Pharmacokinetics of rifampicin in adult TB patients and healthy volunteers: a systematic review and meta-analysis


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Objectives: The objectives of this study were to explore inter-study heterogeneity in the pharmacokinetics (PK) of orally administered rifampicin, to derive summary estimates of rifampicin PK parameters at standard dosages and to compare these with summary estimates for higher dosages.

Methods: A systematic search was performed for studies of rifampicin PK published in the English language up to May 2017. Data describing the $C_{\text{max}}$ and AUC were extracted. Meta-analysis provided summary estimates for PK parameter estimates at standard rifampicin dosages. Heterogeneity was assessed by estimation of the $I^2$ statistic and visual inspection of forest plots. Summary AUC estimates at standard and higher dosages were compared graphically and contextualized using preclinical pharmacodynamic (PD) data.

Results: Substantial heterogeneity in PK parameters was evident and upheld in meta-regression. Treatment duration had a significant impact on the summary estimates for rifampicin PK parameters, with $C_{\text{max}}$ 8.98 mg/L (SEM 2.19) after a single dose and 5.79 mg/L (SEM 2.14) at steady-state dosing, and AUC 72.56 mg/L/C1h (SEM 2.60) and 38.73 mg/L/C1h (SEM 4.33) after single and steady-state dosing, respectively. Rifampicin dosages of at least 25 mg/kg are required to achieve plasma PK/PD targets defined in preclinical studies.

Conclusions: Vast inter-study heterogeneity exists in rifampicin PK parameter estimates. This is not explained by the available modifying variables. The recommended dosage of rifampicin should be increased to improve efficacy. This study provides an important point of reference for understanding rifampicin PK at standard dosages as efforts to explore higher dosing strategies continue in this field.

Introduction

When it was introduced as part of combination therapy for TB in the 1960s, rifampicin revolutionized treatment and shortened the duration of therapy from 18 to 9 months. This would subsequently be shortened further to 6 months with the addition of pyrazinamide.1 Despite experience gained over the past five decades, the optimal dosage of rifampicin has not been established definitively. The current recommendation of 10 mg/kg in guidelines from the WHO has not changed since the introduction of rifampicin, at which time it was based on toxicological and financial concerns, with limited pharmacokinetic (PK) data available.2,3

For therapeutic drug monitoring (TDM) of rifampicin in TB treatment, a $C_{\text{max}}$ of 8–24 mg/L (free plus bound drug) was suggested in the 1990s. This recommendation was based on a review of observed PK parameters and on expert opinion. Data from patients infected with HIV were not included.4,5 There was no pharmacodynamic (PD) component to the target, as MIC data were lacking in...
TB patients. There is an accumulating body of evidence demonstrate with day 2 early bactericidal activity in a near-linear fashion in modest dose increases. Increased dosages of rifampicin correlate with these with summary estimates for higher-than-standard rifampicin dosages; and (iv) to contextualize these PK estimates using the features in predicting long-term clinical outcome. In TB patients, the 0–24 h AUC has a greater value than $C_{\text{max}}$ or clinical features in predicting long-term clinical outcome.

Scientific comparison of the findings of clinical trials investigating high rifampicin dosages requires an understanding of the PK parameters achieved with currently used dosages, so that the impact of dose escalation can be appreciated. For this reason, we conducted a systematic review and meta-analysis of published data describing rifampicin PK. As $C_{\text{max}}$/MIC and AUC/MIC are the PK/PD indices best characterized, we focused on these PK parameters.

The objectives of this study were: (i) to explore the inter-study heterogeneity in rifampicin PK; (ii) to derive summary estimates of rifampicin PK parameters at standard dosages; (iii) to compare these with summary estimates for higher-than-standard rifampicin dosages; and (iv) to contextualize these PK estimates using the available PD data.

### Methods

#### Search strategy and selection criteria

Studies were identified with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. PubMed, Scopus and MEDLINE electronic databases were searched. In PubMed and Scopus, titles and abstracts were searched using the terms ‘rifampicin’ OR ‘rifampin‘ OR ‘antituberculous‘ OR ‘antimycobacterial‘ AND ‘pharmacokinetics’, to identify studies reported in the English language up to May 2017. The MEDLINE database was searched using the keywords ‘pharmacokinetic’ OR ‘bioequivalence’ AND title words ‘rifampicin’ OR ‘tubercul*’. Two reviewers (K. E. S. and G. D.) screened titles and abstracts for relevance and randomized to one or other intervention. We considered this in our selection of studies, as well as ensuring that authors clearly described the pharmaceutical product, biochemical methods and statistical tools used.

#### Data extraction

A data extraction form was designed and one reviewer (K. E. S.) extracted data from the included studies on the following items in addition to rifampicin PK parameters: study design; study population; sex; age; body weight; HIV status; treatment regimen; duration of treatment; rifampicin dose; whether rifampicin was administered as a separate drug or in a fixed-dose combination; whether dosing was daily or intermittent; PK sampling times; assay method; and data analysis method. These variables were selected a priori as it was felt that they were the factors most likely to impact rifampicin PK. Rifampicin was considered to be at steady-state if it had been administered for $\geq 7$ days to allow for saturation of first-pass metabolism and the establishment of metabolic autoinduction.

#### Data synthesis

In many of the studies, more than one group of participants was compared, e.g. HIV-positive and HIV-negative patients. In others, more than one treatment was compared, e.g. in a crossover trial comparing separate drug formulations with fixed-dose combinations. These groups were analysed in the same way that data were presented in the papers; that is, separate study arms were analysed separately rather than mean values being calculated for each study. This meant that some studies contributed two or more sets of PK parameters to the meta-analysis. To enable comparison of PK parameters across all studies, data were collected as means and standard deviations. Where summary statistics were not published in this format, authors were contacted to request that they share either raw data or results of an NCA of their data. If data were summarized as median and range or IQR and raw data or NCA results were unobtainable from the authors, we estimated the mean and standard deviation from the summary statistics provided using previously described methods.

As the $C_{\text{max}}$ of rifampicin occurs around 2 h after ingestion and half-life is of the order of 2.5–4 h, concentrations remaining in plasma after 24 h from ingestion will be negligible. This was supported by the lack of a statistically significant difference between the estimates of AUC produced from the 0–24 h time interval and the 0–48 h time interval and those calculated from the 0–infinity ($\infty$) interval. The AUC$_{0-24}$, AUC$_{0-48}$ and AUC$_{\infty}$ results were therefore combined into a single measure of AUC and only these estimates were included in the final analysis to minimize design-related heterogeneity. Hereafter, any reference to AUC refers to the combined AUC$_{0-24}$, AUC$_{0-48}$ and AUC$_{\infty}$ estimates. Although rifampicin is 80%–90%
protein bound and the active portion is believed to be unbound drug. studies reported total drug PK parameters; this analysis used the same.15,30

**Summary measures**

Data were analysed in Microsoft Excel version 15.28 (Microsoft 2016) and using the metafor package in R version 3.3.1.31 The main objective of the analysis was to collate and summarize available data on the PK parameters of rifampicin derived from subjects taking WHO-recommended dosages. The focus of the meta-analysis was therefore on the 8–12 mg/kg dosing bracket. A linear model was used to incorporate the following variables: HIV status (positive or negative); TB status (positive or negative); combination therapy (limited to patients taking rifampicin monotherapy versus those taking combination therapy with isoniazid, pyrazinamide and ethambutol [RHZE]); intermittent dosing; diabetes status; and treatment duration. A restricted maximum likelihood mixed-effects model was used to perform a meta-analysis of Cmax and AUC estimates, with application of the DerSimonian–Laird estimator of residual heterogeneity. This approach fits a random-effects model. Standard errors of the study-specific estimates are adjusted to incorporate a measure of the heterogeneity among the effects of independent variables observed in different studies.32 The degree to which demographic and clinical variables accounted for inter-study heterogeneity was assessed using meta-regression. Heterogeneity of PK estimates overall and within subgroups was assessed by estimation of the I² statistic and visual inspection of forest plots.

A second objective was to explore the effect of higher-than-recommended doses of rifampicin on drug exposure. The >12 mg/kg group of studies was split into more specific dosing subgroups and the mean and standard error derived from meta-analysis in standard weight-based dosing categories was compared with the summary statistics extracted from studies of higher rifampicin dosages. As the number of studies at higher dosages was small, we were unable to incorporate dose escalation as a variable in the meta-regression, so graphical comparison of summary statistics from studies at standard and higher dosages was performed instead.

**Results**

The search retrieved 3075 titles, of which 70 studies were deemed eligible, containing 179 distinct study arms (Figure S1, available as Supplementary data at JAC Online). The characteristics of the studies are summarized in Table S1. The cohorts contained a total of 3477 study participants. HPLC was used to measure rifampicin levels in 66 of the 70 studies. The remaining studies used spectrophotometry33–35 or a plate diffusion assay.36 These three studies were retained in the meta-analysis because their exclusion did not significantly impact overall PK parameter estimates.

By far the most common weight-based dosing category in the included studies was 8–12 mg/kg (118 of 163 study arms for which dosing information was extracted, 72%), in line with WHO rifampicin dosing guidelines. Unless explicitly stated, results presented hereafter pertain to those studies in which patients received this recommended dose.

**Cmax data were highly heterogeneous and influenced by treatment duration**

Cmax was highly heterogeneous between studies, with an I² statistic of 95.36% (95% CI 95.13%–97.15%). Meta-regression of Cmax estimates with a multivariate model including all variables found two modifiers to have a statistically significant impact on Cmax: duration of treatment and TB status. The effect on inter-study variability was minor, however: I² = 91.36% (95% CI 90.50%–94.77%) after meta-regression. The population summary estimates for Cmax after univariate analysis were 11.51 mg/L (SEM 0.38) after single dosing and 7.04 mg/L (SEM 0.58) after steady-state dosing (P = 0.001) (Figure S2). In multivariate analysis, the difference in Cmax estimate according to dosing duration was upheld. Single dosing (n = 1139 in 66 study arms) resulted in an adjusted mean Cmax of 8.98 mg/L (SEM 1.34) and steady-state dosing (n = 904 in 42 study arms) resulted in an adjusted Cmax of 5.79 mg/L (SEM 0.90) (P = 0.001). The adjusted summary estimate of Cmax for healthy volunteers (n = 946 in 60 study arms) was 6.39 mg/L (SEM 0.85) in TB patients (P = 0.01). Notably, the majority of healthy volunteer cohorts were studied after a single dose of rifampicin (109/120 healthy volunteer cohorts, 91%) and most TB patients were studied after steady-state dosing (53/63 TB patient cohorts, 84%). When multivariate analysis was limited to subjects dosed at steady-state, TB status had a negligible and non-significant modifying effect on Cmax: healthy volunteers 7.08 mg/L (SEM 1.21); TB patients 7.04 mg/L (SEM 1.28) (P = 0.98). No other modifying variables had a significant impact on the adjusted Cmax estimate (Table S2).

**Only treatment duration had a consistently significant impact on AUC in univariate analysis**

In keeping with the findings in relation to the Cmax estimate, inter-study variability in the AUC estimate was extreme, with an I² statistic of 99.53% (95% CI 99.28%–99.60%) in the meta-analysis before inclusion of modifying variables. In univariate analysis, the effect of steady-state dosing was to approximately halve the mean AUC estimate, from 72.56 (SEM 2.60) to 38.73 mg h/L (SEM 4.33) (P < 0.0001) (Table 1 and Figure 1). Univariate analysis indicated significant associations between the AUC estimate and three additional covariates: HIV status, TB status and whether rifampicin was dosed in monotherapy or in combination (Table 1). However, steady-state dosing was disproportionately represented compared with single dosing in both HIV-positive patients and TB patients (100% and 82% of HIV-positive and TB patients, respectively, were studied at steady-state). Once these analyses were repeated with data limited to steady-state dosing, neither HIV status nor TB status had a significant impact on the AUC estimate (Figure 2a and b). Similarly, when the analysis was limited to those who underwent steady-state dosing, combination therapy made no significant difference to the AUC estimate: AUC 39.54 (SEM 2.40) versus 36.73 mg h/L (SEM 4.88) for rifampicin monotherapy versus RHZE combination therapy (P = 0.57).

**Significance of effect of treatment duration on AUC was upheld in meta-regression, but vast heterogeneity remained**

When all modifying variables were incorporated into a mixed-effects meta-regression model, the impact on inter-study heterogeneity was negligible (I² = 98.69%, 95% CI 98.38%–99.14%). Only treatment duration had a significant impact on AUC: adjusted AUC 56.26 mg h/L (SEM 13.90) after a single dose and 20.94 mg h/L (SEM 6.49) after steady-state dosing (Table 2). After multivariate meta-regression analysis, combination therapy with RHZE no longer had a significant impact on AUC. A diagnosis of diabetes
had a negligible, although statistically significant, modifying effect on the AUC estimate (Table 2).

**Current rifampicin dosages for TB are unlikely to be sufficient for PK/PD target attainment**

There appeared to be a slightly greater than proportional increase in AUC with increasing dosage (Table 3 and Figure 3a), although additional data from ongoing trials will help to clarify this. In seeking to relate these reported drug exposures to measures of clinical outcome, we used published PK/PD indices associated with efficacy in murine studies\(^{21}\) and MIC data from human clinical WT M. tuberculosis isolates.\(^{37}\) These murine studies report that an AUC/MIC of 271 is required for a 1 log cfu reduction in vivo.\(^{21}\) The rifampicin WT MIC distribution ranges from 0.03 to 0.5 mg/L, with a median of 0.25 mg/L and proposed epidemiological cut-off value (ECOFF) of 0.5 mg/L.\(^{37}\) Taking the median WT MIC of 0.25 mg/L, doses of 13 mg/kg appear sufficient to achieve the AUC/MIC target of 271. Taking the ECOFF MIC of 0.5 mg/L, however, available data indicate that a rifampicin dose of ≥25 mg/kg is required to attain this PK/PD target associated with a 1 log cfu reduction (Figure 3b).

**Discussion**

This meta-analysis, to our knowledge the most comprehensive to have been conducted on rifampicin PK, has demonstrated vast inter-study heterogeneity in PK parameter estimates. Having collated data collected globally, spanning 35 years and with the inclusion of HIV status, TB status, combination therapy, intermittent dosing, diabetes status and treatment duration as modifying variables, we have been unable to explain this heterogeneity. The vast heterogeneity within and between studies has made it impossible to assess the degree to which physiological differences between individual patients impacts upon rifampicin PK or PK variability, as has been reported with other antimicrobials.\(^{38,39}\)

The summary estimates of \(C_{\text{max}}\) and AUC will serve as useful reference points for clinicians and academics concerned with the dosing of rifampicin for TB. At standard, WHO-recommended doses, mean rifampicin \(C_{\text{max}}\) and AUC are both significantly reduced in patients dosed at steady-state: \(C_{\text{max}}\) 8.98 versus 5.79 mg/L and AUC 72.56 versus 38.73 mg/L/h/L after a single dose and steady-state dosing, respectively. These decreases in PK parameters are expected due to extensive, saturable first-pass metabolism and well-characterized autoinduction of metabolism, resulting in enhanced clearance after repeated doses.\(^{30,40,41}\)

Whilst there was a trend towards HIV positivity being associated with lower rifampicin \(C_{\text{max}}\) and AUC, this did not hold up in meta-regression analysis, which may explain the conflicting results of previous investigations into the effect of HIV positivity on rifampicin exposure.\(^{5,27,42–44}\) The case of AUC in TB patients versus healthy volunteers was similar in that the significance of the association was lost in meta-regression analysis.

With increasing dose, there is a greater than proportional increase in AUC. This is encouraging for the community that is seeking to increase rifampicin exposure. Taking 38.73 mg/L as the mean rifampicin AUC at steady-state dosing of 8–12 mg/kg and the ECOFF MIC of 0.5 mg/L\(^{37}\) gives an AUC/MIC ratio of 77, far
below the optimal PK/PD index suggested by Jayaram et al.\textsuperscript{21} from murine data (prior to reference). Taking the MIC value from the very lower end of the WT range (0.03 mg/L) gives a ratio of 1291. The discrepancy between these ratios may explain in part why some patients develop rifampicin resistance on currently recommended doses while others are successfully treated with the same dose. The PK variability demonstrated herein is likely also to contribute to this phenomenon. Of note, this PK/PD index indicates the potency of a single drug used in isolation and does not reflect the efficacy of rifampicin used in clinical settings and in combination with other agents. There are also likely to be microbiological and host immune factors that influence treatment success. Our calculations nevertheless highlight the inadequacy of current rifampicin doses and the need for these to increase.

This analysis is limited by the fact that many studies summarized their results as median and range or IQR and, as stated, where raw data could not be obtained from authors of those studies means and standard errors were estimated using a previously described method.\textsuperscript{25} This may have introduced inaccuracies. Our categorization of studies according to weight-based dosing was necessarily crude and in some cases based on the average weight of the study population in question. In addition, we were not able to consider the impact of covariates that were not consistently measured on heterogeneity in PK estimates. These included co-medication and associated drug-drug interactions, specific formulations of rifampicin that have been demonstrated to exhibit altered PK\textsuperscript{33,45,46} and patient ethnicity.

We acknowledge that the heterogeneity amongst the included studies, likely caused in part by these and other design and reporting factors, is extreme. Nevertheless, we believe that our largely descriptive analysis has value in highlighting the importance of these factors, in addition to the widely recognized role of inter-individual variability, in terms of their impact on the PK of rifampicin.\textsuperscript{47,48} The extreme residual inter-study variability not accounted for by our meta-regression analysis may thus represent significant true biological variability between study populations, which should be further explored. In addition, the degree of PK variability that is attributable to protein-bound versus unbound rifampicin is not known. Future studies that directly assess these factors would be valuable, as would studies that employ mathematical PK models to quantify rifampicin PK variability. Monte Carlo simulation of rifampicin exposure based upon the AUC distributions presented in this meta-analysis would enable exploration of various dosing regimens. If these simulations could incorporate predictions of toxicity and drug resistance, they would support risk reduction of novel regimens before they enter clinical use.

This meta-analysis has collated and quantitatively summarized the existing literature on the PK of rifampicin, which is believed to be the key driver of PD and ultimately treatment outcome. It provides an important point of reference for understanding rifampicin.

### Figure 1
Forest plot displaying estimated rifampicin AUC after univariate analysis according to dosing duration. In univariate analysis, the effect of steady-state dosing was to approximately halve the estimated rifampicin AUC (P < 0.0001).
Figure 2. (a) Forest plot displaying estimated rifampicin AUC after univariate analysis according to HIV status; data are limited to steady-state dosing. Once data were limited to steady-state dosing, HIV status no longer had a significant impact on rifampicin AUC estimate. *P* values for comparison were >0.05. (b) Forest plot displaying estimated rifampicin AUC after univariate analysis according to TB status; data are limited to steady-state dosing. Once data were limited to steady-state dosing, TB status no longer had a significant impact on the rifampicin AUC estimate. *P* value for comparison was >0.05.
Table 2. Meta-regression of variables influencing estimated rifampicin AUC

<table>
<thead>
<tr>
<th>Variable and category</th>
<th>Adjusted AUC estimate (mg·h/L)</th>
<th>95% CI</th>
<th>SEM</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>single dose</td>
<td>56.26</td>
<td>29.01–83.50</td>
<td>13.90</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>steady-state dosing (&gt;1 week)</td>
<td>20.94</td>
<td>8.28–33.60</td>
<td>6.49</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HIV status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV negative</td>
<td>53.16</td>
<td>41.63–64.68</td>
<td>5.85</td>
<td>0.60</td>
</tr>
<tr>
<td>HIV positive</td>
<td>48.13</td>
<td>33.26–63.61</td>
<td>7.74</td>
<td>0.31</td>
</tr>
<tr>
<td>mixed HIV population</td>
<td>54.53</td>
<td>37.08–71.98</td>
<td>8.90</td>
<td>0.85</td>
</tr>
<tr>
<td>TB status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TB patients</td>
<td>56.26</td>
<td>43.22–69.29</td>
<td>6.65</td>
<td>0.10</td>
</tr>
<tr>
<td>healthy volunteers</td>
<td>67.09</td>
<td>54.11–80.07</td>
<td>6.62</td>
<td>0.10</td>
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<tr>
<td>Drug combination</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rifampicin monotherapy</td>
<td>87.71</td>
<td>59.48–113.93</td>
<td>13.89</td>
<td>0.72</td>
</tr>
<tr>
<td>RHZE</td>
<td>72.19</td>
<td>50.91–101.47</td>
<td>12.90</td>
<td>0.67</td>
</tr>
<tr>
<td>Diabetes status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no diabetes</td>
<td>109.97</td>
<td>61.03–158.91</td>
<td>24.97</td>
<td>0.03</td>
</tr>
<tr>
<td>diabetes</td>
<td>113.30</td>
<td>59.03–167.55</td>
<td>27.68</td>
<td>0.04</td>
</tr>
<tr>
<td>Dosing frequency</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>daily dosing</td>
<td>54.94</td>
<td>24.42–85.46</td>
<td>15.57</td>
<td>0.93</td>
</tr>
<tr>
<td>intermittent dosing</td>
<td>39.02</td>
<td>17.01–60.95</td>
<td>11.18</td>
<td>0.12</td>
</tr>
</tbody>
</table>

Meta-regression of all available variables found that treatment duration alone had a substantial and significant impact on estimated rifampicin AUC. Steady-state refers to dosing for ≥7 days to allow for saturation of first-pass metabolism and the establishment of metabolic autoinduction. P values indicate significance of difference between pooled AUC estimates and overall population estimate.

Table 3. Rifampicin AUC at steady-state: meta-analysed standard dose compared with higher dosages

<table>
<thead>
<tr>
<th>Rifampicin dose (mg/kg)</th>
<th>Number of subjects</th>
<th>Mean AUC (mg·h/L)</th>
<th>SEM</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>8–12</td>
<td>846</td>
<td>38.2</td>
<td>4.3</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>23</td>
<td>79.7</td>
<td>5.4</td>
<td>[16]</td>
</tr>
<tr>
<td>15</td>
<td>55</td>
<td>46.4</td>
<td>3.4</td>
<td>[49]</td>
</tr>
<tr>
<td>17</td>
<td>11</td>
<td>100.1</td>
<td>11.0</td>
<td>[50]</td>
</tr>
<tr>
<td>20</td>
<td>113</td>
<td>95.2</td>
<td>3.8</td>
<td>[23,49,51]</td>
</tr>
<tr>
<td>25</td>
<td>15</td>
<td>140.5</td>
<td>11.2</td>
<td>[23]</td>
</tr>
<tr>
<td>30</td>
<td>15</td>
<td>204.8</td>
<td>22.6</td>
<td>[23]</td>
</tr>
<tr>
<td>35</td>
<td>35</td>
<td>194.6</td>
<td>12.3</td>
<td>[23,51]</td>
</tr>
</tbody>
</table>

With increasing dose, there is a greater than proportional increase in AUC. Data are displayed in Figure 3(a). Steady-state refers to dosing for ≥7 days to allow for saturation of first-pass metabolism and the establishment of metabolic autoinduction. All references in meta-analysis (see Table S1).

Figure 3. (a) Impact of increasing dose on rifampicin AUC. With increasing dose, there appears to be a greater than proportional increase in AUC. Error bars show SEM. Data are displayed in Table 3. (b) Impact of increasing dose on rifampicin AUC/MIC. Taking the ECOFF MIC of 0.5 mg/L, available data indicate that a rifampicin dose of ≥25 mg/kg is required to attain the PK/PD target associated with a 1 log cfu reduction (an AUC/MIC of 271).

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efficacy at current dosages as exploration of higher dosages continues.
None to declare.

K. E. S. and G. D. devised and designed the study. K. E. S. and G. D. conducted the literature search. K. E. S. performed data extraction and analysis. K. E. S., H. P. and G. D. interpreted the data. K. E. S. prepared the manuscript. All authors reviewed, amended and approved the submitted manuscript.

Figures S1 and S2 and Tables S1 and S2 are available as Supplementary data at JAC Online.

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