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A SYSTEMATIC REVIEW OF THE USE OF DOSAGE FORM MANIPULATION TO OBTAIN REQUIRED DOSES TO INFORM USE OF MANIPULATION IN PAEDIATRIC PRACTICE.

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ABSTRACT

This study sought to determine whether there is an evidence base for drug manipulation to obtain the required dose, a common feature of paediatric clinical practice. A systematic review of the data sources, PubMed, EMBASE, CINAHL, IPA and the Cochrane database of systematic reviews, was used. Studies that considered the dose accuracy of manipulated medicines of any dosage form, evidence of safety or harm, bioavailability, patient experience, tolerability, contamination and comparison of methods of manipulation were included. Case studies and letters were excluded. Fifty studies were eligible for inclusion, 49 of which involved tablets being cut, split, crushed or dispersed. The remaining one study involved the manipulation of suppositories of one drug. No eligible studies concerning manipulation of oral capsules or liquids, rectal enemas, nebuliser solutions, injections or transdermal patches were identified. Twenty four of the tablet studies considered dose accuracy using weight and/or drug content. In studies that considered weight using adapted pharmacopoeial specifications, the percentage of halved tablets meeting these specifications ranged from 30% to 100%. Eighteen studies investigated bioavailability, pharmacokinetics or clinical outcomes following manipulations which included nine delayed or modified release formulations. In each of these nine studies the entirety of the dosage form was administered. Only one of the 18 studies was identified where drugs were manipulated to obtain a proportion of the dosage form, and that proportion administered. The five studies that considered patient perception found that having to manipulate the tablets did not have a negative impact on adherence. Of the 49 studies only two studies reported investigating children. This review yielded limited evidence to support manipulation of medicines for children. The results cannot be extrapolated between dosage forms, methods of manipulation or between different brands of the same drug.

INTRODUCTION

Many medicines given to children are used 'off-label' because the medicine has only been researched and authorised for adults. Often the dosage form (e.g., tablets, capsules, suppositories) is suitable for administration to adults but not to younger children (Waller, 2007). Age-appropriate formulations may not be commercially available to provide the wide range of doses required for neonatal and paediatric use (Olski et al, 2011; Fontan et al 2004; Nahata, 1999). In order to tackle these problems medicines are routinely modified, whereby the dosage form is physically manipulated with the aim of achieving the required dose for administration. Differing definitions of 'modification' and 'manipulation' have been used (EMA 2013, Ernest et al, 2012). In the context of this study, a manipulation is defined as the physical alteration of a drug dosage form for the purpose of extracting and administering the required proportion of the drug dose. This work does not consider manipulations done for convenience or due to patient preference.

The Pharmaceutical industry invests considerable time and financial resource in the development of products designed for accurate and appropriate drug delivery. Legislation, in the form of the European Union Paediatric Regulation (2007) was established to drive the development of appropriately licensed and formulated medicines for children, through a system of requirements and incentives. Simultaneously the World Health Organisation (WHO, 2007) spearheaded a global campaign to raise awareness and accelerate action to address the need for improved availability and access to safe, child-specific medicines for all children under 12 years of age. Similar legislation has been enacted in the US (Turner et al, 2014).

However, it will be some time before the influence of this legislation and campaign strategy is realized and suitably formulated medicines are made available for children. Even when age-appropriate formulations are marketed, the need for manipulations will remain as drug development is not able to take account of all the possible circumstances of drug administration.

Table 1 provides examples of the type of dosage form manipulation used with the aim of achieving the required dose. Although drug manipulation is an acknowledged feature of paediatric clinical practice (Nunn, 2003), and a quantitative description of the situation in the UK in 2011 has been described (Richey et al, 2013a), previous studies have noted that there is a lack of information available on the extent to which manipulated drugs are being used (Skwierczynski

& Conroy, 2008; Conroy et al, 2000). Manipulations, such as halving tablets to obtain two doses, are used as a cost reduction measure in some jurisdictions (Berg & Ekedahl, 2010; Gee et al, 2002; Fawell et al, 1999). In other vulnerable groups such as the elderly, those on intensive care and those receiving enteral feeds, manipulation is common to aid administration (Berg & Ekedahl, 2010; Gerber et al, 2008; Paradiso et al, 2002; Verrue et al, 2010). Whole tablets may be crushed and capsules opened and mixed with food or drinks to aid administration to children.

Manipulations are time consuming, may be inaccurate, and the effects on the stability and bioavailability of the drug may be unknown (Skwierczynski & Conroy, 2008). It is thus possible to inadvertently administer toxic or sub-therapeutic doses. Manipulations may also increase the risk of drug errors because calculations are required to determine an amount to be administered and dose calculation errors at the point of administration have been identified as the most common type of medication error in neonatal and paediatric patients (Chua, 2010; Conroy et al, 2007). Concerns about dose accuracy in other patient groups have also been highlighted (Berg & Ekedahl, 2010; Verrue et al, 2010).

This review focuses on manipulations conducted with the aim of obtaining the required dose. Given the lack of age appropriate doses or dosage forms for many drugs, the investigators are particularly interested in manipulations of drugs for paediatric and neonatal use. However, there may be situations where drugs relevant to paediatric practice are manipulated, for older patients. The aim of this systematic review is to establish the evidence base for drug manipulation to obtain the required dose.

METHODS

The systematic review protocol, including details of the iterative approach to developing the search strategy and refinement of a quality appraisal tool, has been previously published (Richey et al, 2012) The review was designed and completed with the support and advice of a steering group consisting of experts in formulation, research, medicine, pharmacy and nursing.

Eligibility criteria

This review excluded case studies, case reports and letters; it did not otherwise restrict on study design. Evidence was also taken from studies where drug manipulation was investigated without administration to patients as these laboratory-based studies considered the weight and/or drug

content of manipulated drugs. Studies investigating any drug, manipulated by any method were potentially eligible.

A hierarchy of outcomes was identified. The primary outcome was dose accuracy of the manipulated medicine as assessed by drug content assay or other relevant study specific methods such as weight. Secondary outcomes included: evidence of safety or harm (which the authors explicitly attribute to the manipulation); bioavailability, physical/chemical/microbial stability; patient experience of drug manipulation; tolerability/palatability/adherence (explicitly attributed to the manipulation); contamination of the areas of the manipulation/healthcare professional/patients/carer and any comparison of methods of manipulation used on similar dosage forms.

Manipulation of a medicine with subsequent administration of the entire dosage form was considered outside the remit of this review. An exception to this was tablets with a modified-release design. Where tablets have a modified-release design, crushing, splitting or dispersing of these tablets, may alter the bioavailability and safety of these tablets, even when the entire dosage form is administered. Studies that involved extemporaneous or compounding preparation within a pharmacy and those which were involved in the drug development process were excluded.

Information sources and searches

The Cochrane database of systematic reviews, MEDLINE (Internet interface PubMed), EMBASE, CINAHL and International Pharmaceutical Abstracts (IPA) databases were searched from inception of data base to August 2015. The review steering group and research and healthcare practitioners with expertise in medicines management were asked to provide references to any additional studies or unpublished data. The reference lists of included studies were checked for any additional eligible studies. The devising of the search strategy was complex as any drug or dosage form was potentially eligible. Furthermore manipulation to obtain the required dose does not have a standard term in databases of the medical and pharmaceutical literature therefore a list of free text descriptions for manipulation had to be identified. As the search strategy underwent a considerable review and revision process (Richey et al, 2012) a balance had to be made between the sensitivity and the precision of the search with the consequential risk that there may be studies that have not been identified. Therefore subsequent

narrower search strategies for three of the known manipulated drugs (omeprazole, captopril and warfarin) were devised and searches completed. The generic strategy has been described in the appendix of the published protocol (Richey et al, 2012). Initial searches were completed in August 2009; update searches were completed in August 2015.

Study selection and data extraction

Due to the considerable number of records identified by the generic search (39,762 hits) and the narrower drug-specific searches (4535 hits) an initial screen was undertaken by one reviewer (Richey et al 2012). A random sample of 5% the titles and abstracts was screened by a second reviewer to confirm the initial screening. Potentially eligible studies identified from the initial screen were independently considered and discussed by two reviewers and the full text of potentially eligible studies obtained. A third reviewer was available for any studies where agreement on inclusion could not initially be reached. Data for the included studies were extracted into data extraction tables by one reviewer, these were then independently assessed by the second reviewer and changes agreed. Drug specific searches did not yield any additional studies.

Quality assessment

An assessment of risk of bias of included studies was carried out at study, rather than outcome level using a bespoke quality assessment form derived from established checklists and supplemented with review specific criteria compiled by formulations, systematic review and healthcare professional experts (Richey et al, 2012). Two reviewers assessed studies independently and then discussed their decision-making to reach agreement on the quality criteria for the included studies. Overall quality ratings were then assigned to the studies using the symbols ++, + and – as described in Table 1. The authors, during the review processes, assessed the confidence/trust that can be placed on the outcomes of the studies. Thus in Table 1 considerable concerns" represents studies where a lot of risk of bias was apparent in the study design/methods or reported results/outcomes and meant that the study was considered as potentially unreliable. "Some concerns" indicates that some risk of bias in the design/methods was recognised that raised questions about the reliability of the reported results/outcomes. "With reasonable confidence" implies that the study design/methods are considered to have a lower risk of bias and the results/outcomes reported can be considered reliable.

Data synthesis

In order to capture as much data as possible that is relevant to clinical practice there was no restriction on study design, type of drug or method of manipulation. Accordingly, this review includes a heterogeneous set of studies. Because the studies were so heterogeneous, a narrative synthesis of the findings was used with no meta-analysis; the data from each study were extracted and tabulated, with studies grouped using the primary and secondary outcomes defined for this review. Results are generally presented descriptively

RESULTS AND DISCUSSION

Fifty studies were included and quality-assessed. Twelve (24%) studies were assigned a ++ quality rating, 30 (60%) studies a + rating and 8 (16%) a – rating (Table 2).

Forty-nine studies were identified that met the inclusion criteria for tablets that were crushed, split or dispersed. These included 24 studies that had outcomes that included an assessment of the weight of split portions and/or their drug content and 10 studies that compared different methods of manipulation. Five studies had acceptance outcomes and included patient issues such as patient experience, adherence, taste or tolerability; nine studies had bioavailability outcomes. Though adverse effects are reported in the bioavailability studies there were no studies that specifically considered evidence of the safety or harm of manipulating medicines.

Primary outcome: dose accuracy of the manipulated medicines – weight and/or drug content outcomes

The dose accuracy of manipulated medicines was assessed by different studies through weight, dissolution profiles and/or drug content outcomes. In the absence of pharmacopoeial tests to establish uniformity of split tablets at the time that many of these studies were undertaken, some authors devised tests adapted from the then current pharmacopoeial criteria for intact (whole) dosage forms. These criteria mimic those currently found in the British Pharmacopoeia (2016) where tablets bearing break-marks that allow subdivision to provide required dose can be assessed. The efficacy of the break-mark(s) must be assessed during the development in respect of uniformity of mass of the subdivided parts. The test is based on 30 randomly selected tablets

which are broken by hand; one part is taken from each of the subdivided tablets and weighed. Each part is individually weighed and the average mass calculated. Compliance is agreed if not more than 1 individual mass is outside the limits of 85% to 115% of the average mass and that individual mass is not outside the limits of 75% to 125% of the average mass.

There were 24 studies that assessed the physical characteristics of halved tablets; 18 studies halved tablets and used adapted pharmacopoeial criteria. It might be assumed that any split fragment of a tablet will contain the fraction of the initial content proportional to the ratio of the fragment weight: whole tablet weight. Analysis of mercaptopurine tablets showed this to be the case (Footitt, 1983). However analysis of fragments from levodopa tablets (Walker et al, 1978) showed a highly significant difference in the variation of percentage of drug content between quarters and tablets.

Table 3 provides a summary of eight studies that were identified as assessing halved or quartered tablets using pharmacopoeial-based outcomes for weight and/or drug content uniformity. There is no assurance that halving or quartering tables provides uniform split products

One study (Horn et al, 1999) halved and quartered tablets and used pharmacopoeial-based outcomes for weight and/or drug content uniformity to compare two tablet splitters. Seven products were examined. These were scored clonidine (branded and generic), scored captopril, unscored amlodipine, unscored atenolol, scored sertraline and scored carbamazepine. Tablets from lots of each product were halved and quartered and assessed by weighing within ±15%, USP specification. The data in Table 4 clearly indicate the difference in batch performance, that different quality of portions may be obtained from different splitters and that the variation in quarters is greater than that for halved tablets.

In another study Stimpel et al (1985) halved 34 products which were scored tablets and contained antihypertensive drugs. The tablets were described as displaying excellent divisibility (7 products), good divisibility (11 products), moderate divisibility (10 products) or poor divisibility (6 products). One commercial controlled release tablet containing isorbide-5-mononitrate tablet of 60 mg is scored and designed to allow division into 20mg and 40 mg segments (Stockis et al, 2002)

Splitting tablets into two or three parts was reproducible with relative standard deviations of 0.8 – 1.5 %. The presence of a score line does not guarantee an even subdivision of tablets (Footitt,

1983; Hill et al, 2009; Polli et al, 2003; Rashed et al, 2003; Rosenberg et al, 2002; Teng et al, 2002; Zaid & Ghosh, 2011; Horn et al, 1999) (Table 3). Uniform splitting was related to the hardness, friability and shape of tablets (Zaid & Ghosh, 2011).

Splitting was also related to tablet shape, size & hardness and the depth of score lines. Tahaineh & Gharaibeh (2012) split tablets (four products) with a knife and assessed the resulting half-tablets for weight uniformity using an adapted USP method. Split warfarin tablets were uniform in weight- which was attributed to hardness and the presence of a deep score line. Splitting digoxin, phenobarbital, and prednisolone tablet produced half tablets whose weights were highly variable (Tahaineh & Gharaibeh, 2012). Splitting sixteen tablet products with a knife was assessed by Helmy (2015) using weight and content uniformity of half tablets. Dose variation exceeded a proxy USP specification for more than one-third of sampled half tablets of bromazepam, carvedilol, bisoprolol, and digoxin. Drug content in half tablets appeared to be due to weight variation due to fragment or powder loss during the splitting process. Tablet size, shape, hardness and presence of score lines were important variables. Quality control standards, other than mass uniformity and drug content may be used to assess the physical quality of manipulated tablets. Vranic & Uzunovic (2008) found that scored whole and halved tablets of four lisinopril products met Ph Eur adapted specifications for crushing strength, friability, disintegration time and mass uniformity. Costa et al (2000) halved and quartered three products containing captopril finding their hardnesses ranked as whole > halved > quartered tablets.

A variety of studies has extended splitting to include quartered tablets. The studies of Tuleu et al (2005) and Horn et al (1999) are discussed in Table 3 and below. Costa et al (2000) extended their studies into three captopril products and devised a divisibility assay value which was defined as the percent standard deviation divided by mean half or quarter weights, in effect a relative standard deviation. Values were 7.7. 5.8 and 8.3% for halves and 15.0, 8.8 and 16.9% for quarters for the three captopril products indicating decreased consistency of weight for quartered compared with halved tablets. In another study, Walker et al (1978) quartered tablets and considered that two products, each containing levodopa, showed no significant difference in weight variation between whole tablets and quarters whilst another levodopa product and a sulphamethoxypyridazine tablet showed significant difference in weight variation between whole tablets and quarters. For one of the levodopa products, significant difference in percentage content between tablets and quarters implied less homogeneity of drug distribution in un-

quartered tablets (Walker et al, 1978).

Eight studies (Costa et al, 2000; Erramouspe & Jarvi, 1997; Kayitare et al, 2009; Mandal, 1996; Shah et al, 1987; Simons et al, 1982; Stockis et al, 2002; Tuleu et al, 2005) used dissolution profiles to assess halved or segmented tablets. Each study identified differences in dissolution profiles between halved and intact tablets, and, with the exception of the work of Costa et al (2000), considered tablets with a modified-release mechanism. This latter study, examining three captopril products demonstrated that halving and quartering the tablets increased the speed of dissolution for the three tablets (Costa et al, 2000). Halved or quartered nifedipine modified release tablets had faster dissolution profiles than intact tablets (Tuleu et al, 2005).

Dissolution profiles of tablet fragments of Isorbide-5-mononitrate 60mg tablets differed by 10% or less relative to intact tablets (Stockis et al, 2002). Mean cumulative dissolution profiles of extended release methylphenidate tablets showed significant differences between halved and whole tablets from the same manufacturers and between halved brand and whole generic tablets (Erramouspe & Jarvi, 1997). Comparing the release of three aspirin products (sustained-release aspirin 800mg, , aspirin 325mg, extended-release aspirin 650mg, microencapsulated particles), Mandal (1996) showed that the dissolution rate of the split tablets of the 800mg tablets was significantly higher than that for whole tablets although the other tablets had similar drug release profiles over time with whole and split tablets. Brands of theophylline 300mg controlled-release had significantly different dissolution profiles between whole and half tablets in simulated gastric fluid and simulated intestinal fluid (Shah et al, 1987). Dissolution from halved sustained release theophylline 100mg tablets was significantly higher than from whole tablets (Simons et al, 1982)

Kayitare et al (2009) developed a novel fixed dose combination tablet, containing 300mg zidovudine and 160mg lamivudine, for paediatric HIV patients to allow easy breaking into a maximum of 8 subunits. The intact tablets and their subunits disintegrated within 20 s and in dissolution tests, > 95% of each drug was released after 30 min.

Tablet shape Outcomes

Six studies (Helmy, 2015; Hill et al, 2009; Polli et al, 2003; Rosenberg et al, 2002; Teng et al, 2002; Verrue et al, 2010) that included tablets which were not flat and round but were alternatively shaped (e.g., trapezoid, octagon, shield-shaped, ovoid-rectangular). Halves of these

tablets did not meet the specified USP weight specification. Another study (Zaid & Ghosh, 2011) showed that of 4 products examined, only one film-coated oblong shaped tablet passed the Ph Eur specification for weight uniformity of scored tablets whereas three other oblong-shaped tablets (one film-coated) did not. A square captopril product (Costa et al, 2000) subdivided into halves and quarters, met weight variation limits whereas two circular tablets did not, despite all three products having crossed grooves on one of their faces.

A novel fixed dose combination tablet, containing 300mg zidovudine and 160mg lamivudine, was developed for paediatric HIV patients (Kayitare et al, 2009). The novel product had a rectangular shape (22.4 mm long, 11.2 mm wide) with multiple score lines (depth 0.89 mm, angle 100º) to allow easy breaking into a maximum of 8 subunits. The tablets were subdivided along the score lines into 1/2 (along shortest axis of the tablet), 1/4 (along shortest axis), 3/4 (along shortest axis) and 1/8 tablet. The average weights of the smallest pieces (1/8 of a tablet) were within the 85–115% range of the average mass limits as required by EP.

Tablet dispersions

Apart from splitting tablets, dispersing tablets in water and taking an aliquot of the resulting suspension is used clinically to obtain reduced doses. Two studies assessed this practice using prior crushing and dispersion of nifedipine tablets (Tuleu et al, 2005) or dispersing dispersible aspirin 75 mg tablets (Broadhurst et al, 2008). Crushed nifedipine 10 mg modified release tablets were suspended in 10ml water. Samples were extracted using 1 or 5 ml oral syringes. Doses ranging from 2.9 to 5.7 mg and 0.6 to 1.5 mg were obtained using 5 ml and 1 ml syringes respectively compared to theoretical doses of 5 and 1 mg (Tuleu et al, 2005). Reproducing clinical practice, Broadhurst *et al* (2008) dispersed dispersible aspirin tablets in 10 mL water and found that, irrespective of dispersion time, the samples taken from the base of a 30 mL container were consistently closer to the intended dose (51-95% of the intended dose) compared with those taken from the highest zone at 8 mL mark of the container (23-80% of the intended dose), with a trend for the dose measured to decrease as the zones ascended up the beaker.

Secondary outcomes: comparison between weight loss, manipulation methods, bioavailability, effectiveness, patient experience, adherence/compliance

Comparison between manipulation methods:

Twelve studies were identified that compared methods of manipulating tablets (Table 5). Overall the use of a commercial tablet splitter (by some authors termed tablet cutter) was more accurate than other splitting methods such as scissors or knives, or splitting manually.

Weight loss during manipulation

Ten studies quantified the weight loss observed during the halving or quartering of tablets. Mean weight losses for mercaptopurine tablets varied from 0.24% to 2.64% depending on the operator, although individual losses as high as 11.7% were recorded (Footitt, 1983). Using tablet splitters, mean weight losses of between 0.1% and 1.3% were recorded for six commercial products (Hill et al, 2009) and 0% to 1.9% for 12 commercial products (Polli et al, 2003) although in the latter study a maximum weight loss of 7.3% was noted for one product and weight loss was not considered to be an indicator of the uniformity of split. Similar mean weight loss ranges were reported as 0.02% to 1.5% for 16 products (Helmy, 2015) 0.1% to 1.2% when halving or quartering captopril tablets (Costa et al, 2000) and 0.3% to 0.9% when quartering tablets made to a model formulation (van Vooren, 2002) where a maximum weight loss of 6.8% was recorded. Although a mean loss of 1.1% was noted for the loss following splitting of hydrochlorothiazide tablets (McDevitt et al, 1998), the range of loss varied from 0% to 19.4%. Recovery (in comparison to weight loss) of misoprostol tablets quartered by a pill splitter and by hand were 96.6 ± 2.8% and 99.0 ± 1.3% respectively (Williams et al, 2002). The most comprehensive study (Verrue et al, 2010) compared three routine splitting methods (grouped as a splitting device, scissors or by hand, and a kitchen knife) to half or quarter eight commercial products. Statistically, the splitting device only produced the lowest weight loss of the three methods for the digoxin tablets when a mean weight loss of 1.4% was recorded as against 7.6% and 5.4% for the scissors/hand and kitchen knife respectively. For five products (warfarin, levodopa/carbidopa each halved; fenprocoumon, methylprednisolone and lisinopril, each quartered) the results obtained by the splitting device or scissors/hand) were statistically indistinguishable. Overall the splitting device produced the lowest weight loss but even with this method a weight loss as high as 26.6% was recorded when halving commercial metformin tablets. For digoxin tablets maximum weight loses of 37.0 and 37.6% were recorded using the scissors/hand and knife respectively (Verrue et al, 2010). Following subdivision of a novel fixed dose combination tablet capable of subdivision into 8 sub-units, weight loss was low (<0.4%) and independent of the subunit size (Kayitare et al, 2009).

These losses compare with those described by Green et al (2010) who discussed potential USP standards for the subdivision of scored tablets and indicated that to comply the mean loss of mass should not exceed 3%

Bioavailability

There were nine studies identified, all with adult participants, where modified-release tablets were split or crushed but, although the whole dose of the tablet was administered, the outcomes were considered relevant due to the potential to alter the drug release characteristics of the formulation Eight of these nine eligible studies were sustained-release formulations and one study used an enteric-coated formulation.

Crushing of pentoxfylline extended-release (Trental) 400mg and 600mg tablets (Cleary et al, 1999) and theophylline matrix sustained-release (Theo-Dur) 300mg tablets (MacKintosh et al, 1985) did not significantly change the bioavailability, though the time taken to reach peak concentration was shorter with crushed tablets than with intact tablets.

Five studies halved modified release tablets. No differences were found in bioavailability for halved and intact theophylline sustained-release (Theo-Dur) 100 mg tablets (Simons et al, 1982) and 300 mg tablets (Fagerström, 1980). One study used theophylline slow-release anhydrous (Uniphyllin®) 400 mg tablets (Primrose et al, 1983) and peak drug levels were significantly higher with halved than with intact tablets. Two studies used verapamil sustained-release 240 mg matrix tablets (McEwen et al, 1989; Moreland et al, 1989) and both studies found no differences in bioavailability for halved and intact tablets. One study involved cutting isosorbide-5-mononitrate tablets into thirds and found no significant differences in bioavailability though maximum peak concentration was higher with the trisected tablets than with intact tablets (Stockis et al, 2002). Ferron et al (2003) crushed enteric-coated tablets (pantoprazole 40 mg) and found that the resultant suspension was 25% less bioavailable than the whole tablet.

Two other studies were identified. There was no significant difference in pharmacokinetic parameters in a bioavailability study using adults between Duovir® and a novel fixed dose combination tablet, containing 300mg zidovudine and 160mg lamivudine, intended for paediatric HIV patients (Kayitare et al, 2009). Corbett et al (2010) manipulated a product to obtain a proportion of the original dosage form. This involved 18 HIV-infected children who received quartered, halved or three quartered generic tablet multiples of lamivudine (3TC) 300mg,

stavudine (d4T) 80 mg and nevirapine (NVP) 400 mg or a generic liquid or trade liquid in a crossover study. There was no significant difference in bioavailability between the different formulations and the time to maximum concentration was delayed for d4T and 3TC for the manipulated tablets compared with the liquid formulations.

Evidence of safety or harms, adverse effects:

Adverse effects considered to be related to the drug manipulation were relevant to this review. There were marginally more adverse effects reported in five of the nine bioavailability studies of modified release tablets with nausea/vomiting (Cleary et al, 1999; Primrose et al, 1983) and headache (Cleary et al, 1999; Primrose et al, 1983; Stockis et al, 2002) with crushed or split tablets than intact tablets. Two studies reported excellent tolerability with both split and intact tablets (Kayitare et al, 2009; Moreland et al, 1989). The one study which split enteric-coated tablets found both treatments to be well tolerated and considered the adverse effects reported to be related to nasogastric tube insertion rather than drug-related (Ferron et al, 2003). The number of adverse effects reported was small and conclusions cannot be drawn about whether manipulated medicines had more associated adverse effects.

Patient experience:

One study considered the experiences of children taking an oral solution compared with those taking a dispersion of crushed prednisolone tablets (Lucas-Bouwman et al, 2001). Taste assessed by visual analogue scores was significantly better for the oral solution than for the crushed tablets. Nine of the 78 children in the study also withdrew due to repeated vomiting while taking the crushed tablets.

There were a further five surveys identified that assessed adult participants' experiences of splitting tablets. Three studies used the same questionnaire or an adapted version of it for tablets split with a tablet splitter. Carr-Lopez et al (1995) surveyed 233 patients (all 55 years old, or older) splitting lovastatin, Gee et al (2002) surveyed 454 patients (average age 66 years old) enrolled in a statin splitting programme and Fawell et al (1999) surveyed patients (median age 65 years old) splitting fosinopril. Across the three studies, a small percentage of respondents (4% (Fawell et al, 1999), 6.3% (Lopez et al, 1995), 7% (Gee et al, 2002)) felt that using the tablet splitter had an effect on their willingness to take the drug as prescribed. Some respondents (7% (Gee et al, 2002), 6% (Fawell et al, 1999), 14% (Lopez et al, 1995)) reported having missed

more split tablet doses in a month when compared to other medicines where the tablet did not have to be halved. One study surveyed 99 patients, the majority of whom were 50 years old or older, with hyperlipidaemia who used a tablet splitter and found that more than 90% agreed that they found that tablet splitting had no t affected their willingness to take their medication and that 90% disagreed that they had missed more medication doses because of tablet splitting (Choe et al, 2007). In a survey of 28 patients, described as outpatient veterans, splitting lisinopril (method of splitting not reported) (Rindone, 2000), tablet splitting was bothersome 'most' of the time for 25% of participants; for 'some' of the time there were more than two pieces of the tablet following splitting for 54%, of the participants.

Adherence:

Three identified studies considered aspects of adherence for 57 participants splitting fosinopril tablets (Fawell et al, 1999) and 111 (Choe et al, 2007) or 3787 participants splitting statin tablets (Parra et al, 2005) with a tablet splitter. There were no differences in adherence between those splitting tablets and those taking whole tablets whether self-reported (Choe et al, 2007), measured by tablet counting, refill history and self-reporting (Fawell et al, 1999) or prescription refills (Parra et al, 2005). A fourth study, which included patients with schizophrenia or schizoaffective disorder splitting risperidone, found that adherence increased with tablet splitting (Weissman & Dellenbaugh, 2007).

Effectiveness

Tablets containing a statin have been frequently given as split tablets and clinical assessment made. No significant difference in total cholesterol, HDL, LDL or triglycerides between baseline levels and post splitting levels were found following split atorvastatin, simvastatin or pravastatin (Choe et al, 2007). In another study no significant difference in total cholesterol and triglycerides pre and post tablet splitting but significant small increases in HDL, AST and ALT and decreases in LDL were noted following the administration of split atorvastatin, lovastatin or simvastatin tablets (Gee et al, 2002). No significant difference in LDL between whole and halved tablets was found following administration of 5, 10, 20, or 40 mg simvastatin (Parra et al, 2005). Overall – significant decreases in total cholesterol and LDL pre and post splitting of simvastatin or atorvastatin (doses not specified) with half tablet dosing as effective as whole tablet taking (Duncan et al, 2002). For other classes of drugs, no significant difference in mean systolic and

mean diastolic blood pressure with tablet splitting of lisinopril was measured (Rindone, 2000) and no change in psychiatric or non-psychiatric admission rate was noted following the administration of splitting Risperidone tablets (Weissman & Dellenbaugh, 2007).

Direct observational study from the literature:

Mercovich et al (2014) reported observations of manipulation of solid oral dosage forms during medicine rounds in aged care facilities. From 160 observations across six medication rounds, 29 residents had a total of 75 medications modified by the nursing staff prior to administration, with 32% of these instances identified as inappropriate. Methods used for crushing and administration resulted in drug mixing, spillage and incomplete dosing. Staff reported adequate resources but a lack of knowledge on how to locate and use resources was evident. Mercovich et al (2014) concluded that improved staff training on how to use available resources was needed to reduce the observed high incidence of inappropriate modifications.

Non-tablet studies:

There were no studies identified through the systematic review which considered the manipulation of capsules, sachets, liquids for oral administration, nebuliser solutions, intravenous injections and injections for subcutaneous administration, enemas or transdermal patches. There was one study (Kim et al, 2005) identified through the systematic review which considered the manipulation of suppositories. This study asked anaesthesiologists to split paracetamol suppositories using the technique they would use in practice. This resulted in wide variation from the intended dose: intended dose 40 mg (range 30-78 mg), 53 mg (range 27-79 mg), 60 mg (range 47-82 mg), 80 mg (range 38-92 mg), 162 mg (range 112-250 mg), and 217 mg (range 113-259 mg)). The study concluded that the lack of accuracy and precision was a reason to use unaltered suppositories.

GENERAL DISCUSSION

This review has demonstrated that there is a dearth of evidence to support the widespread practice of drug manipulation in children. Where evidence was located it almost universally related to the manipulation of tablets for treating adult patients, with only one study which used any other dosage form. Only two studies had child participants (Corbett et al, 2010; Lucas-Bouwman et al, 2001) and, in one of these (Lucas-Bouwman et al, 2001), the taste scores of crushed tablets were considered. In the other study (Corbett et al 2010), the formulations were

well tolerated and 10% of children commented on the enjoyable taste of the liquid formulations.

Splitting tablets was frequently unreliable. The clinical consequences of this finding are difficult to estimate but are likely to be important in medicines with a narrow therapeutic index. When splitting tablets, it is reasonable to expect that the weight or drug content of segments will vary no more than would be expected for intact tablets. Pharmacopoeial standards for intact tablets are well established and usually include tests to establish uniformity of weight or content. When many of these studies were undertaken there were no pharmacopoeial standards for the quality of segmented tablets. Most authors adapted the criteria and methodology for testing the uniformity of intact tablets. Whilst the detail of tests may vary they are essentially ensuring low variability of weight and/or drug content between dosage units and the absence of outliers. In 2002 the European Pharmacopoeia presented pharmacopoeial standards for the subdivision of scored tablets. These standards, which marked the first time this type of pharmacopoeial requirement was established, have been subsequently reviewed and revised (Green et al, 2010). The use of such standards within other pharmacopoeias has been discussed and a stimulus article discussed why standards should be included in the USP (Green et al, 2010) and are currently found in, for example, the British Pharmacopoeia (2016). Here, the efficacy of the break-mark(s) must be assessed during the development in respect of uniformity of mass of the subdivided parts where the selected tablets were broken by hand. Many of the citations in this study utilized tablet splitters or knives in the subdivision of tablets and their use has been broadly scientifically unestablished.

The results identified in this review varied but the majority of studies suggest a lack of uniformity of segment weight or drug content when splitting tablets into halves and even greater variation when splitting in to quarters. Such lack of uniformity is unacceptable for intact ‘whole’ tablets. When weight and content uniformity were tested, of concern is that when weight uniformity was compliant content uniformity often was not, suggesting uneven drug distribution within some tablets. Although there were few comparisons there would appear to be differences in variability of segments between different tablet strengths and between branded and generic tablets. The clinical importance of unequal splitting of tablets cannot be estimated: Only one study was identified that reported bioavailability after a proportion of a tablet (an antiretroviral) had been administered to children. In all other bioavailability studies relevant to this review sustained release tablets were split or crushed and the whole dose administered. Though there

were only nine studies using ten sustained release products there is an indication from four studies that there may be an effect on the intended modified drug release mechanism and consequently on bioavailability following manipulation. Reduction in the time to reach peak concentration was the outcome predominantly affected by the tablet being halved or crushed prior to administration. The modified release mechanism is important in determining whether the release characteristics will be altered upon splitting.

Although results were inconsistent, tablets split using a tablet splitter were more likely to yield segments that had split more accurately than those split using methods including scissors, knife or manual splitting. Similarly scored tablets tended to provide segments closer to the intended weight. While these results can only be considered applicable directly to the products in the studies involved they do nonetheless suggest that use of a commercial tablet splitter and scored tablets may be beneficial if tablets must be split.

In general the segmenting of tablets does not appear to affect adherence in adults although the evidence is based on a limited number of drugs. We found only one study that had paediatric participants and this considered the taste and tolerance of crushed tablets rather than other aspects of manipulation (Lucas-Bouwman et al, 2001). This study concluded that the oral solution was better tolerated than the crushed tablets. The only study of a dosage form other than tablets showed substantial variation in size of the segments cut from paracetamol suppositories by anaesthetists leading the authors to conclude that such suppositories should not be split.

This study sought the evidence for an area of medical and nursing practice that could potentially include any drug and/or dosage form and therefore may be limited by its complex nature. We had specified that the only study type restrictions were on case series/studies, consequently included studies were heterogeneous not only in design and quality, but in terms of types of manipulations, drug types, dose forms, participants and outcomes investigated. Letters and case series excluded from this review may have included some of the anecdotal information on manipulation of dosage forms other than tablets and suppositories. It is also possible that clinical outcomes have been reported as case series or letters. For example, a letter suggesting satisfactory outcomes with split tablets of bosentan used for children with pulmonary hypertension followed an article and letter criticising the lack of information provided on the method of administration of bosentan tablets to young children (Rosenzweig et al, 2005).

Subsequently, regulatory submissions have included a formulation of bosentan tablets which is a quadrisected dispersible tablet containing 32 mg of bosentan to be dispersed in a teaspoon with water (EMA Report, 2012). Such regulatory reports were also not the subject of this review and individual summaries of product characteristics were not searched for information.

What emerges from this review is that there is little published information on manipulation of dosage forms to achieve the required dose and further work is needed to support what is a common practice (Berg & Ekedahl, 2010). The majority of the included studies related to tablets and it is difficult to draw firm conclusions from the outcomes since the products and method of manipulation varied considerably as did the outcomes in terms of compliance with standards for variability derived from those for intact tablets.

An optimum requirement would be studies where a drug was manipulated to obtain the required dose, administered to participants and outcomes reported. There were no studies identified which used this approach in children, the nearest being the study of Kayitare et al (2009) who developed a novel fixed dose combination tablet capable of subdivision to subunits containing a dose suitable for each 5 kg body weight. Biological characteristics were however established in adults.

Each formulation of each drug may provide different results when manipulated. Consequently the planning of future research becomes challenging. This may be aided by the identification of drugs which frequently require manipulations and represent a higher risk if an over or under dose is administered (such as those with a narrow therapeutic index (Shah et al, 2010) or where the adverse effects of a manipulated drug might be a concern or by the recognition of patient groups where a number of the commonly prescribed drugs may require manipulation. The use of standardised research methodologies would help to build a more comprehensive resource of evidence relating to drug manipulation to aid clinical decision-making.

No studies were identified that considered physical/chemical/microbial stability or contamination of the areas of manipulation.

Subsequent to the completion of data searching in August 2015, two publications were noted that considered drug manipulation in children. Mistry and Batchelor (2016) highlighted the need for support knowledge around the acceptability of age-appropriate medicines and presented an algorithm to aid in formulation selection based on age range. Andersson et al (2016) concluded

571 that tablets larger than 8 mm could be split only once to achieve an approximate half dose for
572 paediatric use. The authors could not recommend that tablets be split more than once due to a
573 lack of weight uniformity of the part tablets after splitting. Both Mistry and Batchelor (2016) and
574 Andersson et al (2016) concluded that more age-appropriate dosage forms, including small
575 tablets, should be available to children. Andersson et al (2016) considered that non-functional
576 score lines should be avoided since both patients and health professionals falsely believed that a
577 score line indicates the possibility of dividing the tablet in two equal parts.

578 A change in the manufacturing process of 10 mg hydrocortisone tablets, where an increased
579 compression was used, led to reports (Saimbi et al, 2016) that the newer, harder tablets were
580 more difficult to manipulate. Tablets were either manipulated by breaking along score lines to
581 produce halved or quartered segments or 2mg doses were prepared by dispersing crushed tablets
582 in 10 mL of water and taking a 2 mL aliquot; crushing was accomplished using a spoon onto a
583 plate or a commercial crushing device (Saimbi et al, 2016). The harder tablets showed a better
584 accuracy of split with weight ranges of 41 – 55% and 17 – 35% for halves and quarters
585 respectively compared with weight ranges of 29–70% and 12–42%) for the less hard tablets.
586 Conversely, the 2 mg dosing accuracy was better for both sets of tablets. The use of spoon / plate
587 or the commercial device led to mean doses of 1.3 mg and 1.9 mg for the harder tablets and 1.7
588 mg and 2.1mg for the less hard tablets. The authors concluded that parents or carers should be
589 advised to crush the tablet into a fine powder, where possible, to improve dosage accuracy.

590 Nidanapu et al (2016) used caregivers to split tablets containing anti-epileptic drugs (phenytoin
591 sodium, sodium valproate, carbamazepine and phenobarbitone) intended for adults but
592 prescribed to paediatric patients. The caregivers performed the same splitting process that they
593 normally followed in their homes. 168 caregivers participated and 1098 split tablets were
594 analysed. In total 49.0% of the split parts were above the specified limit of the 2010 Indian
595 Pharmacopeia (IP) for acceptable percentage weight deviation. 41.5% of the split parts were
596 outside a specification for drug content. 253 split parts were outside the acceptable content
597 uniformity range of >85% and <115%.

598 It is clear from the results in this paper that recommendations for the manipulation of products
599 for children have to be advised by practices used in adults. Earlier iterations of the work
600 described in this paper, in conjunction with other studies (Richey et al, 2012, 2013a, 2013b) were

used to develop a guideline (Manipulation of Drugs Required in Children (MODRIC)) for health professionals with recommendations for the Pharmaceutical Industry and regulators. Such recommendations include the need for the Pharmaceutical Industry to note the lack of evidence relating to the manipulation of medicines for the purposes of achieving a suitable dose for administration to children and to support practitioners in their requests for information around manipulations of medicines by recognising that children may require a range of doses that require manipulation of adult dosage forms. Regulatory authorities must recognise that manipulation is being undertaken in the paediatric population despite the lack of evidence and encourage the industry to provide evidence where reasonable and available.

CONCLUSION

Extensive searching yielded limited evidence to support the widespread clinical practice of manipulation of drugs with the aim of achieving the required dose. There is a need to conduct research about the impact of manipulation for dosage accuracy in all age groups. Future research should prioritise areas such as drugs with a narrow therapeutic index or clinical areas such as neonates or paediatric intensive care that are high risk because of manipulations, and should conduct standardised assessments of those manipulations. Where manipulations are a predictable use of a licensed product the effects of manipulations need to be included in drug development programmes.

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837 Table 1: Criteria used to describe the three quality levels used in this study

Quality level	Criteria
++	Included studies where the reported methods and subsequent results and conclusions could be considered (with reasonable confidence) not to be biased. The process of the drug manipulations was at least adequately described.
+	included studies where there were some concerns about the reported study methods or the methods were not reported with enough detail to permit sufficient assessment
-	included studies where there were considerable concerns about the reported methods or there was insufficient reporting of the methods for them to be assessed

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839

840 Table 2. The quality ratings of the reported studies

Reference	Quality	Reference	Quality
Boggie et al (2004)	+	McEwen et al (1989)	-
Broadhurst et al (2008)	+	Mercovich et al (2014)	++
Carr-Lopez et al (1995)	+	Moreland et al (1989)	+
Choe et al (2007)	+	Parra et al (2005)	-
Cleary et al (1999)	++	Polli et al (2003)	++
Cook et al (2004)	++	Powers & Cascella (1990)	+
Corbett et al (2010)	+	Primrose et al (1983)	+
Costa et al (2000)	+	Rashed et al (2003)	+
Duncan et al (2002)	+	Rindone (2000)	+
Erramouspe & Jarvi (1997)	+	Rosenberg et al (2002)	+
Fagerström (1980)	-	Shah et al (1987)	+
Fawell et al (1999)	+	Simons et al (1982)	+
Ferron et al (2003)	++	Stimpel et al (1985)	+
Footitt (1983)	+	Stockis et al (2002)	+
Gee et al (2002)	-	Tahaineh & Gharaibeh (2012)	++
Habib et al (2014)	++	Teng et al (2002)	+
Helmy (2015)	++	Tuleu et al (2005)	+
Hill et al (2009)	++	van Riet-Nales et al (2014)	++
Horn et al (1999)	+	van Vooren (2002)	-
Kayitar et al	++	Verrue et al (2010)	+
Kim et al (2005)	-	Vranic & Uzunovic (2008)	+
Lucas-Bouwman et al (2001)	-	Walker et al (1978)	+
MacKintosh et al (1985)	+	Weissman & Dellenbaugh (2007)	+
Mandal (1996)	+	Williams et al (2002)	-
McDevitt et al (1998)	+	Zaid & Ghosh (2011)	++

841

842 Table 3 Studies which halved or quartered tablets and used pharmacopoeial-based outcomes for weight and/or drug content uniformity

Drugs	Outcomes summary	Ref
One scored and one unscored product	Both products did not meet the BP uniformity of weight specification	Footitt (1983)
Six products 2 scored, oblong, non-coated, scored 2 oval, film-coated, unscored 1 circular, non-coated, scored 1 oval, non-coated, unscored	43/180 (23.9%) of half tablets were outside of USP specification for drug content. 23/180 (12.8%) of half tablets were outside USP specification for weight 22.2% (20/90) of scored tablets were outside the USP specification for drug content compared with 25.6% (23/90) unscored tablets 11.1% (10/90) of scored tablets were outside the USP specification for weight compared with 14.4% (13/90) unscored tablets	Hill et al (2009)
Twelve products 2 oval, unscored 1 oval, scored 3 round, scored 1 trapezoid, unscored 1 unscored 2 oblong, scored 1 shield-like, unscored 1 round/spherical, unscored.	8/12 halved products passed adapted USP weight uniformity test; 6 out of these 8 products were scored. 4/12 did not pass adapted USP uniformity test; lovastatin, Each of these 4 products was unscored.	Polli et al (2003)
Five products Three unscored Two scored on one side	Tablets halved. Only one of the two scored products met the USP weight specification.	Rashed et al (2003)
22 products 1 ovoid-rectangular, scored 5 capsule-shaped, scored 1 round, unscored 8 round, scored 1 oblong, scored	Halved tablets. 6 scored and 1 unscored product met the USP weight specification including the extended release product 13 scored and 2 unscored products did not meet the USP weight specification;	Rosenberg et al (2002)

1 elliptical, scored 1 biconvex, scored, extended-release 1 modified-oval, scored 2 oblong, unscored 1 shield-shaped, scored		
11 Products 3 oval, not flat, unscored 1 oval, not flat, scored 2 not oval, not flat, scored 1 not oval, flat, scored 4 not oval or flat, unscored	Halved tablets. 3 products met the USP weight variation specification; one product was scored and two were oval 8 Products did not meet USP weight variation specification; of these three were scored and two were oval	Teng et al (2002)
One sustained-release round unscored, product	38/40 tablet halves deviated from the percentage deviation allowed by the European Pharmacopoeia for uncoated or film-coated tablets of ≤80mg). There was wide variability for half and quarter tablet weights	Tuleu et al (2005)
14 scored products were studied 4 products were oblong of which 2 were film coated. 10 products were round	Halved tablets Only one film coated, oblong product met the European Pharmacopoeia specification for weight uniformity of scored tablets. The remaining 13 products A following splitting had fragments outside of the 85-115% range of the average mass Only four tablets following splitting (one film coated oblong; one oblong and two round had no fragments outside of the 75-125% range of the average mass	Zaid & Ghosh (2011)

843

844 Table 4. The influence of cutter on the halving and quartering of 7 tablet products on the % halves or
845 quarters weighing within ±15%, USP specification. 3 lots of each product were used and the range across
846 these lots is indicated (Taken from Horn et al, 1999)
847

	% halves or quarters weighing within ±15%			
	Halves	Quarters	Halves	Quarters
Product	First cutter;	First cutter;	Second cutter	Second cutter
clonidine (brand	52.5-100%	43.8-60%	85-90%	57.5-71.3%
clonidine (generic)	47.5-70%	37.5-45%	30-78.9%	25.0-48.8%
Captopril	58.3-95%	37.5-55%	95-100%	26.3-36.1%
Amlodipine	77.5-85.7%		76.9-90.5%	
Atenolol	62.5-95%		27.5-35%	
Sertraline	100%		90-100%	
Carbamazepine	87.5-92.5%		60-80%	

848 Table 5: Summary of the twelve studies that compared the splitting of tablets using different techniques

Observations	Ref
8 products were examined. Tablets split with a tablet splitter had significantly lower deviation from theoretical weight and significantly less weight loss than those split by scissors (unscored)/hand (scored) or with a kitchen knife. There was no significant difference in weight between the scissors/hand and the kitchen knife. There was significantly less weight loss with the scissors/hand than with the kitchen knife.	Verrue et al (2010)
A razor blade based cutting apparatus resulted in quarters where a large proportion were outside acceptable limits for uniformity of weight; non-uniformity was more marked with tablets broken by hand	Walker et al (1978)
Of 11 products halved with a razor blade, 3 passed USP uniformity of weight specification (2 unscored; 1 scored) and 8 failed ((5 unscored; 3 scored). 3 of the scored products which failed the uniformity specification when split with a razor blade, also failed when split by hand	Teng et al (2002)
Two commercial splitters were examined for halving and quartering tablets of 6 different drugs. Neither splitter yielded consistent results for tablet quarters or halves.	Horn et al (1999)
No significant difference between 100 unscored tablets halved with a tablet splitter and 25 tablets of the same drug which were split by hand	Boggie et al (2004)
Halves of round, film coated, unscored tablets, halved with a tablet splitter showed that 16% had a deviation of >15% from the theoretical weight compared with 58% of tablets were split with a kitchen knife	Cook et al (2004)
33% of manually halved round, scored tablets but 40.2% tablet splitter halved tablets and were within 5% of the ideal weight	McDevitt et al (1998)
2 methods of crushing whole tablets for nasogastric tube administration (pestle/mortar and between medicine cups) and dispersing whole tablets showed significant differences in the amount of drug delivered. Suspending the drug in the syringe delivered 18% more drug than crushing with medicine cups and 36% more than crushing with pestle and mortar.	Powers & Cascella (1990)
No significant difference in mean fragment weight was found between round unscored tablets quartered with a tablet splitter or manually cut with a razor blade. There was a significantly greater variance within the group produced from the tablet splitter than that quartered with the manually split tablets.	Williams et al (2002)
Flat, round, cross-scored tablets were manually halved and quartered, using four different tablet orientations or split using a knife. Fracturing to halves, the score-up orientation gave the lowest residual variance. The score-down orientation and the score-up knife halved tablets had the lowest person variability. The score-down break had significantly higher variability than for score-up break or score-up knife orientations for quartered tablets	van Vooren (2002)
Tablets (round, flat, uncoated) were divided by hand or using 6 different proprietary tablet splitters or a kitchen knife. Only hand split half-tablets complied with weight requirements	van Riet-Nales et al (2014)

A tablet splitter was superior to manual splitting in halving scored salbutamol tablets. Drug content variation in half-tablets appeared to be attributable to weight variation occurring during splitting.	Habib et al (2014)

849

WHO harmonised dose schedule for HIV drugs requires **half** tablet doses

Manipulation of dosage forms is often required to provide accurate doses for children

Systematic literature review

49/50 relevant papers referred only to tablets

Limited evidence of accurate dosing; cannot extrapolate between dosage forms, methods of manipulation or different brands of same drug.