

Methodology Used to Assess Acceptability of Oral Pediatric Medicines

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DOI:

[10.1007/s40272-017-0223-7](https://doi.org/10.1007/s40272-017-0223-7)

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Document Version

Peer reviewed version

Citation for published version (Harvard):

Mistry, P, Batchelor, H & SPaeDD-UK project 2017, 'Methodology Used to Assess Acceptability of Oral Pediatric Medicines: A Systematic Literature Search and Narrative Review', *Paediatric Drugs*, vol. 19, no. 3, pp. 223–233. <https://doi.org/10.1007/s40272-017-0223-7>

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Systematic search and narrative review of methodology used to assess acceptability of oral paediatric medicines

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Running head: Review of methodology for acceptability

Abstract

Background: Regulatory guidelines require that any new medicine designed for a pediatric population must be demonstrated to be acceptable to that population. There is currently no guidance on how to conduct or report acceptability testing.

Aim: Our objective was to undertake a review of the methods used to assess the acceptability of medicines within a pediatric population and use this review to propose the most appropriate methodology going forwards.

Methods: A defined search strategy was used to identify literature reports of acceptability assessments of medicines conducted within pediatric populations. Information about the tools used in these studies was extracted to allow comparison across studies.

Results: 61 articles were included in the analysis. Palatability was the most common attribute measured in evaluating acceptability (54/61). Simple scale methods were most commonly used with visual analogue scales (VAS) and hedonic scales used separately and also in combination in 34/61 studies. Hedonic scales alone reported for 14 studies and VAS alone in just 5 studies. Other tools included Likert scales; forced choice or preference; surveys or questionnaires; observations of facial expressions during administration, or the ease or ability to swallow the dosage; the prevalence of complaints or refusal to take the medicine; and the time taken for a nurse to administer the medicine.

Conclusions: It remains unclear which scale is the best with regards to its validity, reliability, feasibility and preference to assess acceptability. Further work is required to select the most appropriate method to justify that a medicine is acceptable to a pediatric population.

Key Points

- Many different methods to assess acceptability of pediatric medicines have been described in the literature however, this lack of standardisation in approach and methodology makes comparisons between products complex.
- Few studies have defined criteria that define acceptability of a product to a pediatric population.
- Simple 5-point hedonic scales or visual analogue scales are appropriate to evaluate acceptability going forwards provided the anchor phrases are meaningful to participants
- Further work is required to define the most appropriate methodology to use to ensure acceptable medicines are available to pediatric populations.

1. Introduction

Pediatric formulation development is currently a 'hot' topic within the pharmaceutical industry and substantial efforts are being invested into developing medicines that are acceptable to children. Acceptability of medicines for children is a challenge, yet critical to ensure adherence to treatment. The palatability of pediatric medicines is one of the most important formulation factors with potential to influence adherence to therapeutic regimens and outcomes [1]. It has been demonstrated that making medications more pleasing to the child can have a positive effect on compliance [2]. Acceptability has previously been defined as, "an overall ability of the patient and caregiver (defined as 'user') to use a medicinal product as intended (or authorised)," which often encompasses taste and palatability testing [3]. The European Medicines Agency (EMA) have issued guidance that requires acceptability to be assessed (preferably in children) yet there is no guidance on the methodology that should be used for this evaluation [4]. Palatability is defined as acceptable to the mouth so incorporates textural and olfactory attributes as well as taste. EMA guidance on the palatability of veterinary products proposed that voluntary acceptance rates should be >80% in dogs, and >70%, for all other species [5]. The lack of a standardised method to assess acceptability of pediatric medicines has been highlighted previously [3, 6].

A key barrier in the development of acceptable, age-appropriate medicines is the lack of knowledge about what is currently considered to be acceptable to pediatric patients and how the acceptability of a new product should be assessed. In support of development of guidance on appropriate methodology to use to assess acceptability going forwards this paper reports on a systematic search of peer-reviewed literature on acceptability and preference testing of medicines in children to provide a review.

2. Methods

Information on methodology to assess acceptability of medicines in pediatric populations was sought from a literature search. Overall, the methods for the search protocol were informed by the Cochrane Handbook for Systematic Reviews of Interventions [7]. This review was limited to acceptability testing of oral dosage forms in pediatric populations.

The literature search identified indexed publications by searching Scopus, PubMed, Embase and Medline databases up until May 2016. Search key words included: acceptability OR preference AND medicine AND (child OR infant OR pediatric OR paediatric) AND palatability OR taste OR smell OR size OR shape OR appearance OR swallowability. The search profile can be seen in online resource 1.

The process to identify the most relevant research included: screening of titles and abstracts; selection of studies based on inclusion criteria with checks from a second reviewer; searching of reference lists of included studies, and contacting experts for the details of any unpublished or ongoing studies (EuPFI network (www.eupfi.org) and consortium members within SPaeDD-UK (Smart Paediatric Drug Development – UK, accelerating paediatric formulation development <http://www.paediatricscienceuk.com>)) and finally data extraction using a bespoke data extraction table.

Only papers where information that specifically related to methodology to assess acceptability of medicines in pediatric populations was extracted and included in the results; many papers described

the acceptability of dosage forms but did not contain sufficient details on the methodology and could not be included.

The SPaeDD-UK project is guided by a steering committee with pharmaceutical scientists from academia and UK industry; this committee provided valuable input throughout the development of this review.

3. Results and discussion

Figure 1 shows the results of the search and the screening of literature to identify studies to include in this review.

3.1. Study Characteristics

A total of 61 unique papers were included in the analysis of acceptability, this is 31 additional papers compared to a previous review on a similar topic (palatability only) conducted by Davies and Tuleu (2008) [8] (17 related to acceptability not limited to palatability and an additional 14 papers on palatability were identified). All papers included measured the acceptability of medicines in a pediatric population; one paper included data pooled from adults and children as the authors stated that the results were similar across these groups [9]. The age of participants ranged from 0-18 years across all studies with more than two thirds of studies involving only those aged 12 years or younger (full details available within online resource 2). Fifteen studies included participants whose ages spanned at least 10 years; this may lead to variability in data capture based on the cognitive function of the younger versus older participants within these studies. Only one study reported using age based scales to assess acceptability where a simple scale was used for those aged 3-5 and an alternative for those aged 6-15 years [10].

In total 147 products were evaluated although some duplications were found. A table of all studies included is available in online resource 2. Brand names were rarely reported within the literature which limits the direct comparison between studies as it is already known that therapeutic equivalents can have very different organoleptic properties (e.g. [11-22]).

The number of products evaluated by each individual within a study varied from 1 to 5 with a mean value of 2.6 and median value of 2 products tasted by each participant. Only two of the studies included a placebo [23, 24].

Palatability with an emphasis on taste was the most common acceptability parameter evaluated in 54 of 61 studies included. Where taste was not assessed, common measures of acceptability included: the swallowability of dosage forms (e.g. [25-28]), or the ease of use of a product (e.g. [29, 30, 19]) with just one study evaluating the volume of liquid swallowed [31].

3.2. Methodology used to assess acceptability

Scale methods were the most popular to be used in assessing the acceptability of medicines in children, this includes direct pediatric reports and reports made by parents/carers or healthcare professionals on behalf of children. Visual analogue scales (VAS) and hedonic scales were used separately and also in combination in 32 of the studies investigated; hedonic scales without VAS reported for 16 studies and VAS alone in just 5 studies. Eight studies used a Likert scale alone or based on a question (e.g. Five point scale from 0 = disliked the taste a lot to 4=liked the taste a lot [32]). Five studies used a forced choice or preference between multiple products to rank their order in terms of acceptability. Surveys or questionnaires were used in eight studies. A range of other methods were reported including the observation of facial expressions during administration; the ease or ability to swallow the dosage form (e.g. [26, 27]); the prevalence of complaints or refusal to

take the medicine was used in one study [19]; and finally, one study evaluated the time taken for a nurse to administer the medicine as a measure of acceptability where it was stated that 60 seconds was the average administration time.[33].

The use of observations to assess swallowing seems to be a recent addition to the battery of tests available to assess acceptability, whereas Likert scales have become less popular with time.

3.2.1. Hedonic scales

Although adult sensory studies typically use a 9-point hedonic scale it has been suggested that fewer points are more appropriate for children; with 5-point hedonic scales being suitable for children aged 4 and over [34]. The number of faces within hedonic scales used to assess acceptability of medicines varied from 2 [10] up to 7 [21]. Gender specific scales were identified (e.g. [35-37]) but, in most cases they were gender neutral. The 5-face hedonic scale was most popular and used in 12 studies; 4 faces were used in 2 studies; 2 and 7 faces were used in one study each. The 2 face scale was used specifically in a young population aged 3-5 as a subset of a larger study where 4 faces were used in children from 6-15 years [10]. It has been suggested that the inclusion of a middle response in scale-based questions can often be selected as an 'easy way out' and prevents thought into the question being asked [38]. However, in determination of what is acceptable (and not necessarily liked) a neutral face seems appropriate.

In the sensory evaluation of food hedonic scales are used with verbal descriptors for children. Chen et al. (1996) showed that 3 faces with verbal descriptors could be used with children from 3-4 years and 5 faces from 4-5 years with a 7 point version being used with children over 5 years. [34]

Hedonic scales provide categorical data which can limit the number of statistical tests that can be applied, although the more points on the scale the better the tool will be. Chi squared statistical analysis is used to determine whether differences are observed between two products assessed. They are proven to be useful for young children although it is critical that the facial expressions are meaningful to the participants. These tests rely on a comparison of two products to determine whether the score for one product are different to the control.

Hedonic scales have been demonstrated to be appropriate to use in sensory testing with children above the age of 4 [39]. There are also reports of parents interpreting the behaviour of a toddler as he/she tasted the food and then reported the child's acceptance on a hedonic scale [40]. Hedonic scales were used with children as young as 3 in several acceptability studies [13, 41, 10, 42, 43, 18].

Age-appropriate VAS and hedonic scales are widely used in the assessment of pain in pediatric populations and these are often used as the basis for other scales of this type. The Wong-Baker FACES Pain Rating Scale has been extensively used in children to rate pain severity and has been validated outside the emergency department, mostly for chronic pain [44]. This validated scale includes 6 faces and reads from no pain (positive happy face) at the left to most painful (negative sad face) at the right. The 9-point hedonic scale that has been the most commonly used scale in adult consumer preference and acceptability of foods showed no difference in reports based on structural variations; that reads from positive to negative or vice versa [45]. In this review the taste

scales reported showed negative (sad face) to positive (happy face) in 22 studies and from positive (happy face) to negative (sad face) in 5 studies.

As with pain, numerous hedonic scales have been developed to measure acceptability of medicines, yet it remains unclear whether any of the scales is better for a particular purpose with regard to validity, reliability, feasibility, and preference [46]. Table 1 shows a range of hedonic scales used in acceptability testing of medicines in children.

3.2.2. Visual Analogue Scales (VAS)

VAS require selecting a point on a straight line (usually 100mm) representing the dimension of agreement with the statements that are written beneath the line (termed anchor phrases). They have been extensively researched in the assessment of pain and they show good sensitivity and validity for most children at age seven years and older [54, 55]. In the assessment of acceptability of a medicine they were used in children as young as 5 years [30].

VAS provides continuous data and is better suited to looking at differences between samples as the data can be used to set significance levels and analysis via statistical t-tests. However, they are limited by the age at which children comprehend their purpose and transpose a feeling or sensation to a linear scale. It is also critical that the anchor phrases at the extremes of the scale are comprehensible to the participants. The misuse of hedonic and VAS has previously been reported (e.g. [56]) where the anchor phrases are not meaningful to the study participants. The anchor phrases used in hedonic scales were included in table 1 and those used with VAS are listed in table 2.

Some studies used a VAS without anchor phrases when in combination with a hedonic scale (e.g. [47, 50, 48]).

3.2.3. Combined VAS and hedonic scales

Combining VAS with hedonic uses facial expressions in place or as well as anchor phrases to generate a tool that is meaningful to participants. In the studies that reported using a combination of VAS with hedonic, 5 faces were also most popular with 10 studies using this combination. In one study, 10 faces were used [41] and in another 2 faces in combination with the VAS [24]. One study stated that a VAS and hedonic were used but no further details were provided [22].

A combination of VAS with hedonic images makes statistical analysis complex as this uses both categorical and continuous scales therefore subsequent analysis is complicated. A participant is likely to select a point on the line that correlates to a face rather than considering the line a continuous scale; therefore interpretation of data is flawed. Despite these methodological flaws, it is acknowledged that this has become common practice in acceptability testing.

The results of an industry survey on tools used to assess palatability and swallowability also reported that 5-face hedonic scales and VAS were most popular although the data are not clear as to whether these were used in combination and this survey only received six responses [62].

3.2.4. Observations of acceptability

Observations of facial reactions were used in acceptability testing of medicines [63, 53, 60]. Moniot-Ville et al (1998) used a simple researcher observation of a child, where if the child smiled whilst taking the medicine it was rated as good or fairly good; if the child accepted the medicine without making faces it was rated as acceptable and if the child made faces or complained about the taste this was rated as poor. Verrotti et al (2012) queried parents about their child's reaction or facial expression as a surrogate for palatability, "On the basis of reaction/facial expression of your child, do you think that the medication is: pleasant; not sure or unpleasant?"

Three studies which investigated the use of minitabets in children used observations to assess the acceptability where swallowing of the dosage form, even with chewing, was reported as an acceptable formulation [26, 28, 27].

Other studies used parent reported outcomes of acceptability where observations of behaviour, and facial expressions were likely to form the basis for this, although this was not explicitly stated [64, 14, 57, 17, 65, 19, 66, 61].

A more detailed protocol of observations was reported by Saez-Llorens (2009) based on a study that assessed the acceptability of famciclovir pediatric formulation [60]. Parents were asked to report the acceptability of taste and aftertaste using the statements listed below which were aligned to hedonic scales:

1. Very badly accepted/unacceptable: child showed great displeasure compromising use of formulation
2. Badly but accepted: child showed displeasure with dosing but could be coaxed to take complete dose
3. Neither good nor bad: child showed no apparent displeasure and with little effort was coaxed to take complete dose
4. Well accepted: child appeared to enjoy the formulation with little coaxing ingested most of dose
5. Very well accepted: child appeared eager and ingested most of dose without special coaxing

3.2.5. Other tools used to assess acceptability

Likert scales (verbal or written categorical response scales) have also been used in the evaluation of acceptability of pediatric medicines. In many cases, Likert scales were combined with facial expressions or used within a questionnaire with responses including: 1 = very tasty to 5 = very bitter [67]; 0 = disliked the taste a lot to 4 = liked the taste a lot [32].

Spontaneous verbal reactions were also captured in some studies (e.g. [21, 18, 12]). These are of value as palatability or acceptability is a subjective measure and the reasons for non-acceptance are critical in adapting the medicine for that individual. The prevalence of complaints or refusals has also been recorded (e.g. [19]) and this data is of value as it records the longer term acceptability, or compliance with the medication which can be essential for therapeutic success. The child's willingness to take the medicine again has also been recorded in some studies (e.g. [23, 48]).

One study recorded the time taken by a nurse to administer the medicine as a surrogate for acceptability [33].

3.3. Criteria to define acceptability

Despite identification of 61 unique literature reports on the acceptability of medicines for pediatric populations only 10 stated criteria (listed in Table 3) used to define an acceptable product; this needs to be addressed in reports going forwards.

A more detailed definition of acceptability was reported that used descriptors aligned to a hedonic scale to classify medicines as unacceptable to very well accepted [60]; these descriptors of acceptability ensured that participants, in this case parents, were aware of the parameter under evaluation. A simple report based on caregivers reports of their child and their perception of the taste being better, the same or worse than other medicines has also been reported [68]. Proxy reports by parents or carers on the acceptability of a medicine may be a useful method to triangulate patient responses from VAS or hedonic scales to assess the validity of such scales.

In veterinary medicine, non-acceptance is characterised as delayed uptake; partial uptake; regurgitation, spitting out the product or direct refusal [69]. Other reports of rejection behaviours in sensory testing include a child closing their mouth firmly, pushing the food/drink away, crying or spitting out the tastant [70, 71].

3.4. Statistical methodology in acceptability assessment

The evaluation of acceptability needs to be underpinned by robust statistical methodology. However, there have been very limited reports of the application of statistics to acceptability testing or of an up-front definition of the hypothesis or criteria for acceptance as reported in Table 3. Existing criteria for acceptance are somewhat limited. A value of 80% of the sample population in agreement that the product is acceptable is generally considered to be the current standard requirement. This 80% threshold value was used in proposed regulatory guidelines on the demonstration of palatability of veterinary medicinal products; which may be similar to considerations given to the palatability of medicines for human use [5]. The choice of sample size is complex in this type of analysis, as previously highlighted from the literature on consumer rejection threshold values in sensory assessment [72].

The literature review conducted demonstrated that the size of the study population varied from 10 – 769 participants, with an average number of 112.6 and a median number of 46 participants evaluating each product. EMA veterinary guidance on palatability proposed a sample size of 50 animals if the product is only observed once or 25 if the product is administered on at least two occasions; the statistical justification for this is not recorded but the sample sizes are similar to those used in sensory analysis for acceptance [5]. Use of the total number that accept a product is more robust than providing a mean VAS or hedonic score as a mean value may not accurately reflect the extremes within the population. The sample size used in sensory testing is also widely debated and is dependent upon the methodology used and the ultimate endpoint. An adequate sample size, to be able to document clear sensory differences in foods, when performing discrimination tests is 25-40

participants [73]. Nevertheless, some discrimination tests can be performed with as few as six participants if differences between samples are large and there are trained panellists [74].

In sensory testing conducted in adults, assessment of differences in two products using either hedonic or visual analogue scales will depend upon the size of difference you consider significant and also the competence of the assessors [75]. Statistical analysis is typically via a t-test for two items and an ANOVA for more than two. A significant ANOVA result may be compared using an appropriate post hoc test depending upon the distribution of data. In cases where different groups of participants are trying different products a simple chi-squared test can be performed.

There have been studies that have reported the statistical parameters used when comparing the tastes of more than one sample. For example, when assessing acceptability of zinc dispersible tablets [65], Nasrin et al (2005) proposed a sample size of 140 children per group to identify a +/- 7.5% difference in acceptability when acceptability is set at 70% with a level of confidence of 95%; this study required parents to report whether the medicine was better, same or worse than other medicines with responses of the same or better being recorded as acceptable. Thompson et al (2015), proposed using a non-inferiority test to a reference product where, to achieve a significance level of 0.05, a sample size of 50 subjects was required based on a VAS scale although basis for this methodology is missing from the original reference [6]. The most important aspect is the clinical significance of a change which needs to be considered as it is feasible that both the reference and sample product are either acceptable or unacceptable depending on the values of the scale. This has previously been observed using pain scales when a child's pain level has diminished from 8 to 7 following intervention, but does this necessarily represent a success in treatment?

4. Conclusions

There are many measurements reported that assess the acceptability of medicines designed for children, however a standardised methodology has not yet been identified and may not be possible due to the wide range in ages and products that require evaluation. It is important that a scale to assess acceptability is suitable for that intended purpose.

A robust method that allows assessment of acceptability of a pediatric medicine, within the target population is urgently required. Pain scales are an established tool used with children; Hester et al. (1998) collated a number of desirable features that pain scales for children should have, including:

- Developmentally and culturally appropriate to participants (i.e. within the child's cognitive and language skills)
- Easily and quickly understood by participants who have minimal formal education
- Well-liked by participants and clinicians
- Places low burden on clinician and participant
- Inexpensive and easy to obtain, reproduce and distribute to clinicians, participants and their families

Existing VAS and hedonic scales are likely to be preferred by those administering and undertaking the evaluation as they meet the criteria outlined above. The use of space, graphics, underlining, bold type, colour, shading and other qualities of design can affect how participants react and engage with

a questionnaire [76]. It is important that the images used are meaningful to the participants within the study. It has been reported that children prefer hedonic scales to VAS when given a choice [77].

A definition on what the meaning of acceptable is in a clinical setting in addition to that provided is required to drive the development of the most appropriate scale such that the sample size, statistical analysis and endpoints allow classification of the medicines under test as either acceptable or not. This may be linked to the use of a standardised control, for example, in taste evaluation whether the medicine under test is better or worse than the control is used. A standardised methodology would allow better comparisons in acceptability across studies and enable comparisons of products to define which are better accepted within a given population provided a better link to clinical relevance. Such methodology would be beneficial both to those working in the development of pediatric medicines and for regulators involved in the approval of pediatric medicines. The tool to assess acceptability may influence the overall results therefore the definition needs to be related to the tool under use. Using the existing definition of acceptability, “an overall ability of the patient and caregiver (defined as ‘user’) to use a medicinal product as intended (or authorised)” [3]; observations are a useful part of the overall toolkit that should be used to assess acceptability.

It remains unclear as to which scale is the best with regard to validity, reliability, feasibility and preference. Current practice demonstrates that hedonic and visual analogue scales are most used and these seem appropriate at this stage. Further work required in this area includes an evaluation of an appropriate standardised scale within the relevant population to ensure that the descriptors are meaningful and that the resulting data is reliable rather than developing new scales (as there are already so many).

Compliance with Ethical Standards

This project was supported by Innovate UK Formulated Products Collaborative R&D project (Ref: 101709). SPaeDD-UK (Accelerating Paediatric Formulation Development through Smart Design and Predictive Science), which is co-funded by Innovate UK and the contributing companies of AstraZeneca, Bristol Myers Squibb, GlaxoSmithKline, Juniper Pharmaceuticals and Pfizer.

All authors (HKB and PM) declare that they have no conflict of interest.

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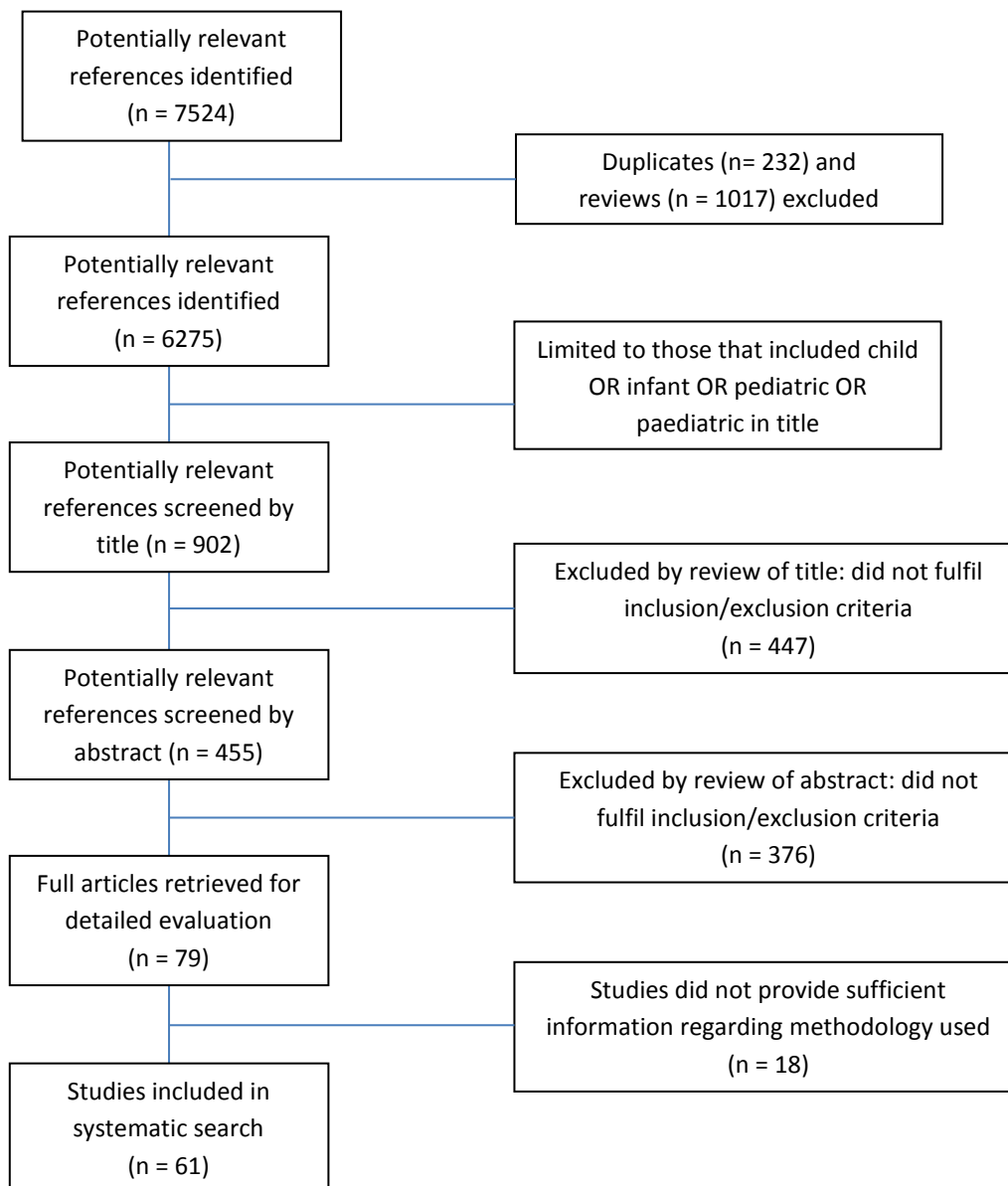


Figure 1. Flow diagram of study identification and selection

Online Resource 1. Search profile for systematic search of documents

Database	Search number	Search word	Remit	Results
Scopus	1	Acceptability OR preference	Title/abstract/keywords	385388
	2	Medicine	Within results above	94688
	3	Child OR infant OR pediatric OR paediatric	Within results above	28432
	4	palatability OR taste OR smell OR size OR shape OR appearance OR swallowability	Within results above	7284
PubMed	5	Acceptability OR preference	Title/abstract	16398
	6	Medicine	Title/abstract	4474574
	7	Child OR infant OR pediatric OR paediatric	Title/abstract	273920
	8	palatability OR taste OR smell OR size OR shape OR appearance OR swallowability	Title/abstract	118121
	9	5 AND 6 AND 7 AND 8		227
EMBASE	10	Acceptability OR preference	keyword	152189
	11	Medicine	keyword	
	12	Child OR infant OR pediatric OR paediatric	keyword	2510551
	13	palatability OR taste OR smell OR size OR shape OR appearance OR swallowability	keyword	1570461
	14	10 AND 11 AND 12 AND 13		11
Medline	15	Acceptability OR preference	keyword	113649
	16	Medicine	keyword	47280
	17	Child OR infant OR pediatric OR paediatric	keyword	2433874
	18	palatability OR taste OR smell OR size OR shape OR appearance OR swallowability	keyword	1255197
	19	15 AND 16 AND 17 AND 18		2

Online Resource 1. Summary of studies included in the review detailing methodology reported for acceptability testing of medicines in children

Reference	Dosage form (drug)	Dosage form (formulation)	Test population (n=)	Test population (age range)	Tool used (VAS alone; VAS + hedonic; hedonic alone; open question; forced choice/preference)	Number of faces in hedonic scale
[13]	Trimethoprim-sulfamethoxazole, Biocraft = generic, Cephalexin monohydrate (Biocraft) = generic, Cephalexin monohydrate Dista (Keflex®) = brand, erythromycin/sulfosoxazole Alra= generic, erythromycin/sulfosoxazole Ross (Pediazole®)= brand, sulfamethoxazole, Roche (Bactrim®)= brand	Liquid	16	3-14 years	Hedonic alone	5
[16]	Prednisolone (generic) Prelone vs Orapred	Liquid	18	6-10 years	Hedonic alone	5
[17]	Colecalciferol vide3 vs Oleovit D3	Liquid	70	<81 days	Hedonic alone (parent reported)	4
[58]	Amlodipine besylate (Norvasc) vs lercanidipine (Zanidip)	Liquid (crushed tablets)	20	4-11 years	Hedonic alone	5
[10]	Sodium valproate	Prolonged release granules (Micropakine®) vs liquid	236	3-15 years	Hedonic alone	2 (for under 5s) 4 (for over 5s)
[42]	Mercaptopurine oral suspension (Xaluprine(R))	Liquid	22	3-16 years	Hedonic scale plus open/closed questions	5

[36]	Clarithromycin vs cefpodoxime proxetil vs cefprozil vs azithromycin vs cefixime vs loracarbef	Liquid	769	4-12 years	Gender specific hedonic After both medications were taken the child was asked which medication had the preferable taste and colour.	5
[37]	Amoxicillin/clavulanate potassium vs cefprozil vs azithromycin vs cefdinir	Liquid	148	4-8 years	Gender specific hedonic scale	5
[60]	Famciclovir	Liquid (sprinkle capsule mixed with 5 ml orasweet immediately prior to dosing)	51	1-12 years	Hedonic scale	5
[43]	Cefuroxime axetil vs clarithromycin vs cefpodoxime proxetil vs amoxicillin	Liquid	153	3-8 years	Hedonic scale	5
[20]	Ondansetron	Liquid	59	Not stated	Hedonic scale	5
[78]	Ranitidine vs lansoprazole	Liquid	110	5- 11 years	Hedonic scale	5
[79]	Ranitidine vs lansoprazole	Liquid vs orally disintegrating tablet	104	6-11 years	Hedonic scale	5
[53]	Valproate	Multiparticulate sprinkle	108	Mean age 6.7 years	Hedonic	5
[21]	Amylmetacresol and 2,4-dichlorobenzyl (AMC/DCBA)	Lozenge	102	6-12 years	Hedonic scale. The spontaneous reaction of the child on tasting each lozenge was observed and recorded.	7
[18]	Bacampicillin (5 brands)	Liquid	19-23	3-12 years	Hedonic scale plus spontaneous verbal judgement	5
[59]	Activated charcoal	Liquid	44	14-19 years	VAS	

[14]	Paracetamol Parapaed vs Paracare double strength	Liquid	106	6-18 years	VAS alone Parent and nurse estimations on a VAS scale	
[30]	Desmopressin lyophilisate	Dispersible tablet (MELT) vs conventional oral tablet	221	5-15 years	VAS	
[57]	Prednisolone	Liquid vs crushed tablets	35	0.25 - 8 years	VAS alone (parent reported)	
[61]	Placebo	Tablet; powder; liquid	148	1-4 years	VAS and observation of intake (parent reported)	
[52]	Strawberry-, orange- and cherry-flavoured oral artemether-lumefantrine suspension	Liquid	48	7-10 years	VAS + hedonic	5
[47]	Amoxicillin-clavulanic acid (Augmentin), cefprozil (Cefzil), azithromycin (Zithromax), cefixime (Suprax)	Liquid	30	5-8 years	VAS + Hedonic	5
[50]	Activated charcoal	Liquid	30	5-9 years	VAS + Hedonic	5
[48]	Oral rehydration Enfalyte, Pedialyte, Pediatric electrolyte	Liquid	66	5-10 years	VAS + Hedonic Volume Consumed Would you take this again? Preference	5
[41]	Activated charcoal (Liqui-Char) + flavourings	Liquid	53	3-17 years	VAS + Hedonic	10
[49]	Prednisolone vs dexamethasone	Liquid	39	5-12 years	VAS + Hedonic	5
[80]	Cloxacillin vs fusidic acid vs cephalixin vs erythromycin	Liquid	20	6-12 years	VAS + Hedonic	5

[81]	Clarithromycin vs erythromycin vs amoxicillin and clavulanic acid vs azithromycin	Liquid	50	Mean age 6.3 years	VAS + Hedonic	5
[35]	Valsartan vs losartan vs ibesartan vs telmisartan vs candesartan cilexetil	Crushed tablets	21	4-11 years	VAS + Hedonic (gender specific)	5
[24]	Ibuprofen	Liquid	151	4-7 years	VAS + Hedonic (2 faces sad and happy)	2
[51]	Codeine (Thornton and Ross Limited, Linthwaite, Huddersfield, UK) vs paracetamol (SSL International PLC) vs ibuprofen (Pinewood)	Liquid	21-66	5-16 years	VAS + hedonic	5
[82]	Amoxicillin/clavulanate vs cefprozil vs azithromycin vs cefixime	Liquid	90	5-9 years	VAS + Hedonic	5
[22]	Ampicillin-cloxacillin (Emzorclox) vs cefuroxime axetil (Zinnat) vs amoxicillin-clavulanate (Fleming, Medreich) vs cefixime (Zemicef)	Liquid	24	6-11 years	VAS + Hedonic	Not stated
[83]	Clonidine + ibuprofen mixture (Nureflex®)	Liquid vs intranasal spray	20	1.2-6.5 years	Three-point Likert scale was applied for evaluation of taste: 1 = good, 2 = indifferent, 3 = bitter, unpleasant	

[64]	Amoxicillin/clavulanate vs Cefixime	Liquid	155	0.5-12 years	A Likert scale ranging from 1 (disliked) to 3 (liked a lot) was used for the following question: Child liked taste of medicine	
[15]	Pivampicillin (Pondocillin)	Liquid	45	1-7 years	Likert scale question: state whether the medicine tasted "very good" = 2; good = 1 or bad = 0	
[84]	Cholestyramine	Tablet vs powder	38	10-18 years	6-point Likert scale	
[32]	Ibuprofen vs paracetamol	Liquid	42	0.4-11.6 years	Five point Likert scale from 0 = disliked the taste a lot to 4=liked the taste a lot	
[63]	Roxithromycin	Liquid (tablet for suspension)	210	2-8 years	Likert scale and observation of child facial responses	
[67]	Carbamazepine vs valproate	Tablets (crushed)	Not stated	5-12 years	Likert scale	
[66]	Pancrelipase	Microtablets	16	0.5-2.5 years	Likert scale Parental assessment of palatability using a 4 point	
[28]	Placebo	Minitablets	60	0.5-6 years	Observations that the child swallowed the minitables	
[19]	Dexamethasone vs prednisolone	Liquid	80	1-11 years	Ease of taking and prevalence of complaints/refusal	

[26]	Placebo	Minitablets vs liquid	306	0.6-5 years	Observations of the ability to swallow the dosage form (not refuse or reject it)	
[27]	Placebo	Minitablets in jelly	30	2-3 years	Observations of the ability to swallow the dosage form (not refuse or reject it)	
[85]	Vivotif BERNA oral typhoid vaccine	Enteric coated capsule	434	4-15 years	Observations of the ability to swallow 3 capsules without breaking them	
[11]	Ranitidine	Liquid (Zantac®) vs effervescent tablet (Zantac® Efferdose)	102	4-8 years	Forced choice preference question	
[86]	Antiretroviral therapy	Liquid and tablets	267	0.25-17 years	Questionnaires to caregivers about issues with formulations and a preference	
[65]	Zinc sulfate	Liquid (dispersible tablet)	303	0.25-5 years	Questionnaire with response options better, same, or worse than other medicines	
[87]	Creon®	Minimicrospheres within a capsule vs conventional microspheres	51	3-17 years	Preference based on ease of swallowing presence/absence of an aftertaste and feeling of fullness after the capsule	
[88]	Oral montelukast and inhaled cromolyn	Chewable tablet of montelukast or comolyn via metered dose inhaler	236	6-11 years	Child satisfaction questionnaire and preference	
[29]	Inhaled corticosteroids with either zafirlukast tablets or inhaled beclomethason	Inhaler plus tablets vs inhaler plus inhaler	132	12-17 years	Questionnaire on preference and ease of use	

	dipropionate					
[25]	Oral medicine (not specified)	Number of tablets that are acceptable	202	5-11 years	Survey - questionnaire	
[12]	Phenoxymethylpenicillin	Liquid	316	3-10 years	Open question (scored verbal assessment following a non-leading open question)	
[89]	Valproate	Sprinkle vs liquid	12	5-16 years	Questionnaire with preference of sprinkle vs syrup	
[90]	Ondansetron vs placebo	Orally disintegrating tablet	31	5-11 years	Each child was asked to evaluate the tablet according to taste, sensation, and willingness to take the medication in the future	
[31]	Pediapred (1 mg/ml; Medeva, Surrey, UK) vs Prelone (3 mg/ml; Muro Pharmaceuticals, Tewksbury, MA)	Liquid	51	< 10 years	Survey - questionnaire	
[91]	Antimicrobial suspensions used to treat otitis media	Liquid	16	Not stated	Score out of 10 for appearance; smell; texture; taste and aftertaste	
[9]	Oral rehydration solution (flavours)	Liquid	30	Adults and children	Grade as good, not good or bad	

[33]	Erythromycin ethylsuccinate vs phenoxymethyl-penicillin potassium	Liquid	20	0.2-8 years	The time a nurse required to give the drug to a child was recorded and a score of the acceptance was given by the nurse.	
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Table 1. Overview of hedonic scales used in acceptability studies in children

Comments	Reference
Two gender specific 5-face hedonic scales used in children aged 4- 8 years to assess palatability of antibiotic suspensions. Male faces were shown to male subjects and female faces to female subjects. The expression change is demonstrated by changes in the eyes, eyebrows and mouth. The age of the child images reflects the age of the participants The scale direction was positive at the left to negative at the right	[37, 36]
A 5-face hedonic scale used to assess palatability of a range of medicines in children aged 3-16 years. The faces are gender neutral with no hair and the only expression change is the mouth. The scale direction was negative at the left to positive at the right	[47-51] [42, 52]
A 5-face hedonic scale used to assess the palatability of modified release granule formulation of valproate The faces are gender neutral with no hair. The expression change is demonstrated by changes in the eyes, eyebrows and mouth. The negative face shows tears and the most positive face is winking. The scale direction was negative at the left to positive at the right	[53]
A 5-face hedonic scale proposed as the best practice scale for assessing palatability of paediatric medicines by the Global Alliance for Pediatric Therapeutics, a public-private consortium under the guidance of the Institute for Pediatric Innovation The faces are gender neutral with no hair. The expression change is demonstrated by changes in the eyes, eyebrows and mouth. The scale direction was negative at the left to positive at the right	[6]
Two hedonic scales used to assess the acceptability of a microgranule formulation of sodium valproate. Children aged 3-5 used a 2 face scale and those aged 5-14 a four face scale The faces are gender neutral with short hair. The expression change is demonstrated by changes in the eyes and mouth. The negative face shows tears. The scale direction was negative at the left to positive at the right	[10]

Table 2. List of phrases used in VAS to assess acceptability of medicines in children

Phrases		Reference
I did not like it	I liked it very much	[52]
Did not like at all	Liked very much	[14]
I find it very easy to use this medicine	I find it very difficult to use this medicine	[30]
Nice taste	Foul taste	[57]
Really good	Really bad	[35, 58]
Bad	Good	[42, 59]
Very poor taste	Very good taste	[60]
Very much unpleasant, bothersome*	Not at all unpleasant, bothersome*	[61]

*This is a direct translation from a Dutch study

Table 3. Literature reports of criteria to define acceptability of medicines

Limit of acceptance/palatability	Products deemed to be acceptable	Study reference
<i>Hedonic Scales</i>		
In a 2 face hedonic the positive face was considered acceptable = score >1/2 In the 4 face hedonic the two positive faces were considered acceptable = score >2/4	33-43% of children found the sodium valproate syrup acceptable 77-88% of children found the sodium valproate sustained release granule acceptable	[10]
In a 5 point hedonic scale; neutral to positive was recorded of acceptable = score >2/5	17/22 (77%) participants reported that the taste was neutral to positive which was considered to be acceptable	[42]
Excellent palatability = mean score of 4.21/5	The amoxicillin reference product was stated to have excellent palatability	[43]
Acceptable taste = mean score of 3.4/5 Unacceptable taste = mean score of 2.1/5	Two products were included that were stated to be acceptable and unacceptable in terms of taste Acceptable taste was brand W penicillin Unacceptable taste was brand U penicillin	[18]
Primary endpoint was % of participants with a score of >4/7	85.3 % of subjects found the strawberry flavour lozenge to be acceptable and 49.0 % for the orange flavour lozenge	[21]
<i>Visual Analogue Scale</i>		
50mm point on a 100mm VAS stated to be ambivalent taste, scores above 50 mm are palatable	Paracare double strength paracetamol stated to be palatable and acceptable compared to Parapaed	[14]
<i>Observations/Carer reports</i>		
A child accepting the drug without making faces or smiling whilst observed taking the medicine	70.5% of children accepted roxithromycin tablet for suspension	[63]
Observations were used to assess swallowing of the dosage form. Swallowing the dose, even with chewing, was measured as an acceptable formulation	Minitablets 2-3 mm in diameter are acceptable to children ≥ 6 months When suspended in jelly up to 10 minitables are acceptable as a single dose	[26, 28, 27]
Carers needed to state that the product was equally or more acceptable to their child than other medicines (70% of population agreeing was used as basis for statistical powering)	93.1 % of the treated children thought that zinc tablets were equally or even more acceptable than other medicines. 83.5% of caretakers stated that they would use these tablets again	[65]