that they are contributing to the advancement of knowledge; non-publication of study results negates this reasonable assumption and betrays those volunteers.

Failure to publish all the results from clinical trials distorts the evidence base for clinical decisions. In a Personal View published in the *BMJ* eight years ago, Alessandro Liberati protested that the unpublished results of clinical trials could have informed his choices as a patient with multiple myeloma. "Why was I forced to make my decision knowing that information was somewhere but not available? Was the delay because the results were less exciting than expected? Or because in the evolving field of myeloma research there are now new exciting theories (or drugs) to look at? How far can we tolerate the butterfly behaviour of researchers, moving on to the next flower well before the previous one has been fully exploited?"[10] Liberati died from the complications of his disease, waiting for researchers to publish information relevant to his treatment choices.



Proportion of clinical trials registered by 1999 and published by 2007[9]

Many academic trials have failed to report their findings, including important trials supported by major funders. A large trial of adenoidectomy funded by the UK's Medical Research Council remained unpublished for more than a decade after it was concluded.[11] And this week the *BMJ* reports on the failure of US academics to publish protocol defined follow-up data from a trial of sentinel node biopsy in malignant melanoma.[12]

What can explain this failure to publish academic trials? Journals have been blamed for a bias towards accepting positive results, and some of the blame does lie with them. But the evidence indicates that the principal culprits are authors and research sponsors for not submitting reports for publication.[13] Financial conflict of interest is well understood as a motive for suppression of unfavourable results from commercially sponsored trials. But what are the motives of authors and sponsors of non-commercial trials? Authors admit failure to write up and submit their results.[14] Anecdotes suggest a range of reasons, such as losing interest or moving on to new institutions and projects, poor organisation, inadequate resources, writer's block, or unwillingness to accept the results of a trial owing to investment in the outcome. There has been too little systematic effort to monitor the extent of non-publication, let alone investigate the reasons for it.

The responsibilities of authors are clear: the Helsinki Declaration leaves no room for ambiguity. It states that, "Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports . . . Negative and inconclusive as well as positive results should be published or otherwise made publicly available."[15]

But authors' behaviour is unlikely to change without firm action from those who give ethics approval, institutional hosting, and funding support for trials. Research ethics committees were challenged long ago to behave ethically by ensuring that results of trials were published,[16] yet these committees have been noticeably absent among those exposing under-reporting of clinical trials and taking steps to tackle the problem. It is clear from the figure that academic institutions and funders of research have similarly failed in their responsibilities. There are exceptions, however: the figure also shows that 98% of the studies funded by the National Institute for Health Research Health Technology Assessment Programme have led to the publication of full reports (Ruairidh Milne, personal communication). The programme has achieved this by holding back a proportion of the research grant until a report has been submitted for publication, by chasing authors, and by providing a publication vehicle—*Health Technology Assessment*—for all trials.

This shows what can and should be done. Information made public through trial registration means that research funders and institutions that continue to under-report clinical trials can now be identified. Patients who are invited to participate in trials should consider the track record of the institutions and funders concerned and refuse to participate unless they receive written assurance that the full study results will be made publicly available and freely accessible (box above).

A campaign to ensure that all trials are registered and their results published, or otherwise made publicly available, is launched this week (www.alltrials.net). We invite all *BMJ* readers to sign the campaign's petition.

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Interaction can occur after ingestion of freshly squeezed juice, juice from concentrate (as little as 200 mL), and consumption of the fruit itself

Drug-grapefruit juice interactions

Two mechanisms are clear but individual responses vary

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Grapefruit juice, which is widely consumed for its positive health benefits, can have severe, sometimes fatal, interactions with drugs. This phenomenon was first identified serendipitously about 20 years ago for the calcium channel antagonist felodipine,[1] and a recent review found that more than 85 drugs can be affected by grapefruit juice.[2] Two main mechanisms, which have different clinical consequences, have been defined (table).

Firstly, grapefruit juice contains furanocoumarins (such as 6′,7′-dihydroxybergamottin),[3] which can cause irreversible inhibition of the cytochrome P450 enzyme, CYP3A4, mainly in the small intestine.[4] CYP3A4 is involved in the metabolism of around 50% of drugs, so a wide variety of drugs can be affected by the consumption of grapefruit juice. The net effect is a reduction in the pre-systemic metabolism of these drugs, which increases their systemic exposure, sometimes by more than 700% (as has been shown for simvastatin).[5] Because inhibition of CYP3A4 is irreversible, it can last for longer than three days after ingestion of grapefruit juice, until new enzyme has been synthesised in the gut wall.[2]

The interaction can occur after ingestion of freshly squeezed juice, juice from concentrate (as little as 200 mL), and consumption of the fruit itself.[5] The effect on drug pharmacokinetics seems to be greater with regular consumption. The clinical consequences can vary from an asymptomatic increase in drug concentrations to life threatening events.[2 5] Such a life threatening event is described in a case report of impaired metabolism of amiodarone after ingestion of grapefruit juice that led to an increase in QT interval and torsades de pointes.[6] Similarly, rhabdomyolysis has been described after co-ingestion of grapefruit juice with atorvastatin.[7]

A second mechanism involves the inhibition of a member of the influx transporter protein family (organic anion transporter polypeptide; OATP) by grapefruit.[8] Flavonoids such as naringin and hesperidin have been implicated in the mechanism of OATP inhibition. The net effect is reduced bioavailability of the drug, with a decrease in its systemic and tissue concentrations and thus a decrease in its efficacy. In contrast to the effect of grapefruit juice on CYP3A4, the inhibition of OATPs shows a clear volume (dose)-response association, which is competitive in nature, with inhibition lasting about four hours. Thus, a simple way to avoid this interaction is to have a four hour gap between the intake of grapefruit juice and drug administration.[8] Drugs affected through this mechanism include aliskiren, celiprolol, fexofenadine, and ciprofloxacin.

The clinical consequences of both types of interaction are difficult to predict for individual patients. Sequelae depend on the bioavailability of the drug, the intrinsic level of expression of CYP3A4 or OATPs in the gut, the amount and frequency of grapefruit juice consumption, and the characteristics of the grapefruit juice ingested (fruit species, geographical origin, maturity, manufacturing processes, storage conditions, and seasonal variability).[2 5 8] The first of the two mechanisms is most important clinically because of the serious toxic effects that can arise with certain drugs and because the inhibition is irreversible. It is therefore important to ask patients about consumption of grapefruit juice, to document this in the clinical notes, and to provide information on avoiding grapefruit juice, particularly if drugs have a narrow therapeutic index or toxic manifestations that can be severe. For some drugs that are known to interact with grapefruit juice, it has been proposed that the dose given may be reduced; however, it is difficult to predict the consequences of an interaction for different people taking the same drug.[2] Thus, it is probably wise to prescribe an alternative drug that is not affected by grapefruit juice consumption.

The table lists the commonly used drugs that are affected by grapefruit juice, but many other drugs can also be affected. Further information can be obtained from other sources such as the *British National Formulary* (appendix 1). More research is needed to define which other drugs currently on the market can be affected by grapefruit juice, and to develop better methods to assess the severity of the interaction for different people. Efforts to reduce the furanocoumarin content of grapefruit juice are also under way through crossbreeding,[9] alternative processing techniques,[10] and the use of edible fungi.[11]

Finally, although this editorial has focused on grapefruit juice, furanocoumarins are also present in Seville oranges and pomelos. Furthermore, other fruits and juices, including cranberry, Goji berry, and apple, contain other active moieties that can affect different P450 isoforms and transporters and interact with different drugs. It is therefore important to take a careful dietary history from patients and provide them with the relevant information to minimise the effects of these potentially serious interactions.

Drug interactions with grapefruit juice[2 8]

Mechanism	Site of action	Protein affected	Mechanism of interaction	Effects of interaction	Examples of drugs affected
1	Intestinal wall	Inhibition of cytochrome P450 3A4 (CYP3A4)	Irreversible inhibition; non-competitive; long lasting (>3 days)	Decreased presystemic metabolism; increased drug bioavailability; drug toxicity	Anticoagulants (apixaban, rivoraxaban); antiarrhythmics (amiodarone, propafenone, dronedarone); calcium channel blockers (verapamil, amlodipine, felodipine, nifedipine, nicardipine); drugs that act on the central nervous system (carbamazepine, pimozide, quetiapine, buspirone, triazolam); cytotoxics (nilotinib, sunitinib, lapatanib); immunosuppressants (ciclosporin, tacrolimus, sirolimus); statins (atorvastatin, simvastatin)
2	Intestinal wall	Inhibition of organic anion transporter polypeptides	Reversible inhibition; competitive; short lasting (~4 hours)	Decreased absorption; decreased drug bioavailability; lack of drug efficacy	Aliskiren, celiprolol, fexofenadine, talinolol

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In the United Kingdom, long stay institutions were officially closed in 2009, but privately run hospitals have been stealthily replacing them

Acting on the lessons of Winterbourne View Hospital

"Because we'd failed them by our disregard"

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Panorama's broadcast of *Undercover Care: The Abuse Exposed* during May 2011 made "real" the abusive treatment of patients with intellectual disabilities and adults with autism at a private hospital owned by Castlebeck Care (Teesdale) Ltd, which had become their "home." The BBC's undercover reporting enabled millions to watch the degradation and distress of patients as nurses and support workers exercised merciless power. Viewers witnessed the cruelties endured by patients and heard the shallow rationales of support workers and nurses as they encouraged each other to use considerable force. They covered patients' heads, laid across patients' chests, put their arms across patients' throats, and generally immobilised patients with bodily weight and objects.

The Department of Health in England's final report on the Winterbourne View scandal was recently published.[1] It recommended rapidly reducing the number of people with challenging behaviour in hospitals or in large scale residential care, particularly those away from their home area. It also recommended improving strategies to deliver integrated care so that individuals could stay at home or close to their homes.

The serious case review commissioned by South Gloucestershire's Safeguarding Adults Board was published after the trial of 11 support workers and nurses. It asserted that business opportunism after the hospital closure programme and the failure to commission the local services recommended by the Department of Health and its advisers led to the situation at Winterbourne View Hospital.[2] The review found that the healthcare provided at Winterbourne View Hospital was inadequate, as was the ongoing monitoring of patients' health status. Extensive dental problems and constipation were common. Many patients without a diagnosis of serious mental illness were prescribed antipsychotics and antidepressant drugs. Furthermore, in a specialist hospital, commissioners should have expected a psychiatrist to prescribe and monitor drugs, but this was left to a local general practitioner.

Such abuses—where patients were placed and forgotten, as in long stay institutions—have

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BBC footage of abuses at Winterbourne View

occurred in the past in NHS hospitals and around the world. In the United Kingdom, long stay institutions were officially closed in 2009, but privately run hospitals have been stealthily replacing them.[3] What makes the failings in care at Winterbourne View Hospital even more appalling is that, unlike the long stay NHS hospitals, it was not starved of funds. Its average weekly fee was £3500 (€4315; $5689) per patient, with one primary care trust paying almost £10 000 a week for one patient.

The Department of Health's final report acknowledges the serious failure of commissioning and advises that when children, young people and adults need specialist support, including crisis support, the default position should be to put this support into the person's home.[1] It asserts that people should not live in hospitals, and it sets out timetabled actions for health and local authority commissioners with a view to transforming care and support for people with intellectual disabilities or autism who also have mental health conditions or behaviours viewed as challenging. The report was influenced for the better by the concerns of people with intellectual disabilities, their relatives, and health and social care professionals.

Any large scale reduction in the number of vulnerable adults cared for in institutions away from their home will require the parallel development of a range of local services to prevent admissions to hospitals or other large institutional settings.[3-5] For more appropriate care to be delivered to people with intellectual disabilities who are cared for in the community, mental health services will need to make reasonable adjustments. Commissioners are expected to work together to draft and agree a joint plan to ensure high quality care and support services for all people with challenging behaviour. Such integrated care should be based on the needs of individuals and designed to help people stay in their communities. The Department of Health will shortly commission a wider review of the prescribing of antipsychotic and antidepressant drugs for people with challenging behaviour. There is already a compelling case for GPs and psychiatrists to review all drugs prescribed to patients with intellectual disabilities and autism and to ask questions about the use of antipsychotics and antidepressants.[1 6 7]

There are lessons to be learnt from the Winterbourne View scandal for all clinicians, not just specialists, and implications for clinical care. In sourcing patients from all over the country, Castlebeck Ltd weakened essential relationships between patients and their families, friends and support structures, particularly GPs and other primary care professionals. Primary care practitioners must pay careful attention to patients whose communication may be compromised. Emergency doctors also have a role to play in transforming adult protection through concerned and careful questioning at each encounter.

There is no case for the delegation of the ordinary health and social care needs of patients with intellectual disabilities and autism to an imagined, all purpose specialism. All doctors must be comfortable and competent to attend to the routine needs of people with intellectual disabilities and autism in their own branch of practice. Achieving effective, non-discriminatory and skilled clinical practice will require some new educational initiatives. Participatory development activities with patients, family members, and advocates is increasingly recognised as crucial in educating practitioners and monitoring service provision.[8 9]

Taken as a whole, the scandal of Winterbourne View Hospital requires us to face the insistent themes of neglect, exclusion, exile, and punishment. The healthcare of patients with intellectual disabilities and autism is at a crucial juncture if these themes are not to prevail.

Competing interests: SH's son has an intellectual disability and uses services; she chairs Beyond Words, a charitable organisation that publishes picture books on topics relevant to the editorial; MF chaired the serious case review into Winterbourne View Hospital. She has a brother with a learning disability.

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