

1 **Can a flavoured spray (Pill Glide) help children swallow their medicines? A pilot study**

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26 Marking (Conformit e Europ eenne); Great Ormond Street Hospital (GOSH); Human
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Contributors' Statement Page:

Mamta Jagani conceptualized and designed the study, coordinated, assisted and supervised data collection, drafted the initial manuscript, reviewed and revised the subsequent manuscript drafts until completion

Hélène Legay coordinated study documentation, assisted in data collection, critically reviewed and revised the various manuscript drafts until completion.

Sejal Ranmal contributed to the design of the data collection instruments, drafting the application for research ethics (REC) approval, and reviewed and revised the manuscript.

Julie Bertrand undertook the statistical analysis and reviewed and revised the various manuscript drafts.

Kuan Ooi substantially contributed to the conception and design of the study and critically reviewed the final draft of the manuscript.

Catherine Tuleu was the Principal Investigator, designed the study, obtained the R&D and REC approvals, carried out the initial analyses, reviewed and revised the subsequent manuscript drafts until completion.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

1 **Abstract**

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Paediatric pharmacists are constantly faced with the challenges of supporting children and caregivers for whom the difficulties of swallowing medicines can be a daily struggle. Most medicines are only available as tablets and capsules, and where liquid alternative exist, these products often have issues with palatability and high costs. The objective of this study was to evaluate whether the swallowing spray Pill Glide could help children in taking their solid and liquid medicines.

This open label pilot study compared the spray with a behavioural approach alone, the current standard of care at the paediatric hospital. Patients were children on long term drug therapies, either transitioning from liquid preparations to tablets and capsules, or known to be experiencing swallowing difficulties. Using age-adapted diaries, patients self-reported the difficulty of taking medicines on a 6 point hedonic scale, for two week prior to the intervention, and then for one week while using the spray.

Data was analysed from 10 children aged 6-16 years, with an average burden of 3.5 tablets per day. Pill Glide,(strawberry was the most popular flavour) was shown to significantly decrease the overall medicine taking difficulty score by 0.93 [0.33-1.53], almost 1 hedonic face point on the scale used ($p=0.002$). There was insufficient data for liquid medicines.

The flavoured spray Pill Glide could help children with pill swallowing, thus improving patient acceptability of medicines and potentially adherence. It could also be implemented as a useful cost-saving intervention as solid dosage forms are cheaper.

1 **Introduction**

2 Swallowing difficulties affect people of all ages, but may be more prevalent in children, with
3 many unable or unwilling to swallow conventional tablets or capsules. Issues with palatability,
4 storage, stability, and costs often occur where liquid alternatives exist. Acceptability of
5 medicines¹ is likely to have a significant impact on patient adherence, and consequently safety
6 and efficacy. Size and shape are critical acceptability attributes for monolithic dosage forms to
7 be swallowed intact; however the need for training or dosing aids should also be considered.²

8 A recent systematic review detailed various swallowing interventions, including behavioural
9 therapy, a flavoured spray (Pill Glide), specialized cups, and head posture training³. All were
10 successful in their own right, but studies were limited by their observational nature, small
11 sample size, and lack of controls, highlighting the pressing need for further research.

12 Pill Glide (CE approved medical device) is a flavoured swallowing spray. Encouraging
13 testimonials⁴ claim that it significantly helps people to swallow medicines. In one uncontrolled
14 study, 7/11 teenagers (9-17 years) with self-reported swallowing difficulties successfully took
15 one tic-tac candy (~8 mm) using Pill Glide.⁵ However, no prospective, controlled studies with
16 younger children have been published. This study was prompted by anecdotal evidence⁶
17 whereby Pill Glide helped a young patient with human immunodeficiency virus (HIV) at Great
18 Ormond Street Hospital for Children (GOSH) leading to significant improvement in viral load.
19 In order to improve adherence and quality of care, this pilot study objectively compared Pill
20 Glide with the current GOSH behavioural approach based on information leaflets to support
21 parents/carers in the administration of medicines to children. Furthermore, Pill Glide could be
22 resource effective for healthcare providers as evidence suggests that switching from oral liquids
23 to solid dosage forms could lead to considerable cost savings⁷.

24

25 **Case reports**

1 This open label study (Figure 1) was approved by a National Health Service (NHS) research
2 ethics committee (REC) (REC Number 11/LO/0831). Over 3 weeks, patients used age-adapted,
3 self-reporting diaries to record difficulty/ease of swallowing their medicines, using a 6-point
4 numeric or facial hedonic scale, ranging from 0 “not difficult” (happiest face) to 5 “most
5 difficult” (saddest face). For the first two control weeks, baseline data was recorded while
6 implementing the GOSH behavioural training package⁸. For the third week, patients used the
7 Pill Glide sprays (grape, orange, peach or strawberry flavours, courtesy of FLAVORx, Inc).
8 Patients were instructed to spray once before and once after taking each dose of every
9 medication. For patients taking liquid medications, taste improvement was recorded as a
10 secondary outcome, as was flavour preference. A 2 week baseline measurement and 1 week
11 intervention period was recommended to avoid bias and placebo effect. All study material
12 including diaries, information sheets and consent/assent forms, were reviewed for age and
13 cognitive appropriateness by members of the Young People’s Advisory Groups (YPAG) of the
14 Medicines for Children Research Network (MCRN) .

15 Participants were children on multiple drug therapies and those transitioning from liquid to
16 solid medicines; patients were recruited from the Bone Marrow Transplant (BMT), and
17 Infectious Diseases (ID) wards, and HIV out-patients setting. Children were excluded if they
18 had any known swallowing impairment, or food or drug allergies. A total of twenty-five
19 children aged 6-17 years old were enrolled after 11 months, mostly from the HIV outpatient
20 clinic but only 10 fully completed diaries were returned (response rate: 40%). The average age
21 of participants (60% female) was 12.3 years (median 13, range 6-16). The size and shape of
22 solid dosage forms varied widely but the burden of administration was relatively high for most
23 patients (Table 1). Participants took a total of 15 non manipulated solid and 3 liquid forms,
24 with the number of medicines per child averaging 3.5 tablets per day.

1 For each patient ($i=1,\dots,10$) and prescribed drug ($k=1,\dots,n_{ik}$; e.g. for patient F13, $n_{ik}=4$), an
2 overall Medicine Taking Difficulty Score ($MTDS_{ik}$) was calculated as the sum of the reported
3 scores at each administration (d) of the drug ($MTDS_{ikd}$) divided by the corresponding total
4 number of administrations n_{Dik} taken over a given period, $MTDS_{ik} = \frac{\sum_{d=1}^{n_{Dik}} MTDS_{ikd}}{n_{Dik}}$. This
5 MTDS (from 0 to 5) was calculated for both the behavioural and Pill Glide periods, with
6 score values for each period compared in pairs as defined by the indexes i and k .
7 Figure 2 illustrates MTDS for the two periods for each participant, for all dosage forms and for
8 solid dosage forms only. A subject had as many score estimates as drugs taken. Overall, the
9 results were excellent for solid medications for which the strawberry spray was used most
10 frequently. The mean difference in overall MTDS between the behavioural approach and Pill
11 Glide intervention periods (Figure 3) was 0.93 [0.33-1.53], almost 1 hedonic face point on the
12 scale. This decrease with Pill Glide was statistically significant (p -value=0.002, paired t-test,
13 24 degrees of freedom). Only one patient (a 6 year old taking lamivudine solution) had an
14 increased score of more than 1 point with Pill Glide.

15 Exposure to Pill Glide excipients was minimal and deemed safe. There were no reports of acute
16 reactions nor adverse events or choking episodes at enrolment and during the study period . In
17 contrast, some very positive comments were received: *“The tablet just slid down my throat”*;
18 *“I don’t have to cut my tablets in half any more”*; *“I never thought I could swallow whole*
19 *tablets”*.

20

21 **Discussion**

22 These results support the use of Pill Glide in children, as it aided their ability to swallow
23 relatively large solid oral dosage forms and avoided the need for manipulations. This is a
24 widespread practice in paediatrics, and can have detrimental consequences on safety and
25 efficacy. For example the unpleasant Kaletra® (lopinavir/ritonavir) oral solution is poorly

1 accepted by children; it has a high ethanol (42.4% v/v) and propylene glycol content (15.3%
2 w/v).^{9,10} If swallowing whole is not feasible, the alternative, is either breaking or crushing the
3 tablet. This has shown to significantly reduce drug exposure, with area under the curve (AUC)
4 halved¹¹ and patients potentially requiring higher doses and therapeutic drug monitoring. While
5 such manipulation should be avoided, patients and their carers are often left with very few
6 alternative options. In the present study, two participants reported how they stopped halving
7 their efavirenz tablets by the fifth day of using Pill Glide, while another 6 year old participant
8 successfully transitioned from liquid to tablet formulation.

9 Efforts have been made in recent years to try to establish a relationship between acceptable
10 tablet and capsule sizes/shape and the age of children^{12,13}, but the evidence behind prescriptive
11 limits is lacking¹⁴, and numerous other factors (e.g. indication, patient and carer motivation,
12 counselling from healthcare professionals) are equally important.¹⁵ One third of adults also
13 reportedly suffers from difficulties swallowing medicines¹⁶. Therefore a positive self-
14 implementing strategy such as Pill Glide could have wider benefits. This study demonstrated
15 the ease and resource-effectiveness of this intervention (excluding the cost of the device),
16 which is not disease specific and applicable to different/any solid dosage forms. Tablet crushers
17 are often provided to patients so Pill Glide could simply be another medical device supplied to
18 aid administration and improve therapeutic outcomes. The NHS recognises the importance of
19 offering patients the opportunity to be more involved and make choices regarding their
20 treatment.¹⁷ Pill Glide provided children with some control and autonomy in taking their
21 medicines (for which they have no choice) with the additional choice of four flavours (to avoid
22 aversion or monotony). This empowering and positive experience may have further assisted
23 with successful pill swallowing.

24 The small number of patients recruited for this pilot study was just above the recommendations
25 for improved quality of evidence.³ Fifteen patients did not return all diaries, some due to the

1 cumbersome nature of completing them, while others disliked having the diaries around the
2 house due to the stigma associated with taking HIV medicines. The study could have been
3 extended to other specialities such as cardiac or renal transplant patients, who are also
4 prescribed relatively large tablets long-term (such as mycophenolate and tacrolimus), and for
5 which therapeutic levels can be monitored. However, monitoring clinical parameters would
6 have required further REC scrutiny and was not included for the purposes of this unfunded
7 pilot study. During REC review, the need for an extra control group using water or another
8 non-flavoured spray was proposed. However, considering both clinical issues (absence of an
9 aid in practice) and ethical issues (potential negative discrimination in this arm), it was
10 concluded that patients would act as their own control for a baseline measurement period. This
11 is in line with recommendations for improved quality of evidence³ with the advantage of fewer
12 confounding factors and the need for fewer participants to detect a relevant score difference.
13 From the present study, it was not possible to determine whether the spray could mask the
14 unpleasant taste or aftertaste of liquid medicines. This apparent negative effect was only based
15 on data for 2 patients and 3 preparations that were unlikely to have palatability issues (medium
16 scores). . However, it helped some patients transition to solid medications. Further research
17 incorporating more patients and unpalatable liquids is required to draw appropriate
18 conclusions. Similarly, different patient characteristics (e.g. age and gender) and formulation
19 attributes (size/shape) could be explored in a larger study.

20

21 **Conclusion**

22 The present pilot study demonstrated Pill Glide to be safe, easy and effective to help children
23 6 years of age and above to take their solid medicines compared to a standard behavioural
24 approach alone. It is recommended that Pill Glide should be widely available, given the current
25 paucity of age-appropriate dosage forms for children. A larger study is warranted to further

1 examine these findings over a longer time period which may be further strengthened by
2 including measurable clinical compliance markers. Establishing any pharmaco-economic
3 impact may also highlight such interventions to be a cost-effective solution for healthcare
4 providers.

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6 1615 words

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3 on pharmaceutical development of medicines for paediatric use (2013)
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1 **List of tables and figures**

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3 Table 1: Gender, age and medicines (including sizes, shapes of solid dosage forms) taken by
4 patients in the Pill Glide study [**information missing; the size of capsules have been*
5 *estimated; OD: once daily*]

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7 Figure 1: Flow chart of the Pill Glide study

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9 Figure 2: Overall medicine taking difficulty score (MTDS) for the behavioural and Pill Glide
10 periods: (A) scores for each subject and all dosage forms; (B): scores only for the solid
11 dosage forms. Paired scores were linked together by a solid line if the score was lower for Pill
12 Glide and a dashed line if the score was higher.

13

14 Figure 3: Overall medicines taking difficulty score (MTDS) average trendlines for the
15 baseline behavioural approach and Pill Glide intervention periods grouped by dosage form
16 type.