Compliance with Occlusion Therapy for Childhood Amblyopia

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Abstract

Purpose: Explore compliance with occlusion treatment of amblyopia in the Monitored and Randomised Occlusion Treatment of Amblyopia Studies (MOTAS and ROTAS), using objective monitoring.

Methods: Both studies had a 3-phase protocol: initial assessment, refractive adaptation and occlusion. In the occlusion phase, participants were instructed to dose for 6 hrs/day (MOTAS) or randomized to 6 or 12 hrs/day (ROTAS). Dose was monitored continuously using an Occlusion Dose Monitor (ODM).

Results: 152 patients (71 male, 81 female; 122 Caucasian, 30 non-Caucasian) of mean ± sd age 68±18 months participated. Amblyopia was defined as an inter-ocular acuity difference of at least 0.1 logMAR and was associated with anisometropia in 50, strabismus in 44, and both (mixed) in 58. Median duration of occlusion was 99 days (interquartile range 72 days). Mean compliance was 44%, mean proportion of days with no patch worn was 42%. Compliance was lower (39%) on weekends compared to weekdays (46%, $p=0.04$), as was the likelihood of dosing at all (52% vs. 60%, $p=0.028$). Compliance was lower when attendance was less frequent ($p < 0.001$) and with prolonged treatment duration ($p<0.001$). Age, gender, amblyopia type and severity were not associated with compliance. Mixture modelling suggested three subpopulations of patch day doses: under 30 minutes; doses that achieve 30%-80% compliance; and doses that achieve around 100% compliance.

Conclusions:

This study shows that compliance with patching treatment averages less than 50% and is influenced by several factors. A greater understanding of these influences should improve treatment outcome.

Introduction

Conventional treatment for unilateral amblyopia has two principal components: i) refractive correction by spectacles and ii) occlusion of the fellow eye. Currently, 'patching' is the mainstay type of occlusion although other methods such as atropine penalization have been shown to provide equivalent remediation for moderate and severe amblyopia.[1,2]

Understanding therapeutic effectiveness requires a knowledge of the amount of treatment received, which may differ from that prescribed. Compliance with occlusion is variable but often problematic due to a range of factors including: skin irritation, forced use of an eye with degraded vision, poor cosmesis and lengthy treatment periods. It has been shown[3,4] that the stress suffered by both parent and child during patching makes compliance difficult to achieve, with treatment likely to be abandoned if no improvement in vision is seen or if the child continues experiencing difficulties or suffers socially or educationally. Consequently, occlusion dose received is often considerably less than the prescribed dose.[5] Knowledge of the occlusion dose received, compared to that prescribed, informs practitioners of compliance and its variability over the course of the treatment. We consider compliance, qualitatively expressed, as *"the extent to which the patient's behaviour matches the prescriber's recommendations."*[6] Compliance is distinct from 'concordance'- a more recent term and previously used by ourselves [5] where *"an agreement is reached after negotiation between a patient and a healthcare professional that respects the*

beliefs and wishes of the patient in determining whether, when, and how medicines are to be taken." [7,8] In the context of this article the appropriate term is compliance.

Studies using electronic monitoring devices to evaluate compliance with prescribed medicines (tablet-taking) report overall mean ± sd compliance to be 71% ± 17%, decreasing as the complexity of the regimen increases.[9] It is possible that a similar decrease in compliance might be observed in the prescribing of occlusion therapy, because the regimen of the prescribed dose may vary.

Estimates of compliance with patching can be gleaned from parental/patient interview; however this provides qualitative data only, and is subject to both interviewer and interviewee bias. A refinement of this subjective method is the use of parental diaries, which, though semi-quantitative, remain subject to bias. Devices are now available to objectively measure compliance; these are known generically as occlusion dose monitors (ODMs).[10-12] The ODM developed by us consists of an eye patch with two small electrodes attached to its under surface connected to a battery powered data logger.[11] These devices are important research tools and pending technical refinement may have a routine role in facilitating concordance: shortening treatment and improving overall effectiveness.

In this study we explore objectively monitored compliance with two prescribed occlusion regimens: 6 hours a day and 12 hours a day. The analysis utilizes datasets of the Monitored Occlusion Treatment of Amblyopia Study (MOTAS)[5] and the Randomised Occlusion Treatment of Amblyopia Study (ROTAS)[13] in which participants were prescribed a specific dose of occlusion. Both MOTAS and ROTAS were designed to investigate the dose-response function of amblyopia therapy and included *non-overlapping* phases of refractive adaptation and occlusion therapy.[14] Here, we analyse the variable patterns of dose received with respect to the fixed doses prescribed, and identify factors that influence the relationship between these variables.

Method

Study Design

The design and principal findings of MOTAS and ROTAS have been reported separately elsewhere.[5,13,14] Each comprised three distinct phases: 'baseline', 'refractive adaptation' and 'occlusion'.

Baseline

The baseline phase comprised a minimum of two consecutive assessments to ensure a robust measure of visual function at study entry. The two assessments occurred within 2 weeks of each

other. If a difference of 0.1 logMAR or greater between vision measurements was observed then additional assessments were undertaken at 2 weekly intervals until stability occurred. Children who required spectacle correction entered the refractive adaptation phase.

Refractive adaptation phase

Refractive error was assessed by author ARF using cycloplegic retinosocopy. Significant refractive error was considered to be ≥ 1.50DS bilateral hypermetropia; ≥ 1.50DS bilateral myopia; ≥ 0.75DC bilateral astigmatism and ≥ 1.00DS anisometropia. Children who required spectacle correction entered the refractive adaptation phase, while those not requiring spectacle correction entered the occlusion phase. Children in the refractive adaptation phase were instructed to wear spectacles full-time and were scheduled to return for vision assessment at 6-week intervals from week 0 (onset of spectacle wear) until 18 weeks, when refractive adaptation was completed: a period that our previous research indicated would allow for all improvement attributable to spectacle wear to have occurred.[15,16] Those children who demonstrated improvements between weeks 12 and 18 continued refractive adaptation for further 6-week cycles until no additional gains were seen.

Occlusion phase

Children in MOTAS were prescribed 6 hours occlusion per day while in ROTAS they were randomly assigned to 6 or 12 hours of prescribed occlusion per day. Allocation to a prescribed dose-rate was undertaken by author CES and achieved using a random number generator in the

statistical package ‘R’ (http://www.r-project.org/), stratified, but not blocked, by amblyopia type and implemented by means of a concealed, typed allocation list. Neither investigator nor participants’ parents were masked to the prescribed occlusion dose. The investigator was not masked to the prescribed dose as the investigator became the patients clinician for the duration of the trial and therefore full care would not have been possible without knowledge of the prescribed dose. Parents of ROTAS were aware of the two different regimens of occlusion (6 or 12 hours) but fully consented to be randomized to a prescribed dose allocation. Although it is possible that a parent whose child was randomized to the 12 hour dose of occlusion perceived that dose as excessive (given that it was twice that of the alternative dose), they could not have drawn upon any evidence available at the time to substantiate such a belief; such doses were not untypical of practice at the time the study was undertaken.

Occlusion episodes were recorded using an occlusion dose monitor (ODM).[10,11] This device logs, to the nearest minute, the time of day and whether the patch is attached, from which the duration of occlusion episodes can be derived. At the start of the studies’ occlusion phase, the investigator explained to the parents and child the practicalities of wearing the monitor. The children were required to wear the monitor connected to the patch for each patching episode. At each subsequent visit, data from the ODM were downloaded to a PC and parents were given the opportunity to review their child’s compliance. At every visit. parents and the child themselves

were reminded of the prescribed daily dose-rate. Although multiple occlusion episodes could be recorded in a single day, dose data were aggregated to provide a 'daily dose' measure.

In both MOTAS and ROTAS visual function and monitored occlusion dose were recorded at 2-week intervals until acuity ceased to improve (2 inflexions in acuity over time or identical measurements on 3 consecutive visits).[5] Hence the occlusion phases were of variable duration depending on an algorithm to detect 'stability' of visual outcome (i.e. the best visual outcome likely to be achieved for any given child). The visual outcome of individuals with respect to dose — 'the dose-response' — has been reported previously.[5,13,17]

Study Participants

Children were recruited from two London hospitals between January 2000 and December 2001, and February 2002 and May 2004 for MOTAS and ROTAS respectively. Inclusion eligibility criteria were: 3 to 8 years of age; anisometropia and/or strabismus; an inter-ocular acuity difference of at least 0.1 logMAR (e.g. R 20/20 L <20/25); and no history of previous occlusion therapy, ocular pathology or learning difficulties. The rationale for these inclusion criteria is presented elsewhere.[5,13,14] Participants were classified as being anisometropic, when refractive errors were ≥ 1 Dioptre sphere or Dioptre cylinder different between the eyes. Participants were classified as being strabismic if a manifest deviation was present with and/or without glasses, at near and/or distance fixation. Written parental consent was a prerequisite of enrollment. Both

studies were administered according to the Helsinki Declaration II and approved by Hillingdon and St Mary's Hospital NHS Trusts' Local Research Ethics Committees.

Assessment of visual function

The primary visual function outcome measure was logMAR visual acuity.[18,19] Three logMAR visual acuity charts were employed: ETDRS (Precision Vision), crowded (Keeler Ltd), and uncrowded (Keeler Ltd) logMAR charts. Standard protocols for visual acuity testing were used and were scored by letter. The type of chart used depended on the reading ability of the child, and was generally age-dependent. If a child was able to undertake a more difficult test as they progressed through the trial, the initial test(s) was used in addition for this child. The results from the initial test(s) were used for dose-response analysis.

Statistical Analysis

Our analyses draw a distinction between days on which no patching was undertaken (*no-patch* days) and days on which at least some patching was undertaken (*patch* days). Three operational measures of compliance were considered:

1) *Compliance*: the percentage of total prescribed dose received;

2) *Patch days compliance*: the percentage of total prescribed dose received ignoring no-patch days (days on which no patching was undertaken); and

3) *Patch days proportion:* percentage of days on which any patching was undertaken.

To further illustrate these concepts consider a hypothetical patient prescribed 6 hours/day for 10 days of treatment. Suppose for the first five days they did not undertake any occlusion and then across the remaining five days they managed a total of 30 hours. Their *compliance* compared their 30 hours received with their 60 hours total prescribed, giving 50% compliance. Their *patch days compliance* ignored the five days on which no patching took place and instead compared their 30 hours received with their prescribed dose over those five days: their patch days compliance was therefore 100%. Finally, as they undertook occlusion on five of their 10 days in treatment, their *patch days proportion* was 50%.

By investigating patch days compliance and patch days proportion separately, we gain information about days on which a child wore their patch, and if they did, how long the patch was worn. Summary statistics of these compliance measures are reported, along with relationships between compliance and some individual factors. Unless otherwise stated, p-values result from Wilcoxon rank-sum tests.

Individuals left the studies once their visual outcome had stabilized. Those with lower compliance were slower to reach this point and so remained in treatment longer, making it difficult to establish whether there is a causal relationship from time in treatment to compliance (rather than the converse). We therefore performed a set of regression analyses modelling the above compliance measures recorded between pairs of consecutive clinic visits (which we term 'treatment intervals'). By using a mixed-effect modelling approach to these data, individual-level effects were accounted for, allowing us to identify the effect of time in treatment. For 64 treatment intervals, precisely zero dose was recorded, and as such patch days compliance was not defined. These intervals are excluded in our analyses of patch days compliance.

Finally, we examined the distribution of compliance on patch days, both in terms of overall average patch days compliance as well as compliance on a day-to-day basis, by fitting mixtures of log-normal distributions to the data. All analyses were conducted using the statistical package 'R'.

Results

Compliance summary statistics

In MOTAS, of the 94 participants, 80 were eligible for occlusion. Of these, 8 left the study at this point (three did not attend, five declined to use the ODM and returned to standard care) leaving 72 participants who entered the monitored occlusion phase. One participant of unknown amblyopia type was not included in the analyses. In ROTAS, of the 98 participants, 91 were eligible for occlusion, but 10 left the study at this point (three relocated, seven declined to use the ODM and returned to standard care). The remaining 81 participants were randomly assigned to a prescribed occlusion dose-rate of 6 hours a day (N = 41) or to 12 hours a day (N = 40).

In the combined studies there were occlusion data for 152 participants for the occlusion phases, 71 male, 81 female, age range was 36-120 months (mean ± sd 68 ± 18). Amblyopia was associated with anisometropia in 50, strabismus in 44, and both anisometropia and strabismus (mixed) in 58 participants. Median time spent in the occlusion phase of treatment was 99 days (25% and 75% quartiles of 64 and 136 days respectively). Median time to best visual acuity was 71 days (with analogous quartiles at 43 and 106 days).

Mean compliance across all participants for the duration of occlusion was 44%. Mean compliance of participants in MOTAS (33%), was significantly ($p<0.001$) less than in ROTAS

(54%). In ROTAS, compliance for the complete duration of the study was not significantly different ($p=0.08$) between prescribed groups (mean ± sd 61% ± 30% and 47% ± 29% for the 6 and 12 hours a day groups respectively). If we consider doses received up to the point each participant reached their best visual acuity, compliance rates were significantly different between MOTAS (40%) and ROTAS (65%) participants ($p<0.001$), and between 6 (75%) and 12 hours (55%) ($p<0.001$), for those in ROTAS.

Across all participants, the percentage of days on which at least some occlusion dose was received was 58% (patch days proportion). There was a significant difference ($p<0.001$) in patch days proportion between MOTAS (49%) and ROTAS (66%). Within ROTAS there was not a significant difference in patch days proportion ($p = 0.921$) between prescribed groups, with both groups dosing, on average, on 66% of days.

Ignoring days with no patching, we obtain rates for patch days compliance. Overall patch days compliance was 70%, with significant differences ($p<0.001$) between MOTAS (63%) and ROTAS (77%), and between the two arms of ROTAS (88% for 6 hours and 65% for 12 hours). There was a significant correlation between individual patch days proportion and individual patch days compliance ($r = 0.44$, $p < 0.001$), suggesting that patients more likely to dose were also

more likely to dose greater amounts.

Mean compliance on weekdays (Monday to Friday, inclusive) was significantly greater than that on weekends, at 46% and 39% respectively ($p = 0.041$), as was patch days proportion (60% and 52%, $p = 0.028$), but not patch days compliance (71% and 67%, $p = 0.392$).

Clinic visits were scheduled every two weeks, although some participants attended either more or less frequently. Figure 1 summarizes this for the first 6 weeks of follow-up, indicating that those with more frequent clinic attendance tended to have higher compliance. Note that this figure (as with later plots) illustrates that some participants undertook more occlusion in total than they were prescribed, leading to compliance rates of over 100%.

(Figure 1 about here)

Compliance and time in occlusion

There was an association between compliance and time spent in the occlusion phase of treatment. This relationship is illustrated in Figure 2a, which shows the mean compliance of all individuals

who were still in the study for each day since the start of their respective occlusion phases. There is a clear trend, with compliance decreasing as time in treatment increases.

Figure 2b summarizes the proportion of participants who dosed on a particular day, which also decreases over time. Figure 2c summarizes the average compliance when days with no patching are excluded. Now there is no longer a clear trend over time between patch days compliance and time since start of occlusion ($r = -0.02$, $p = 0.139$). This suggests that much of the change seen in Figure 2a is driven by individuals becoming less likely to dose at all, rather than individual daily doses ('dose-rates') decreasing, over time. Figure 3 (a-c) groups data shown in Figures 2 (a-c) above for overall, 0-6 weeks, 6-12 weeks and over 12 weeks follow-up for percentage compliance, patch days proportion and patch days compliance.

It is important to acknowledge that these analyses do not control for the fact that, as more compliant patients may have reached best visual acuity earlier, those later into treatment are biased towards low compliance. We address this issue with the regression analyses that follow.

(Figures 2a-c about here)

(Figures 3a-c about here)

Regression analyses

The following variables were considered: age at start of interval (categorized into < 48 months; ≥ 48 and < 72 months; and ≥ 72 months); gender; type and severity of amblyopia at start of interval (categorized as mild: < 0.4 logMAR in the amblyopic eye; moderate: ≥ 0.4 to < 0.7 logMAR; or severe: ≥ 0.7 logMAR); study (MOTAS or ROTAS); prescribed dose (6 hours or 12 hours a day); time spent in occlusion phase at start of interval; and length of interval. Lower compliance has been reported when a treatment is perceived as not having an effect,[20] so we also considered improvement in visual acuity of the amblyopic eye across the previous interval (categorized as either improved or not improved according to two definitions outlined below).

Incorporating improvement during the previous treatment interval necessitates ignoring each participant's compliance during their first treatment interval, reducing our data approximately 20%. Regression models on this reduced dataset found improvement of visual acuity in the amblyopic eye was not a significant factor for any of the three compliance measures, either when improvement was defined as *any* decrease in logMAR visual acuity, or as an improvement by at least 0.14 logMAR to account for test-retest variability[21] (all p-values > 0.2). We therefore ignored this variable and used the full dataset. Our analyses thus included all 152 participants, across whom there are 769 treatment intervals (705 for which patch days compliance was defined).

Regression models for each compliance measure initially included all of the above variables. From these, model selection proceeded via a backwards selection method based on Akaike's Information Criterion[22], with the resulting final models summarized in Table 1. Validity of underlying model assumptions were assessed graphically and analytically.

Table 1 about here

Compliance and patch days proportion decreased with later and longer treatment intervals (see table 1 for p-values). However, the evidence that these two variables impact patch days compliance is relatively weak (with time into follow-up not significant). ROTAS participants exhibited greater compliance across all three measures, while there is no evidence that prescribed dose affects patch days proportion. Age, gender, type and severity of amblyopia were not significantly associated with any compliance measure.

Distribution of patch days compliance

Finally, we investigate the distribution of patient compliance on days when patching occurred - "patch days". Inspection of average patch days compliance data across all participants suggested they were unlikely to be representative of a single probability distribution and therefore we

considered a mixture model approach. A three component model provided the optimal fit (Figure 4) suggesting participants fell into one of three categories:

1) A small proportion (around 2% according to this model) exhibited very low patch days compliance;

2) The majority (around 60%) exhibited low to moderate patch days compliance (most averaging between 30% and 70% of their prescribed dose on patch days), but with large variability;

3) A large minority (around 40%) exhibited excellent patch days compliance (averaging around 90% of their prescribed dose on patch days), with relatively small variability.

(Figure 4 about here)

To take advantage of the large number of patch days of data available to us, we decided to conduct a similar analysis but on pooled daily dose data (as opposed to simply the average patch days compliance of our individual participants). With over 9,000 patch days of data available across our 152 patients, such an approach provides considerably more information, along with offering a different perspective on patient behaviour.

Inspection of these data again suggested that a mixture model would be appropriate, and a three component model was found to provide the optimal fit (Figure 5). This suggests that along with not dosing at all, there is the possibility of 3 'types' of daily compliance behaviour, any of which an individual may demonstrate from one day of treatment to the next:

1) A small proportion of patch days (fewer than 10% according to this model) consisted of an attempt to patch, but only for a very short time.
2) Majority of patch days (around 60%) consisted of highly variable compliance with most of these days exhibiting between 30% and 80% compliance.
3) A minority of patch days (around 30%) consisted of full compliance (or slight over- or under-compliance) with very little variation about this target.

While there are notable similarities between these mixture distributions (figure 5) and those found in the analysis of patient-by-patient average patch days compliance (figure 4), it is important to keep in mind that these two analyses reflect different aspects of the data. The first summarizes how patients behave in terms of their overall patch days compliance, whereas the second summarizes behaviours that any individual may exhibit on any particular day during their treatment.

(Figure 5 about here)

Discussion

This study has explored the occlusion dose data for amblyopia treatment and the factors affecting compliance. This is the first study that has been able to continuously observe compliance in this way for an entire treatment period. Mean compliance across all participants for the duration of follow-up was 44% — substantially less than the prescribed dose. The percentage of days where

some occlusion was achieved was 58%, correspondingly no occlusion took place on 42% of days. Compliance was better on weekdays than at weekends and decreased as time in study increased.

Through our objectively monitored occlusion dose data we have been able to describe the extent to which amblyopia patients comply with their prescribed patching regimen, and investigate what factors do (and do not) influence their compliance.

Days on which a patient received no occlusion dose were important for overall compliance. While average patch days compliance was 70%, days with zero dose reduced the overall compliance figure to 44%. For an individual prescribed 6 hours of occlusion per day, who remained in treatment for 99 days (the median follow-up in our dataset), this reduction represents receiving over 150 fewer hours of occlusion than prescribed. Days where no patching was undertaken were more frequent at weekends (reflecting the importance of routine on compliance[4]) and became more frequent the longer treatment continued. These particular features should be kept in mind when managing patients undergoing occlusion. For example, one could encourage patients/parents to establish a specific weekend patching timetable, or allow for more time at later clinic visits to more thoroughly discuss any problems they may have been encountering with their treatment.

Compliance was higher among those who attended review assessments more frequently. There are two possible explanations for this. Firstly, individuals that attend regularly are presumably attending because they understand the importance of the treatment and the benefit of attending regularly, and are therefore more likely to comply. Secondly, if an individual is struggling to comply with the treatment one might infer that attendance would be less likely, or less frequent. Encouragement to attend clinics may improve compliance or allow for modifications to treatment to be made early on in the treatment program.

We have shown that prescribing larger doses does not affect the likelihood that an individual will patch on an individual day, and that while proportionally patients' compliance was lower with 12 hours a day regimens compared to 6, the total daily dose under a 12 hour regimen was still greater. Thus a strategy of prescribing larger daily doses to expedite treatment, and thus shorten follow-up (time to optimal visual acuity) could be considered. However, with only two prescribed doses available for our analysis, future research investigating the relationships between a greater variety of prescribed doses and compliance would be informative.

Compliance was better in ROTAS compared to MOTAS. This may be due to differences in the study design. In MOTAS, children were prescribed 6 hours a day but the aim of this study was to observe compliance and the dose-response effect. In contrast, in ROTAS children were

prescribed 6 or 12 hours a day, therefore the actual dose appeared more important to parents as they knew they were prescribed one of two possible doses. Recorded compliances from other studies have been similar to that shown here (Tjaim et al.,[23] 52% compliance monitored for a limited period only; Awan et al.,[24] 57.5% for 3-hour group and 41.2% for 6 hour group).

Wearing an occlusion dose monitor with the patch could be observed as an additional burden. However individuals entering the occlusion phase that disliked the ODM left the study at this point and underwent conventional patching treatment in standard clinical care. This study reports those individuals that completed the occlusion phase of the trial and thus underwent occlusion dose monitored patching. Unfortunately it is impossible to assess the impact of wearing an occlusion dose monitor on compliance as without its use patching cannot be quantitatively measure.

Our mixture model analysis of compliance on patch days (Figures 5) suggests three 'types' of daily compliance (in addition to the large proportion with days where no patching took place). Of interest was a spike in daily occlusion doses at near-100% compliance (with these making up around 30% of all daily doses), perhaps reflecting days when a participant made a particular effort to comply fully, or a tendency to 'push on' to a prescribed occlusion target once it was in sight. Meanwhile, a small (but not negligible) number of near-zero doses suggests that very short 'failed' attempts to occlude are relatively common place. The analogous analysis of mean patch

days compliance across participants (Figure 4) suggested that individual patients may also be identified as one of three ‘types’ of doser in broadly similar terms, although this result is based on a considerably smaller dataset. Future work could investigate this aspect of dosing behaviour more rigorously, such as by investigating how often an individual’s daily dose falls into each of the three identified behavioural categories, with a view to more thoroughly identifying ‘types’ of doser. This in turn could be used by a clinician when discussing a patient's occlusion history and making suggestions for future dosing practice.

Our data suggest (figure 3a) that 25% of participants exhibited low or poor compliance (less than 20% of prescribed dose). This is consistent with the general body of data on compliance rates that suggests poor compliance is expected in 30-50% of individuals regardless of the disease, prognosis or type of medicines.[25]

Emotional impact [4,26-28] and poor parental understanding[29] seem to be important factors affecting compliance with occlusion therapy. In a randomized clinical trial Loudon et al.[30,31] demonstrated that an educational programme, consisting of a cartoon story explaining to the child, without text, the rationale for treatment, together with a calendar and reward stickers, and an information sheet for parents, was effective in improving compliance for those that were likely to not dose at all or would have had very low compliance.

In summary, overall compliance declines the longer a patient is in treatment although this is primarily through the increased proportion of days where zero dose occurs rather than through steadily decreasing doses. Dosing on weekends is lower. Prescribed dose does not affect the probability of whether someone will dose on a particular day, but does affect (proportional) compliance. ROTAS participants had better compliance. Age, gender, type and severity of amblyopia, and previous improvement seem not to affect compliance.

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Figure Legends

Figure 1: Compliance and total clinic visits during first 42 days of occlusion treatment (only participants with at least 42 days of total follow-up included). Boxes indicate 25% and 75% quartiles, with whiskers extending to the most extreme point not more than 1.5 times the interquartile range from the median.

Figure 2a: Mean compliance with prescribed dose across all individuals still in treatment. Days with fewer than 10 individuals remaining in treatment not shown.

Figure 2b: Proportion of individuals still in treatment recording some patching on a particular day. Days with fewer than 10 individuals remaining in treatment not shown.

Figure 2c: Mean patch days compliance with prescribed dose across all individuals still in treatment. Days with fewer than 10 individuals remaining in treatment and recording any dose not shown.

Figure 3: Distribution of participants' mean compliance measures; a) Compliance b) Patch days proportion c) Patch days compliance (overall and stratified by time since start of occlusion phase of treatment). Boxes range from 25% to 75% quartiles with median highlighted. Whiskers extend to lowest and highest mean compliance.

Figure 4: Distribution of participants' mean patch days compliance and the densities of three log-normal distributions estimated after fitting a three-component normal mixture model to the log-transformed data. Bracketed legend percentages are the estimated proportion of all daily doses that belong to each distribution. Note that mixture distribution 1 (which has an exceptionally high peak) is not depicted on the figure to aid readability.

Figure 5: Distribution of all daily dose compliances (days where no patch was worn are excluded) and the densities of three log-normal distributions estimated after fitting a three-component normal mixture model on the log-transformed data. Bracketed legend percentages are the estimated proportion of all daily doses that belong to each distribution. Percentages over 100 refer to days of over compliance.

Table Legend

Table1: Final (reduced) mixed-effect normal linear models of interval (between-visit) compliance on 152 participants across 760 intervals (696 intervals for patch days compliance). Coefficients give the increase in the relevant outcome measure for either a one unit increase in the associated covariate or (in the case of binary covariates) relative to the defined baseline, all other covariates being held fixed. (For example, one would expect to see 3.96% lower compliance in a 1-week longer treatment interval.) '-' indicates variables that were dropped during the model selection procedure for a particular outcome, but were included for other outcome measures.