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SYSTEMATIC REVIEW AND META-ANALYSIS

A systematic literature review of LASA error interventions

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Aims: The aim of this systematic review was to explore and evaluate the efficacy of interventions to reduce the prevalence of look-alike, sound-alike (LASA) medication name errors.

Methods: We conducted a systematic review of the literature, searching PubMed, EMBASE, Scopus and Web of Science up to December 2016, and re-ran the search in February 2020 for later results. We included studies of interventions to reduce LASA errors and included randomized controlled trials, controlled before-and-after studies, and interrupted time series. Details were registered in Prospero (ID: CRD42016048198).

Results: We identified six studies that fulfilled our inclusion criteria. All were conducted in laboratories. Given the diversity in the included studies, we did not conduct a meta-analysis and instead report the findings narratively. The only intervention explored in RCTs was capitalization of selected letters ("Tall Man"), for which we found limited efficacy and no consensus.

Conclusions: Tall Man lettering is a marginally effective intervention to reduce LASA errors, with a number of caveats. We suggest that Tall Man gives rise to a "quasi-placebo effect", whereby a user derives more benefit from Tall Man lettering if they are aware of its purpose. Keywords: (on scholar one).

KEYWORDS
confusion errors, drug nomenclature, look-alike, name confusion, sound-alike

1 | INTRODUCTION

Medication errors are a leading cause of patient harm in the UK. Between July 2018 and June 2019 they accounted for 10.7% of incidents (206 485 medication incidents out of a total of 1 936 812 incidents), 66 deaths and 159 instances of "severe harm".[1] When medications have names that look or sound alike, and/or have similar packaging, they may be confused, leading to medication errors. These look-alike, sound-alike (LASA) errors are a type of *wrong drug* error under the 5Rs framework.[2] LASA errors can occur at any point on the treatment pathway during prescribing, dispensing or administration of medicines. They may result in overdosing, under-dosing or inappropriate dosing, representing a significant threat to patient safety.[3–6]

This systematic review explores interventions to reduce the prevalence of LASA errors due to similar-looking or -sounding names. It is based on the study protocol published in PROSPERO[7] and is accompanied by a review article looking at drivers and solutions to the problem of LASA errors.[6]

Review protocol: PROSPERO, published in 2016 (http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42016048198).

1.1 | Previous reviews

When our initial literature search was carried out in 2016, no systematic reviews of LASA error interventions had been published and only one literature review of LASA errors existed.[6] That review focused on the prevalence of LASA errors, searching for (look AND [sound/exp OR sound] AND alike AND [drug/exp OR drug]) and reviewing 14 papers from PubMed and EMBASE. It included interventions such as Tall Man lettering, but there was no meta-analysis. Other papers nonsystematically reviewed the literature, such as Emmerton and Rizk,[3] and included interviews with key industry experts, such as pharmacists and psycholinguists.

A systematic literature review[8] was subsequently published in 2018 on strategies to avoid look-alike labelling errors. The authors of this review[8] looked only at "original studies" published in English involving healthcare professionals or "consumers", with no restrictions on study design. Although this review and our own were carried out concurrently, we view them as complementary. Our inclusion criteria comprised *all* types of LASA error, including spoken errors, in four languages. We have included studies on healthcare professionals and only study designs that used a comparator as a basis of analysis. Our primary objective was to systematically identify and evaluate comparative studies of interventions, delivered in any healthcare setting, that aimed to reduce the rate of LASA errors.

2 | METHODS

We reviewed interventions used in any type of (sub)population. The search strategy criteria for inclusion and exclusion, and data extraction are described below.

2.1 | Primary outcome measures

1. Any measure of effect on LASA error rates, or relative measures of LASA error rates (increased, the same or decreased) derived from any intervention, compared with "no intervention" or usual care or placebo.
2. Any marker used to test an intervention, such as readability, which is used to test the efficacy of Tall Man lettering.

2.2 | Literature search and screening

We conducted searches for full-length peer-reviewed articles in electronic databases, hand-searching reference lists in included articles and hand-searching references in systematic reviews and literature reviews. We searched the following electronic databases in the autumn of 2016: MEDLINE (via PubMed), EMBASE, Scopus and Web of Science. Search strategies are given in the appendices. Owing to variations in LASA terminology, reference lists of the results were hand-searched for further relevant results. The inclusion criteria are given in Table 1. The search was re-run on Medline only on 14 February 2020 and results were screened by RB. Results from the new search are combined with those from the first search in the PRISMA diagram in Figure 1.

A PubMed search for (LASA AND [drug OR name OR error]) revealed that the acronym LASA was first used in any PubMed source in 2011 by Kovacic and Chambers,[9] and there were a few earlier papers using "sound-alike" or "look-alike", such as Dembicki[10] in 1967. LASA is thus a recently coined term, and much of the literature pertaining to LASA errors uses alternative discourse, such as "name confusion" or "similar drug names", and

TABLE 1 Study inclusion and exclusion criteria

	Inclusion criteria	Exclusion criteria
Type of study	Randomized controlled trials Controlled before-and-after studies Interrupted time series	Any other designs, eg, cross-sectional surveys Case studies
Interventions	Interruptions and distractions Typographic adaptation: font size, font weight, colour, tall man, capitalization Barcoding Computerized physician order entry Indication alerts Must look at an intervention	Cannot be solely focused on incidence or prevalence
Medication errors	Look-alike, sound-alike errors only Medication errors committed by healthcare practitioners, not patients, carers, manufacturers etc	Must look at wrong drug errors, not wrong dosage, wrong patient, wrong route of administration etc
Stage of treatment process	Prescribing (making the decision) Prescription writing Dispensing Transcribing Administering	
Subjects	Healthcare practitioners Medical or healthcare students	Students of other disciplines Parents/carers Patients
Language of publications	English Italian Spanish Russian	Other languages
Country	Any country	None
Date	Any date	
Human or veterinary	Human studies	Veterinary studies

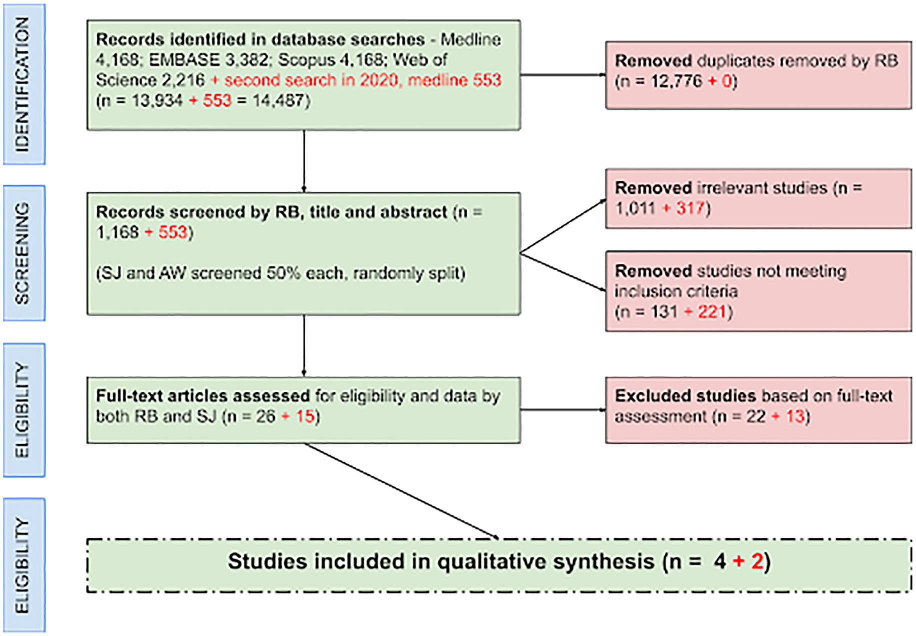

FIGURE 1 PRISMA flow diagram: green indicates studies added and red indicates studies removed

even other acronyms such as SALA (sound-alike, look-alike)[9] or LASARA (look-alike, sound-alike, read-alike).[11] The search strategy in this review therefore accounted for inconsistency in terminology in this relatively recent field.

2.3 | Inclusion and exclusion criteria

2.4 | Data extraction and assessment of study quality

The two reviewers independently extracted the name of the first author, year of publication, study type, participants' professions or education focus, types of intervention, types of outcome measure, study aims and study type. GRADE criteria were used to assess the quality of the evidence. If there was any disagreement, the data were rechecked, with resolution via discussion or by inviting a third author to give a final decision.

3 | RESULTS

3.1 | Outcomes of the search

The outcomes of the search strategy, by stage, are shown in the PRISMA diagram (Figure 1). The first (main) literature search identified 922 research papers from four databases, which were then screened by RB, AW and SJ. A total of six papers were selected for data extraction from both searches, but one[12] was subsequently removed because the data were unavailable (Rachel Bryan communicated via email with lead author Ramzi Shawahna in October 2016; he was unable to access the data needed for inclusion in the review). The six studies[13–18] are described in Table 2, with a description of excluded studies in Table 3. The screening process is shown in the PRISMA flow diagram in Figure 1, combining results from both searches.

3.1.1 | Differences in terminology usage

There is surprising variation in terminology relating to LASA experiments and measures, and some harmonization of terms would aid communication and discussion in the field.

Three studies[13,14,17] distinguished between two types of errors: one in which the person mistakenly identifies a LASA pair as the same name (type 1 in Table 4) and one in which the same name is mistakenly identified as two different names (type 2 in Table 4). Filik[13] explored findings for both of these outcomes, but only deemed the first type (her "target absent") as relevant. Accuracy in identifying "target present" shows that the name is easy to remember and recognize, while "target absent" requires the participant to distinguish the LASA names. An error means that they incorrectly identify them as being identical and reveals a potential to confuse them in practice. Or and Wang[15] only looked at how accurately two different names in a LASA pair were distinguished, not how accurately two names were recognized as being identical. Because the participant responded only when they detected a change, there was no mechanism for them to mistakenly identify two names in a LASA pair as a single name. Schell[14] explored two error rates. First, errors of omission, wherein two distinct names are misidentified as the same (Filik et al's[13] "target present" and Liu et al's "correct rejections and false alarms"[17]), and second, errors of commission, wherein a single name is misidentified

TABLE 2 Characteristics of the included studies

Citation	Methods	Participants	Intervention	Outcomes and procedure	Test stimuli	Findings
13	Randomization of exposure to intervention and randomization of the order in which interventions appeared to the participant (confirmed via email with Ruth Filik in October 2016) Experiment 2 (with healthcare professionals) took place between December 2008 and February 2009.	127 healthcare professionals in the NHS (in Experiment 2 only), comprising 48 general practitioners, 16 community pharmacist, 18 community pharmacy technicians and one medical student Mean age 36 years (SD 9.6)	The influence of Tall Man lettering on the rate of drug name confusion errors Comparators: 1. Tall Man lettering applied to the typography of digitally presented drug names 2. Control: natural case (all lowercase lettering for generic names, initial capitalization for brand names)	Laboratory outcome, tested electronically Outcome 1: Accuracy of name differentiation. Each participant was shown a medication name (part of a LASA pair), followed by five names (one of which was either the medication name again or its counterpart in the LASA pair). They were asked to select either "target present" (the name is shown again) or "target absent" (the LASA counterpart is shown) Outcome 2: Response times	20 LASA pairs chosen by an expert panel, both brand and generic names	Tall man letters reduced the error rate from 4.34% (lowercase control) to 3.07%, $P < .05$, a reduction of 1.27%, or 1.0 error per 80 test phases
14	Simulated same-different test using enhanced text interventions to highlight differences between confusable name pairs Exposure to comparators was randomized and a Latin square technique was used to counterbalance enhancement conditions between participants	Pharmacists and technicians from community and long-term care pharmacies who had practised pharmacy for at least 12 months Total 11 (three men, eight women), ages not specified	Examined the effect of enhanced text on immediate recognition of names, using comparators: lowercase 1. Tall Man 2. colour enhanced 3. colour + tall man 4. size 5. colour + size	Laboratory outcome, tested electronically Outcome 1: Accuracy of name differentiation, measured by the rate of "errors of omission". Participants were shown a drug name (one part of a LASA pair), then shown either the same name again or the other name in the LASA pair. They selected either "same" or "different".[2]	80 confusable pairs taken from the USAN list, generic names	Null effect and a small sample size, 10 out of 11 people selected the correct answer in both conditions, Tall Man and lowercase
15	Two-way, repeated measures design	Study 2 only, with 40 student pharmacists (21	Accuracy of name differentiation for five	Laboratory outcome, tested electronically.	28 confusable pairs taken from the ISMP and US	Tall Man letters increased accuracy from 90.2%

(Continues)

TABLE 2 (Continued)

Citation	Methods	Participants	Intervention	Outcomes and procedure	Test stimuli	Findings
	The participants were exposed to all five comparators The order in which test stimuli were presented was randomized	female, 19 male). Mean age 21 years (SD 2.5)	typographic adaptations of digitally presented drug names Comparators: 1. Tall Man 2. boldface 3. boldface + Tall Man 4. colour (red text) 5. contrast 6. lowercase lettering (acting as control)	Outcome 1: Accuracy of name differentiation for five interventions and one control. Participants were shown two names on a screen (either two identical names or both names in a LASA pair) and asked whether they were the "same" or "different". Pairs were shown in all six test comparisons. Accuracy was defined as correctly identifying a pair as different.	name differentiation project, generic names	(lowercase control) to 95.5%, an increase of 5.3% or 8.9 more correct differentiations per 168 test phases
16	Change detection on a computer screen interchanging between test stimuli Participants were exposed to all comparators "Careful randomization schemes were designed to mitigate potential effects of the order of appearance of trials and the position of change on the screen"	40 healthcare professionals, 16 nurses, 24 "other" They attempted to recruit those who interfaced in some way with medications, eg, pharmacy technicians. Participants had to be at least 18 years old, have no history of seizure and not be legally blind. Authors gave a breakdown of age, sex and experience of errors.	Accuracy of change detection when a pair of similar names are purported to be a pair of identical names. Of a total 32 loops, 16 tested change detection of a medication name, eight of which used Tall Man letters (the other eight used lowercase). Comparators: 1. Tall Man 2. "traditional font", presumably lowercase as they are generic names	Laboratory outcome, tested electronically Outcome 1: Accuracy of change detection. Participants were shown two screens flickering in a cyclic loop, each displaying 16 drug labels in a grid. They pressed the space bar when they detected a change in the drug name. Outcome 2: Time taken to detect a change.	Eight confusable pairs taken from the US name differentiation project, generic names	Tall Man letters increased accuracy from 85.9% (lowercase) to 95.1%, an increase of 9.2%, actual numbers not reported
17	Three-way, repeated measures, same-different tests of text	30 student nurses, and two groups of 15 practising nurses	Explored the effect on accuracy of name differentiation for three	Laboratory outcome, tested electronically	28 pairs of names, 14 from the ISMP list; generic names	Student nurses, Experiment 1: Tall Man + boldface increased mean

TABLE 2 (Continued)

Citation	Methods	Participants	Intervention	Outcomes and procedure	Test stimuli	Findings
	enhancements to highlight differences between confusable name pairs. Participants were exposed to all five comparators. Experiment 3 tested recognition memory in particular, but all three experiments measure the accuracy of drug name differentiation. "The order of the three blocks was counterbalanced across participants, and the order of trials within each block was randomized. … there were 36 trials in total and their testing order was randomized."	"All reported normal or corrected-to-normal vision and all provided written informed consent" Authors gave a breakdown of age and years of working experience	forms of text enhancement Comparators: 1. Tall Man + boldface 2. inverted text 3. lowercase lettering (acting as control) 4. disfluency 5. fluency (acting as secondary control)	Outcome 1: Accuracy of drug name differentiation. Participants were shown an image on the screen of a pair of drug names (on mock bottles). After each image disappeared, they were asked to select if the two names were the "same" or "different".		differentiation accuracy from 93.2% (lowercase) to 97.1%, an increase of 3.9%, actual numbers not reported Practising nurses, Experiment 2: Tall Man + boldface increased mean differentiation accuracy from 92.7% (lowercase) to 96.2% Practising nurses, Experiment 3: Tall Man + boldface decreased mean differentiation accuracy from 96.6% to 87.2%
18	Experiment 1 only. Four-way, repeated measures, visual search experiment. All participants were exposed to all interventions and controls. The authors state that the "blocks were counterbalanced" and "trials were randomized within blocks" (p. 5)	40 nurses, recruited through flyers and emails. The authors gave a breakdown of age. All had at least 2 years of working experience, normal or corrected-to-normal vision, and normal colour vision. Volunteers received a financial incentive to participate.	Explored the effect of text enhancements on recognition error. Comparators: 1. Tall Man 2. reverse Tall Man 3. boldface + red 4. boldface + contrast 5. lowercase (acting as control)	Laboratory outcome, testing electronically. Participants were asked to read a name on an e-prescription, memorize the name and then, when ready, search and physically locate it on a mock-up of a pharmacy shelf inside a physical room, and scan with a barcode scanner.	60 pairs of names from ISMP and FDA lists. Examples display generic names only.	There was no significant main effect of text enhancement on recognition error, with all *P* values >.05. Recognition error rate for lowercase was 2.2% (SD 0.024) and for Tall Man was 2.7% (SD 0.043).

FDA, US Food and Drug Administration; ISMP, Institute for Safe Medication Practices; LASA, look-alike, sound-alike; USAN, United States Adopted Name.

TABLE 3 Characteristics of excluded studies

Source	Study design without comparator or not randomized	Not looking at a listed intervention	Participants not healthcare practitioners	Not looking at LASA error	Paper unavailable	Full data unavailable, clarified via email with lead author
8	*	*				
12						*
19	*	*				
20	*	*				
21	*					
22	*					
23		*				
24			*			
25	*					
26		*				
27		*		*		
28	*	*				
29			*			
30		*				
31		*				
32		*				
33			*			
34					*	
35			*			
36	*			*		
37			*			
38					*	
39	*					
40		*		*		
41	*		*	*		
42	*			*		
43		*		*		
44	*			*		
45	*		*			
46	*					
47	*			*		
48		*				
49		*		*		
50	*			*		
51	*			*		

LASA, look-alike, sound-alike.

TABLE 4 Types of LASA error

Type	Action	[13]	[14]	[15]
1	Stating that two different names in a LASA pair are the same name	Target present error	Error of omission	False alarm
2	Stating that two identical names are different	Target absent error	Error of commission	Miss

LASA, look-alike, sound-alike.

as two distinct names (Filik et al's "target absent" and Liu et al's "hits and misses"[17]). Only outcomes measuring the accuracy of distinguishing between two names in a LASA pair were deemed relevant in this review, as this could lead to a LASA confusion error between two medications. However, mistakenly identifying a single name as two distinct names suggests that the name may be difficult to remember and recognize, and, as Schell[14] points out, hints at the likelihood of false error alerting and is a good measure to be used when an intervention may heighten a user's sensitivity to error identification by drawing attention to particular names. All authors referred to *P* values when reporting their findings and took $P < .05$ as "statistically significant".

3.2 | Analysis of studies

All six studies were undertaken in laboratories. The number of participants was 11-127. Six studies were selected[13–18] after all the papers had been scrutinized under the inclusion/exclusion criteria. A summary of outcome measurements is given in Table 5. All six studies assessed the efficacy of Tall Man lettering in emphasizing differences between similar (LASA) names, using a change in typography as an intervention to reduce the rate of drug name confusion errors. The accuracy of drug name differentiation was an outcome measure in four studies[14–17] and measurement of the *error rate* of drug name differentiation was an outcome in the other two.[11,16] Four of the six studies[13–15,17] used some form of "same *vs* different" procedure to test a participant's ability to distinguish two names. In the other two studies, DeHenau et al[16] used a change detection test procedure and Wang and Or[18] used a visual search and selection procedure. Mistakenly identifying that two different LASA names (eg hydroxyzine and hydralazine from Filik et al[13]) are the same reveals a potential for confusion in clinical practice; this type of error is more likely to reach patients, as the difference between the names has been overlooked and thus the medicines could be substituted. Therefore, figures for that type of error are given below and compared with counterparts from the other two studies.

In four of the six studies, Tall Man lettering statistically significantly increased the accuracy or reduced the error rate of drug name differentiation. Two studies, Schell[14] and Wang and Or[18] found no significant support for Tall Man lettering. In the case of Schell,[14] this is most probably because of the small sample size (n = 11). In the case of Wang and Or,[18] they hypothesized that the nonsignificance may have arisen because participants performed too few drug search trials (160). It was impossible to combine the findings from the four studies given that each study used different test procedures and outcomes, and since other potential confounders, such as the drug names, their orthographic similarity, test environments and conditions, and the levels of education and experience of the participants, were unstated or not accounted for in the analysis.

Filik et al[13] found that Tall Man lettering led to a small but significant reduction in name differentiation errors compared with no intervention (using correct or orthodox typography "the natural case", ie, lowercase for generic names and initial capitalization for brand names).

Schell[14] reported that name recognition was not significantly affected by the various typographic adaptations, with the caveat that the sample size (n = 11) was too small, resulting in a lack of statistical power.

Or et al[15] confirmed that Tall Man lettering can reduce errors in differentiation, but added that the most effective form of typographic adaptation was Tall Man + bold, presumably because it highlights salient letters and reduces the difficulty of visual search and detection.

DeHenau et al[16] found that Tall Man lettering can reduce errors in differentiation and that this effect was compounded by the user's particular knowledge of the names: when a user was familiar with only one of the names in a pair (rather than neither or both), Tall Man letters had a significant positive effect on accuracy because the familiar name will be recognizable more readily to the user and so the additional typographic change should amplify this effect. However, it can be surmised from this that if the user is familiar with both names the benefit is cancelled out.

Findings from Liu et al[17] support Tall Man plus boldface lettering as a method of increasing accuracy in drug name differentiation, but they did not test Tall Man lettering alone, so it may be that combined text enhancement is a stronger intervention. They found that for nurses this effect was only seen with short exposure times, indicating that Tall Man lettering is most beneficial in the immediate stages of visual search because the highlighted letters attract attention.

Wang and Or[18] found that Tall Man lettering increased the error rate, although the effect was not significant. They found limited support for boldface plus contrast and suggested that greater efficacy may lie in combinations of text enhancements, which is supported by Liu et al.[17]

3.2.1 | Concerns about Tall Man lettering

The interplay between Tall Man lettering and response time is complicated: Filik et al[13] reported a small but possibly clinically significant increase in response time (39.6 ms for lowercase letters, 42.9 ms for Tall Man letters, $P < .001$), whereas DeHenau et al[16] found that Tall Man lettering reduced response times. Wang and Or[18] found that Tall Man lettering increased "perceived mental effort" and response times, but the effect was not clinically or statistically significant (all *P* values of independent variables >0.05). Schell,[14] looking at errors of commission (when the user misidentifies a single name as two distinct names), found that Tall Man letters can increase response bias, which will lead to more false alarms, whereby the user identifies an error where there is none. This could be because a change in typography indicates that the name is at risk of confusion. Of course, a more liberal response bias will necessarily lead to capture of actual errors.

DeHenau et al[16] found a difference in magnitude in the benefit of Tall Man letters between their participant groups, with healthcare professionals deriving more benefit. This could be the "quasi-placebo

TABLE 5 Summary of outcome measurements

Types of outcomes and covariates Paper	Outcome measure	Effect of Tall Man letters	Lowercase (indicated as either mean error rate or accuracy) [SD]	Tall Man lettering (indicated as either mean error rate or accuracy) [SD] {SE}	Difference in error rate or accuracy
Filik et al,[13] Table II	Same *vs* different test Specifically, error rate of 'target absent' - Incorrectly saying that two LASA names are the same name.	Reduced error rate	Error rate 4.34% [5.41, calculated from reported SE] {0.48}*	Error rate 3.07% [4.85, calculated from reported SE] {0.43}*	1.27% fewer errors *P* < .05
Schell,[14] Table 3	Same *vs* different test Specifically, the number of participants (total n = 11) who accurately distinguished between two names in an LASA pair	Null effect	Error rate 0.91 errors [1.45]**	Error rate 0.91 errors [1.45]**	0%, no difference
Or and Wang,[15] Table 3	Same *vs* different test Specifically, the accuracy rate of detecting different names, correctly distinguishing between two names in an LASA pair	Increased accuracy	Accuracy 90.2% [0.14]	Accuracy 95.5% [0.07]	5.3% improvement in accuracy, *P* < .01
DeHenau et al,[16] section 3.1	Change detection test Specifically, the accuracy rate of detecting a change from one drug name to its LASA counterpart	Increased accuracy	Accuracy 85.9% [3.3]***	Accuracy 95.1% [1.4]***	9.2% increase in accuracy, *P* < .0001
Liu et al,[17] Tables 2-4	Same-different test; two experiments Experiment 1: 30 student nurses Experiment 2: 15 practising nurses	Increased accuracy	Accuracy, Experiment 1: 93.2% [0.10] Accuracy, Experiment 2: 92.7% [0.09]	Accuracy, Experiment 1: 97.1 [0.06] Accuracy, Experiment 2: 96.2% [0.05]	Increase in accuracy, Experiment 1: 3.9%, *P* < .001 Increase in accuracy, Experiment 2: 3.5%, *P* < .001
Wang and Or,[18] Table 3	Visual search, Experiment 1 only Specifically, the rate of recognition error rate of selecting the wrong name from a range of LASA distractors	Increased error rate, but not significant (all *P* > .05)	Error rate 2.2% [0.024] *P* > .05	Error rate 2.7% [0.043] *P* > .05	0.5% fewer errors *P* > .05

LASA, look-alike, sound-alike.
*Note to Filik et al[13]: Means and SEs (converted to SDs) are reported. However, the data are not normally distributed and should have been reported as median (25th-75th centiles) plus full ranges.
**This was confirmed with Schell via email correspondence in August 2018. To illustrate, a mean error rate of 0.91 means that 10 errors were committed, averaged over 11 participants.
***Note to DeHenau et al[16]: Not specified if these are SE or SD. No response to correspondence on this?

effect" of Tall Man letters: when users are aware of the method they are primed to be more wary of look-alike names and so they will be less likely to make a look-alike name confusion error.[13] Conversely, Filik et al[13] found a greater reduction in error rate in laypersons from Tall Man lettering, so the effect is unclear.

3.2.2 | Limitations of the studies

The numbers of study participants were low, ranging from 11[14] to 127.[12] Only large differences would have yielded statistically significant findings. Future studies would benefit from larger test cohorts, although this may not be feasible when restricting participants to healthcare professionals and in-person testing. Using eye-tracking technology can also complement experiments in drug name selection and recognition[13,18] by providing researchers with more information on the user's selection process. Furthermore, the transferability of laboratory-based studies to the real world is unclear.

The full versions of two papers were unavailable[34,38] and a further paper was removed because the data were not accessible.[12] These papers were not included in the analysis.

There is no standard method for applying Tall Man lettering to names. Filik et al[13] used a bespoke method in their study, dubbed CD3, and Schell[14] noted that Tall Man lettering methods vary considerably. Future research efforts should work to build consensus on a standardized method for Tall Man lettering and also consider how to apply it in trios of names with asymmetric similarities (such as carboplatin, cisplatin and carboprost), and in electronic prescribing software, where medicines are arranged alphabetically and/or by condition, eg salbutamol/salmeterol.

3.3 | Risk of bias

The risk of bias varied between studies, as outlined in Table 6. None of the four studies described the participant selection or recruitment process, so there is a high risk of volunteer bias. Performance bias is deemed high in all four studies. Because Tall Man lettering or other typographic adaptations are visual changes to the presentation of names, there is no way to blind participants in a trial.

3.4 | Quality of evidence assessment using the GRADE criteria

Using GRADE, the quality of the body of evidence explored in this review was overall low. We considered each of the GRADE criteria (risk of bias, directness of evidence, consistency and precision of results, risk of publication bias, magnitude of the effect, dose-response gradient and influence of residual plausible confounding; see Table 7).

4 | DISCUSSION

From 1721 titles and abstracts read, we explored six studies, all looking at the capacity of Tall Man lettering to emphasize differences between similar names and thus to reduce the rate of drug name confusion errors. Four of the six studies suggested that Tall Man lettering can increase the accuracy of drug name differentiation (or alternatively reduce errors), compared with standard lowercase lettering. The effect of Tall Man lettering on response time is not clear from these studies. However, the indirectness of the measures used and the varying absolute differences seen reduced the quality of the evidence.

4.1 | Limitations of the review

We carried out this review in four databases, but did not search grey literature, white/green papers or e-theses. References in each full paper screened were hand-searched for additional relevant studies, but we found none, suggesting that our initial search was effective.

Although we opened the search to four languages (English, Italian, Spanish and Russian), all the search terms were in English and we therefore identified only papers whose abstracts and keywords had been translated into English from the source language. This assumes that correct English terminology and vernacular was used, which may not be the case when machine translation is used. Consequently, we identified only English studies. It is possible that we missed results in other languages not included in the search strategy or that we missed papers that did not translate their abstract into English. A lack of papers in languages other than English does not mean that LASA errors are an Anglophone phenomenon or that only Anglophone countries report medication errors, but simply that English language literature is easier to locate (eg, the European Medicines Agency's publications are in English).

4.2 | Generalizability

From such small numbers and laboratory settings, it is difficult to generalize to real-world wider populations working under intense pressure in safety-critical environments. Participants in the same *vs* different drug name differentiation tasks reviewed here were healthcare professionals, whom the authors presume to have high levels of literacy and knowledge of concerns about patient harms, and perhaps even knowledge of interventions such as Tall Man lettering. The findings cannot be automatically extrapolated to lay people or student nurses/doctors.

In this review, varying levels of bias restricted the quality of the evidence. All the experiments described relied on volunteers and so volunteer selection bias must be taken into account. Participants were all healthcare professionals, but the studies included in this review did not detail the recruitment processes or the first language of the respondents, and so it may be that those who volunteered had an

TABLE 6 Risk of bias assessments

Citation	Selection bias: Random sequence generation	Selection bias: Allocation concealment	Performance bias: Blinding of participants and personnel (all high since participants cannot be blinded to visual interventions)	Detection bias: Blinding of outcome assessment	Attrition bias: Incomplete outcome data	Other bias, including reporting bias: Selective reporting	Other biases
13	Low, confirmed via email with lead author, as little information included in paper	Low	High	Low	Not stated, so unclear	Unclear	Sampling of participants not described; high risk of selection bias
14	Low	Low	High	Low	Not stated, so unclear	Low	The selection of participants is open to volunteer bias
15	Unclear	Not sure	High	Low	Not stated, so unclear	Low	Selection of medicinal product names from lists was not random; potential for bias
16	Unclear	Unclear	High	Low	Not stated, so unclear	Unclear, some outcomes just given a *P* value, which does not allow data to be extracted	…
17	Unclear	Unclear	High	Low	Low	Unclear	Volunteer bias is high owing to self-selection of participants
18	Low	Unclear	High	Low	Low	Low	Volunteer bias is high owing to self-selection of participants

interest in drug name confusion, patient safety, typography, LASA errors or other relevant topics, or were highly motivated practitioners. This could lead to dissonance between their performance and the likely performance of the "average" healthcare professional.

The Hawthorne effect, in which knowledge of being observed causes an individual to modify some aspect of their behaviour,[52] must not be discounted. During the experiments it is likely that participants had increased sensitivity to differences between medication names, compared with everyday practice, and so error rates may have been underreported. Similarly, the Rosenthal effect, in which expectations affect performance,[53] is relevant. It is possible that healthcare professionals felt higher expectations to perform well in medication name differentiation, but this is difficult to determine because the included studies did not describe how fully participants were informed of the purpose of the experiments.

Larmene-Beld et al[8] cited a recent study conducted in a hospital environment[54] exploring 1 676 700 hospitalizations in which Tall Man lettering had no beneficial effect. That study was excluded from this review as it was a before and after observational study and not a randomized controlled trial. They examined paediatric pharmacy data from 42 children's hospitals over 9 years to explore the occurrence of errors involving 12 particular LASA name pairs. Among 1 676 700 hospitalizations, implementation of Tall Man lettering was not associated with a reduction in the LASA error rate.

4.3 | Comparison with other reviews

Hand-searching and cascade-reading of the field revealed two literature reviews focused on interventions for LASA errors. Neither

TABLE 7 GRADE criteria assessment

Criterion	Assessment
Risk of bias	Unclear
Directness	Very low (laboratory only)
Consistency and precision of results	Low; wide range of effect, from null to ∼9% improvement
Risk of publication bias	Uncertain; small negative studies are often not published; these studies were not registered in research databases
Magnitude of effect	Small
Dose-response gradient	Not explored in any studies
Residual plausible confounding	Unknown, but likely to be low in artificial laboratory settings; not reported
Other bias	Volunteer selection bias

conducted meta-analyses because of the heterogeneity of the included studies.

Larmene-Beld et al[8] included 16 studies in their systematic review (with no restriction on study design or type of participant), of which 11 evaluated the use of Tall Man lettering and seven had statistically significant findings. Six of these showed that participants made fewer errors when the drug names contained Tall Man lettering than when the drug names were displayed in lowercase. They cited Schell[14] as showing an increase in overall error rate using Tall Man letters over lowercase (taking as the only significant outcome measure overall error rate in Study 1 with nonhealthcare professionals). In this review we took outcome measures relating to Study 2 with healthcare professionals, which found a null effect (but this was nonsignificant, all *P* values >.05). They similarly noted that the interaction between Tall Man letters and response time is mixed and seems to depend on an individual's knowledge of Tall Man letters.

Ciociano and Bagnasco[55] included 14 studies in their narrative review, two of which looked at the effect of Tall Man letters. The first[23] found no effect of Tall Man on error rate in a same *vs* different task (laboratory outcome), but the participants were not healthcare professionals. This aligns with the findings from this review regarding the Tall Man quasi-placebo effect, in that when users are aware of the intervention and its purpose, they are more likely to derive an outcome from it. Healthcare professionals are presumably more aware of medication errors and interventions such as Tall Man letters. The other included paper[56] described how Tall Man letters were integrated into a hospital network. The authors describe a number of interventions and emphasize the importance of policymaking in reducing errors. Policymaking is crucial both in creating international regulations to limit confusability of names when they are chosen by pharmaceutical companies and nomenclature bodies, and in best use of technological approaches such as Tall Man lettering.

4.4 | Wider context

Under Reason's theory of error mitigation, a system approach recognizes that humans are fallible and that errors occur through latent conditions in the system (in this case, healthcare).[57] The presence of LASA names is a latent condition: it increases the risk of error. The system approach mitigates the risk of error by putting up multiple safeguards, which block the pathway of an error and prevent it from reaching the end user. We have shown that as one such safeguard, Tall Man lettering, has unclear effectiveness.

Or and Wang[15] looked at the interplay between orthographic similarity and various methods of typographic adaptation. They found a statistically significant increase in accuracy with a corresponding reduction in similarity, ie, names are harder to differentiate when they are very similar to each other. This is hardly surprising, but the authors pointed out that the effect of orthographic similarity was sustained in all the various typographic adaptations. This means that there is a ceiling of efficacy and in certain high-risk situations (with highly similar names) the risk of confusion cannot be mitigated by typography alone.

The effect of Tall Man lettering on response time is unclear: in one study it reduced response time[16] and in another increased it.[13] Larmene-Beld et al[8] similarly found a mixed response in their included studies. It may be that response time is mediated by how frequently a particular medication name is used by the individual practitioner: names for commonly prescribed medications will be better known and thus may take less time to recognize. Medication names are specialist items in a language and some are used very infrequently. Frequency of prescription is positively correlated with accuracy in the visual perception of medication names[31]: lesser used names are more likely to be confused or misunderstood.

Linguistically, Tall Man lettering involves a mixture of cases, normally with lowercase at the beginning and end of the word and a block of capitalization in the middle, eg, hydrALAzine. Case has historically been disregarded in linguistics as having an impact on reading speed or visual perception based upon an influential experiment on the effect of AlTeRnAtInG cAsE.[58] However, recent reading experiments have found a lowercase advantage in reading,[59] in which case Tall Man letters could reduce the readability of names. It may also be that blocks of uppercase letters in a Tall Man name are treated as acronyms, which can slow down perception by increasing the number of times users' eyes fixate on them.[60]

5 | CONCLUSIONS

Based on the criteria outlined in the search and screening strategy for this systematic review, the evidence suggests that Tall Man lettering is a marginally effective intervention to reduce LASA drug name confusion errors in laboratory settings. Its effectiveness may be mediated by additional typography, such as emboldening,[15] whether or not a user is familiar with one more of the names[16] and orthographic similarity.[15] We have identified a “Tall Man quasi-placebo effect”, wherein a user derives more benefit from Tall Man lettering if they are aware of its purpose.[16]

The paucity of evidence for the efficacy and effectiveness of Tall Man lettering suggests that it should be used with caution and as one part of a larger arsenal of medication error-reduction strategies.

5.1 | Implications for practice

Tall Man lettering is no panacea or substitute for adequate education. Policymakers should be mindful that there is no evidence from clinical practice that Tall Man lettering reduces clinically significant errors and take care when advising the use of Tall Man lettering until the evidence base matures.

5.2 | Implications for research

Trials with much larger samples need to be undertaken and, as far as possible, interventions should be evaluated in clinical practice. More detailed exploration of LASA errors using linguistic theory is needed to understand the problem and propose amelioration strategies based on more than one aspect of linguistics.

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COMPETING INTERESTS

R.B., A.W. and S.J. have no conflicts of interest to declare. J.K.A. has published papers on adverse drug reactions and medical linguistics, and has edited textbooks on adverse drug reactions. He has also acted as an expert witness in cases related to adverse drug reactions, chairs an expert working group on nomenclature for the British Pharmacopoeia Commission, is an Associate Editor of *BMJ Evidence Based Medicine* and is President Emeritus of the British Pharmacological Society.

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APPENDIX

PubMed search strategy

Terms were searched in title and abstract ([tiab] on PubMed) to retrieve results that are both focused (title) and closely related (abstract) to LASA errors. First several broad parameters that may co-occur with LASA error discourse, such as the method of delivery (eg, dispensing), the type of incident (eg, near miss), medication or a synonym (eg, drug), the type of medication name (eg, generic), aspects such as packaging or labelling, and interventions such as font adaptation and automated alerts (eg, Tall Man lettering) were defined. These were then combined with Boolean operator AND to form an array of search terms. This array was combined with variants of LASA to find more specific papers, and the search was finally narrowed by searching for only those papers fulfilling the preceding conditions and with relevant MeSH terms as a major subject heading([majr] on PubMed).

First search run 16 December 2016 with open dates; second search run 14 February 2020 for publications after 16 December 2016 (adding 22016/12:2020/02 [edat]" to search strategy)

KEY: [ti] = Title field only; .**[tiab]** = Title & Abstract fields; **MESH** = Medical Subject Headings No Limits Applied Search run: 2015 12 16: RESULTS = 4168 #1prescri*[tiab] OR drug administ*[tiab] OR dispens*[tiab] OR pharmacist*[tiab] OR drug*[tiab] OR medicine*[tiab] OR medication*[tiab] OR pharmaceutical*[tiab] OR pharmacotherapeutic agent*[tiab] OR medicinal product*[tiab] OR "Drug Therapy"[Mesh] OR "Prescriptions"[Mesh] OR "Pharmaceutical Preparations"[Mesh] #2Error*[tiab] OR mix* up[tiab] OR "mix ups"[tiab] near* miss*[tiab] OR oversight*[tiab] OR wrong*[tiab] OR mistake*[tiab] OR suboptimal practice[tiab] OR "Medical Errors"[mh] #3(#1 AND #2) #4"Medication Errors"[mh] #5drug incident*[tiab] OR medication incident*[tiab] OR medication error*[tiab] OR drug* error*[tiab] #6(#3 OR #4 OR #5) #7(lookalike[tiab] OR "look-alike*"[tiab] OR soundalike[tiab] OR sound-alike*[tiab] OR LASA[tiab] OR LASAs[tiab] #8similarity[tiab] OR similar[ti] #9confus*[tiab] #10((name*[tiab] OR title*[tiab]) AND (generic[tiab] OR brand*[tiab] OR trade[tiab] OR proprietary[tiab] OR commercial[tiab] OR international nonproprietary[tiab] OR INN[tiab] OR INNs[tiab] OR BAN[tiab] OR BANs[tiab] OR British approved[tiab] OR pharmacopoeial title*[tiab] OR nomenclature*[tiab] OR packag*[tiab] OR label*[tiab])) #11(colour[tiab] OR color[tiab] OR font[tiab] OR fonts[tiab] OR typograph*[tiab] OR Tall Man[tiab] OR tall man[tiab] OR lettering[tiab] OR upper case[tiab] OR lower case[tiab] OR automated alert*[tiab] OR CPOE*[tiab] OR computerized physician order entry[tiab] OR barcod*[tiab] OR distract*[tiab] OR interrupt*[tiab]) #12(#7 OR #8 OR #9 OR #10 OR #11) #13(#12 AND #6) #14animals[mh] NOT humans[mh] #15(#13 NOT #14)

Web of Science search strategy

KEY: **TS=** Topic Search (Title, Abstract & Keywords); **TI=** Title Only Search No Limits Applied Search run: 2016 01 26: RESULTS = 2,126 #1TS=(prescri* OR "drug administ*" OR dispens* OR pharmacist* OR drug* OR medicine* OR medication* OR pharmaceutical* OR "pharmacotherapeutic agent*" OR "medicinal product*") #2TS=(error* OR "mix* up" OR "mix-up*" OR "near* miss*" OR oversight* OR wrong* OR mistake* OR "suboptimal practice" OR "medical error*") #3(#1 AND #2) #4TS=("drug incident*" OR "medication incident*" OR "medication error*" OR "drug error*") #5(#4 OR #3) #6TS= (lookalike* OR "look-alike*" OR soundalike* OR "sound alike*" OR LASA OR LASAs OR "LA-SA" OR "LA-SAs") #7TI= (similar) #8TS=(similarity OR similarities OR confus*) #9(#6 OR #7 OR #8) #10TS=(name* OR title*) #11TS=(generic OR brand* OR trade OR proprietary OR commercial) #12TS=("international nonproprietary" OR "international non-proprietary" OR INN OR INNs OR BAN OR BANs OR "British approved" OR pharmacopoeial OR nomenclature OR Packag* OR label*) #13(#10 AND (#11 OR #12) #14(TS=(colo*r OR font OR fonts OR typograph* OR "tall man" OR Tall Man OR lettering OR "lower case" OR "upper case" OR capitali?ation OR "automated alert" OR CPOE OR "computeri?ed physician order entry" OR barcod* OR distract* OR interrupt*) #15(#9 OR #13 OR #14) #16 (#15 AND #5) #17(Exclude: Letters, Editorials, News Items, Notes, Item about an Individual, Book Chapter)

EMBASE search strategy (via OVID)

KEY: .ti. = Title field only; **ti,ab.** = Title & Abstract fields; **/** = EMTREE index term No Limits Applied **Search run**: 2015 12 16: **RESULTS** = 3382 #1(prescri* or drug administ* or dispens* or pharmacist* or drug* or medicine* or medication*).ti,ab. #2(pharmaceutical* or pharmacotherapeutic agent* or medicinal product*).ti,ab. #3drug administration/

#4prescription #5drug/ #6drug therapy/ #7(#1 or #2 or #3 or #4 or #5 or #6) #8(error* or mix* up or mix-up* or near* miss* or oversight* or wrong* or mistake* or suboptimal practice).ti,ab. #9medical error/ or error/ #10(#8 or #9) #11(#7 and #10) #12medication error/ #13(drug incident* or medication incident* or medication error* or drug error*).ti,ab. #14(#11 or #12 or #13) #15(lookalike* or look-alike* or soundalike* or sound alike* or LASA or LASAs or LA-SA or LA-SAs).ti,ab. #16similar.ti. #17(similarity or similarities or confus*).ti,ab. #18(#16 or #17) #19(name* or title*).ti,ab. #20(generic or brand* or trade or proprietary or commercial).ti,ab. #21generic drug/ #22(international nonproprietary or international non-proprietary or INN or INNs or BAN or BANs or British approved or pharmacopoeial or nomenclature or Packag* or label*).ti,ab. #23*drug labeling/ #24*drug packaging/ or *packaging/ #25(#20 or #21 or #22 or #23 or #24)

Scopus search strategy

KEY: TITLE = Title field only; TITLE-ABS-KEY = Title , abstract & keyword fields No Limits Applied Search run: 2015 12 16: RESULTS = 4168 SCOPUS - Rachel Bryan – 2016 01 27 (Health Sciences and Social Sciences & Humanities only) No other Limits applied except for final exclusion as per #17 Search Run – 2016 02 04 RESULTS – 2344 Search Saved to Scopus by CB #1TITLE-ABS-KEY(prescri* OR "drug administ*" OR dispens* OR pharmacist* OR drug* OR medicine* OR medication* OR pharmaceutical* OR "pharmacotherapeutic agent*" OR "medicinal product*") #2TITLE-ABS-KEY (error* OR "mix* up" OR "mix-up*" OR "near* miss*" OR oversight* OR wrong* OR mistake* OR "suboptimal practice" OR "medical error*") #3#1 AND #2 #4TITLE-ABS-KEY(drug incident*" OR "medication incident*" OR "medication error*" OR "drug error*") #5#4 OR #3 #6TITLE-ABS-KEY(lookalike* OR "look-alike*" OR soundalike* OR "sound alike*" OR LASA OR LASAs OR "LA-SA" OR "LA-SAs") #7TITLE(similar) #8TITLE-ABS-KEY(similarity OR similarities OR confus*) #9#6 OR #7 OR #8 #10TITLE-ABS-KEY(name* OR title*) #11TITLE-ABS-KEY(generic OR brand* OR trade OR proprietary OR commercial) #12TITLE-ABS-KEY("international nonproprietary" OR "international non-proprietary" OR INN OR INNs OR BAN OR BANs OR "British approved" OR pharmacopoeial OR nomenclature OR Packag* OR label*) #13#10 AND (#11 OR #12) #14TITLE-ABS-KEY(colo*r OR font OR fonts OR typograph* OR "tall man" OR Tall Man OR lettering OR "lower case" OR "upper case" OR capitali?ation OR "automated alert" OR CPOE OR "computeri?ed physician order entry" OR barcod* OR distract* OR interrupt*) #15#9 OR #13 OR #14 #16#15 AND #5 #17Exclude: Letters, Editorials, Notes, Book Chapter, Books