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Article *in* Obesity Reviews · May 2016

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Review

The effect of (L-)carnitine on weight loss in adults: a systematic review and meta-analysis of randomized controlled trials

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Received 21 January 2016; revised 21 April 2016; accepted 9 May 2016

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Summary

This study provides a systematic review and meta-analysis of randomized controlled trials, which have examined the effect of the carnitine on adult weight loss. Relevant studies were identified by systematic search of PubMed, Embase, Cochrane Central Register of Controlled Trials and reference lists of relevant marker studies. Nine studies (total $n = 911$) of adequate methodological quality were included in the review. Trials with mean difference (MD) of 95% confidence interval (CI) were pooled using random effect model. Results from meta-analysis of eligible trials revealed that subjects who received carnitine lost significantly more weight (MD: −1.33 kg; 95% CI: −2.09 to −0.57) and showed a decrease in body mass index (MD: −0.47 kg m^{-2}; 95% CI: −0.88 to −0.05) compared with the control group. The results of meta-regression analysis of duration of consumption revealed that the magnitude of weight loss resulted by carnitine supplementation significantly decreased over time ($p = 0.002$). We conclude that receiving the carnitine resulted in weight loss. Using multiple-treatments meta-analysis of the drugs and non-pharmacotherapy options seem to be insightful areas for research. © 2016 World Obesity

Keywords: (L-)carnitine, BMI, meta-analysis~~, placebo,~~ weight change.

obesity reviews (2016)

Introduction

Obesity, an epidemic worldwide issue, can lead to some chronic diseases such as dyslipidemia (1), type 2 diabetes mellitus (2), fatty liver (3) and cardiovascular diseases (4). Pharmacotherapy is a popular approach to weight loss among individuals. Carnitine is one of the drugs claimed to increase weight loss.

Carnitine or L-b-hydroxy-c-N-trimethylaminobutyric acid is synthesized in the liver and kidneys. (L-)carnitine decreases the intramitochondrial acetyl-CoA/CoA ratio through trapping of acetyl groups and activation of the pyruvate dehydrogenase complex (5).

This leads to simultaneous decrease in acetyl-CoA levels in the cytosol contributing to activation of the glycolytic pathway (6). (L-)carnitine, thus plays some roles in the glucose metabolism and may increase energy expenditure (7,8). Carnitine has an important role in lipid metabolism as well. It facilitates the transfer of long-chain fatty acids across the mitochondrial inner membrane as acylcarnitine esters and acts as an obligatory cofactor for ß-oxidation of fatty acids (9). Because of these two effects of L-carnitine

on glucose and lipid metabolism, it may help weight loss by increasing energy expenditure (10).

Supplementing carnitine as for weight-loss agent is based on the fact that regular oral ingestion of this substance leads to the increase of its intracellular concentration. This in turn activates fat oxidation and helps reduction of the body's fat reserves. A number of studies have shown that oral carnitine ingestion (up to $6\,g\,d^{-1}$ for 14 d) does not change muscle carnitine concentration in healthy non-obese humans and does not cause weight loss (11,12). Other clinical studies, however, do report the effectiveness of carnitine supplementation in the treatment of obesity (13). A report has revealed that inhibition of hypothalamic carnitine palmitoyltransferase decreases food intake (14). Dietary carnitine stimulates carnitine palmitoyltransferase activation (15), which could underlie diminished appetite by L-carnitine supplementation. Thus, claiming that carnitine supplementation promotes weight loss in healthy non-obese individuals is not sufficiently substantiated, begging more investigations. Here, we have performed a systematic review and meta-analysis of randomized clinical trials to evaluate the effectiveness of L-carnitine supplementation on weight loss.

Methods

Data source and search strategy

A systematic review and meta-analysis of studies was conducted based on the Preferred Reporting Items for Q4 Systematic Reviews and Meta-analyses guidelines (16). Comprehensive search strategies were used to identify reports of randomized controlled trials indexed in PubMed (from inception to May 2015), the Cochrane Library and Google scholar (from inception to May 2015). The following keywords were used for studies pertinent to the study objectives: (carnitine OR (L-)carnitine OR Levocarnitine) AND (weight OR weight loss OR weight reduction OR BMI OR weight change OR lipid oxidation OR anthropometry) AND (randomized controlled trial OR controlled clinical trial OR placebo OR randomized OR trial OR randomly OR group). Moreover, the reference lists of selected studies were searched to find other relevant trials. The language of publication was not restricted.

Study selection

The randomized controlled trial studies comparing the effects of (L-)carnitine and placebo on the subjects' weight loss were included. Studies carried out on animals and the ones with follow-ups of less than 30 d were excluded. (L-)carnitine is defined as accelerator of fatty acid oxidation in mitochondria. Placebo was also defined as a medically ineffectual treatment similar to intervention supplementation in shape and colour. Weight change was considered as primary outcome. Other outcomes such as body mass index (BMI) change and body fat were considered as secondary outcomes.

Having pooled the retrieved papers and removing duplicates, two reviewers (M. P. and M. N.) independently skimmed the title and abstracts of searched paper to detect potentially eligible papers. Then, the body of the selected studies was scrutinized to exclude non-eligible ones and include qualified randomized controlled trials reports based on predetermined criteria. Any discrepancies raised between reviewers were discussed with a third reviewer (A. O.) in order to reach a consensus.

Data extraction and quality assessment

A data abstraction form was developed, and the reviewers extracted the outcomes of interest from the selected studies. General information (authors, title, journal of publication and date of publication), the study population characteristics (age, sex, race, health condition and BMI) and the study results (predefined outcomes) were extracted. Jadad scale (14) was used to appraise the included studies. Randomization allocation, allocation concealment and blinding of outcome assessment were some of the criteria.

Qualitative and quantitative analysis

Mean difference (MD) was used as the main measure to summarize clinical effect of the arms on the outcomes. Inverse-variance method was used to analyze the prepared data. To calculate pooled estimate of MD with 95% confidence interval (CI), the fixed effects and random effects models were used. I^2 test was used to assess heterogeneity. $I^2 > 50\%$ was assumed to represent heterogeneity among studies. If heterogeneity of the studies was not significant, the fixed effects estimation was reported. Sensitivity analysis of results was used to explore heterogeneity among trials. Meta-analysis was performed using REVMAN 5.2 software and meta-regression analysis was performed using STATA 14 software.

Results

A total of 2,145 studies were retrieved through search databases as depicted in Fig. 1. Having excluded the duplicates, **F1** the summaries of the 1,236 remaining studies were screened by the reviewers. Next, the body of the remaining 83 studies were scrutinized. At the end, nine studies were included in the review. Four of the studies had been conducted in Italy (18–21), and two in Iran (22,23). The other trials had been conducted in New Zealand (24), Australia (25) and Brazil (26). Of the total 911 individuals participated in the

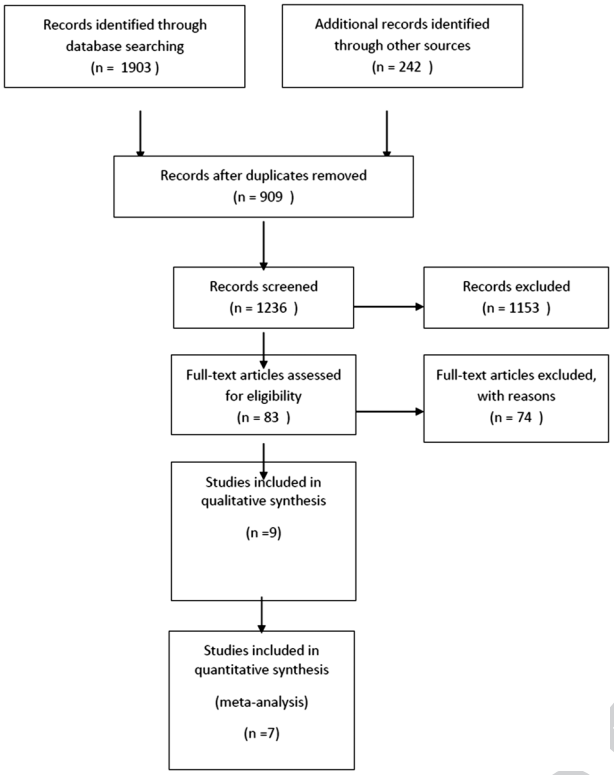

Figure 1 Flowchart of identification of included trials.

included trials, 449 had received carnitine, and the remaining 462 subjects had been allocated to placebo/control arm. The publication year of included trials ranged from 2000 to 2013, spanning 13 years.

Moreover, four trials had compared (L-)carnitine with placebo (18,19,24,26). However, in the comparative arms of some studies, the subjects of both arms also had followed exercise protocol (12,23) or some complementary drugs (20,21). Four studies had included diabetic patients (18,20–22). One study had been conducted on subjects with bipolar disorder (24), and two studies had investigated obese subjects (12,23). One study had focused on physically active individuals (26), and the last trial had included subjects with muscle fatigue (19). Table 1 summarizes characteristics of the included trials. **T1**

Assessment the quality of studies

All of the included studies had adopted randomization criteria but some of them did not delineate clearly the schedule of randomization process (12,22,26). The blinding had been conducted in all of the included studies except for two studies (22,26). According to the Jadad scale, five studies received score 5 (18,20,21,23,24). Last column of Table 1 provides detailed results of quality assessment of the studies.

Table 1 Characteristics of included studies

Author	Year	Population	Arms (dosage)	Sample size (women %)	Mean age (SD)	Baseline weight	Follow-up duration (day)	Quality assessment
Barzegar *et al.*	2013	Diabetic obese women	(L-)carnitine (2 g d^{-1}) and low calorie diet	30 (0)	Range from 20 to 50	83.8 (8.21)	56	1
			Placebo and low calorie diet	30 (0)		84.23 (7.8)		
Coelho *et al.*	2009	Physically active individuals	(L-)carnitine (1.8 g d^{-1})	11 (0)	46.7 (4.8)	82.35 (16.36)	30	2
			Placebo	10 (0)	44.7 (5)	83.57 (14.35)		
Derosa *et al.*	2003	Diabetic patients	(L-)carnitine (2 g d^{-1})	46 (47.8)	52 (6)	78.2 (5.8)	90	5
			Placebo	48 (52.1)	50 (7)	77.6 (6.4)		
Derosa *et al.*	2010	Obese diabetic patients	(L-)carnitine (2 g d^{-1}) and orlistat	132 (50.7)	51 (4)	94.5 (9.6)	360	5
			Orlistat	126 (50.7)	53 (6)			
Derosa *et al.*	2011	Diabetic patients	(L-)carnitine (2 g d^{-1}) and sibutramine (10 mg)	129 (49.6)	54 (5)	97.7 (11.4)	360	5
			sibutramine (10 mg)	125 (49.6)	51 (4)	96.9 (10.8)		
Elmslie *et al.*	2006	Patients with bipolar disorder	(L-)carnitine (15 mg kg^{-1} d^{-1})	30 (20)	42 (10)	94.7	182	5
			Placebo	30 (16.6)	42 (13)	94.1		
Pistone *et al.*	2003	Elderly patients	Levocarnitine (4 g d^{-1})	42 (47.6)	81.5 (6.7)	66.9 (9.4)	30	4
			Placebo	42 (42.9)	80.7 (6.9)	65.4 (11.3)		
Rafraf	2012	Diabetic women	(L-)carnitine (2 g d^{-1})	11 (100)	34.4 (5.48)	87.72 (6.31)	60	5
			(L-)carnitine (2 g d^{-1}) and exercise	11 (100)	34.8 (6.25)	85.08 (11.65)		
			Placebo	11 (100)	36.5 (7.33)	85.6 (8.87)		
			Placebo and exercise	11 (100)	36.1 (7.2)	82.61 (6.06)		
Vilani *et al.*	2000	Obese women	(L-)carnitine (4 g d^{-1}) and aerobic training programme	18 (100)	27.2 (9.6)	70.1 (9.9)	56	3
			Placebo and aerobic training programme	18 (100)				

SD, standard deviation.

Data synthesis

Nine trials were included in this review, but only six of them had reported the mean (standard deviation) of weight and five of them had reported mean (standard deviation) of BMI. One trial was excluded from meta-analysis because of reporting findings with median and two of the remaining trials did not report neither BMI or weight outcomes properly.

The eligible trials for quantitative analysis had reported their findings in different time points and with no estimation of changes in weight or BMI outcomes. Some reviews had used different implicit methods to determine the effect of the treatment (27,28). The steps followed in this study are clearly defined in the Tables S1–S4. This method had been used in different review studies (29,30). The subgroup analysis was considered for some chronic conditions such as diabetes and obesity. Insufficient available data on other potential causes of heterogeneities such as age and gender of subjects hinder an assessment of subgroup differences in the included trials.

Weight change

Six trials had reported weight changes in control and intervention groups. Using inverse-variance method, a significantly greater loss in weight was observed in participants who received the carnitine compared with control group, (MD: −1.33 kg; 95% CI: −2.09 to −0.57) $I^2 = 96\%$. **F2** Figure 2 represents the forest plot of these results.

Body mass index change

Five trials had used this outcome to report their findings. Our analysis indicates that using the carnitine leads to significantly lower BMI compared with subjects who had received control, (MD: $-0.47\,kg\,m^{-2}$; 95% CI: −0.88 to −0.05) $I^2 = 93\%$. Figure 3 represents the forest plot of these results. **F3**

Subgroup and meta-regression analysis

Diabetic versus non-diabetic patients

Three trials had been conducted on patients suffering from diabetes. Pool estimate of their results indicated that those who received carnitine had significantly much weight loss compared with control group, (MD: −1.96 kg; 95% CI: −2.21 to −1.7) $I^2 = 0\%$. In non-diabetic people a significant weight loss was observed, (MD: −0.54 kg; 95% CI: −0.6 to −0.49) $I^2 = 0\%$. Figure 4 show the forest plot of this analysis. **F4**

Obese versus non-obese participants

Totally, five trials involved obese subjects. Our results show that those who had received carnitine experienced a significantly much weight loss compared with the control group, (MD: −1.25 kg; 95% CI: −2.14 to −0.36) $I^2 = 97\%$. In non-obese –as well- a significant weight loss was observed, (MD: −1.75 kg; 95% CI: −2.37 to −1.12) $I^2 = 0\%$. Figure 5 represents the forest plot of this analysis. **F5**

Dosage and duration of consumption

Duration of the trials included varied from 1-month to 1-year follow-up. Meta-regression analysis showed that the duration of consumption were negatively related to effect size (regression coefficient = −0.24; 95% CI: −0.38, −0.09 $p = 0.002$). It means when the carnitine was used for longer time, it expected that the magnitude of weight loss will decrease.

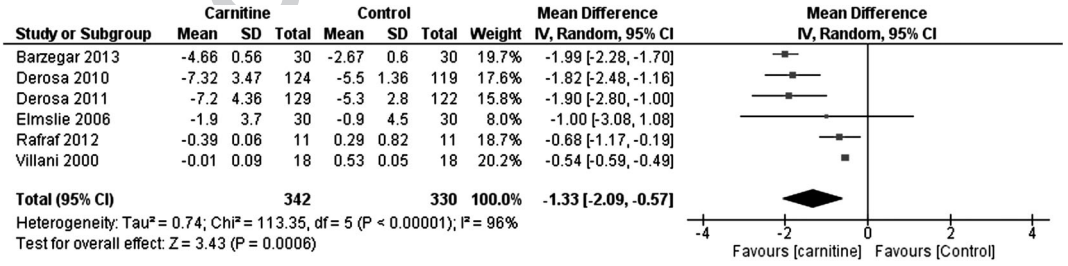

Figure 2 Forest plot of weight change outcome.

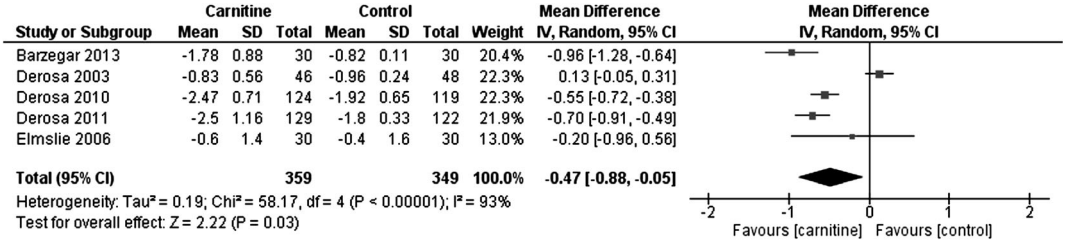

Figure 3 Forest plot of body mass index (BMI) change outcome.

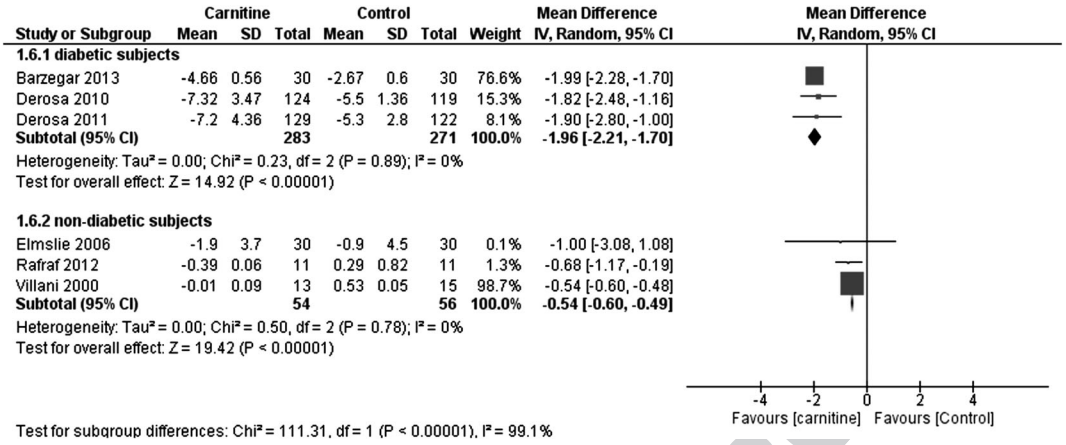

Figure 4 Forest plot of diabetic patents.

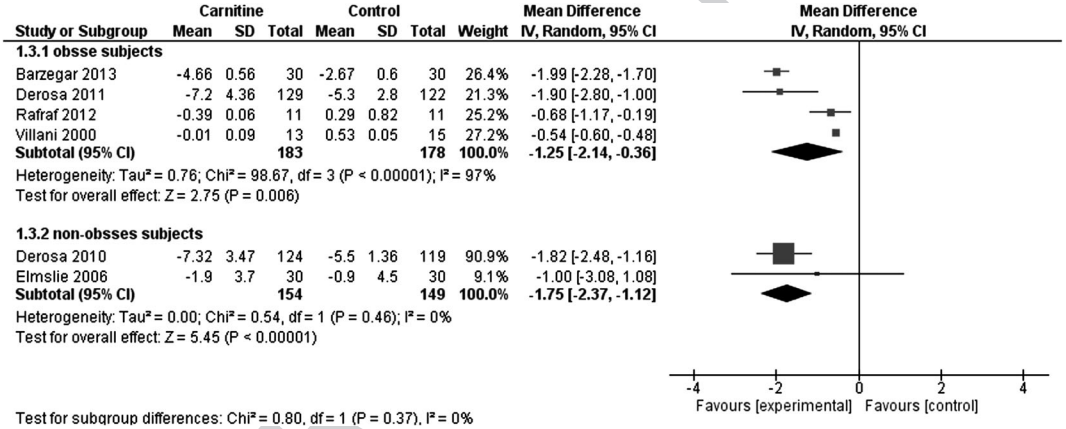

Figure 5 Forest plot of obese people.

The carnitine dosage varies from 1.8 g d^{-1} to 4 g d^{-1} in the trials. Meta-regression analysis done emphasized that dose of the carnitine did not significantly change the effect size (regression coefficient = 0.06; 95% CI: −3.16, 3.28 $p = 0.972$).

Sensitivity analysis

Regarding the considerable heterogeneity among the included trials, it was found that most heterogenic trials in pool estimation of the outcomes were related to those studies that had low score in methodological quality assessment such as Villani *et al.* (12) and Barzegar *et al.* (22). However, the sensitivity analysis of these trials did not affect our final results.

Discussion

Obesity is a serious health problem, which has increasingly become associated with higher rate of mortality and morbidity in the world. Along with weight control as becoming more difficult in this industrialized world, weight loss is getting more attention. Anti-obesity drugs have no side effects of invasive surgeries, and hence, they are more commonly used than other options like physical activities. Carnitine has been applied for prevention of cardiovascular disease (31), end-stage kidney diseases (32), dialysis-related hypertension (33), treatment of persistent depressive disorder (34) and treatment of non-alcoholic fatty liver disease (35). However, evidence regarding the anti-obesity effects of the carnitine is still inconclusive. Here, we pooled the trials comparing the effect of carnitine and control on weight loss in adults. Weight and BMI were two variables that were considered as for assessing weight loss of the participants. After, excluding the studies that did not meet our criteria, nine studies were accepted for final analysis. However, only seven of them were eligible for quantitative analysis. Most of the included trials were of relatively adequate methodological quality. We found that carnitine has had a decreasing impact onto weight and BMI in these trials. Positive influence of carnitine onto weight loss was found in chronic conditions such as diabetes and obesity. Our meta-regression analysis

indicates that magnitude of weight loss would decrease over time. Although the analysis indicated that dosage of carnitine had positive, but not significant, impact on weight change, insufficient power of analysis precluded us to have any recommendation regarding the best dosage of the carnitine. No study had systematically reviewed anti-obesity impact of the carnitine. There was, however, a narrative review, which had focused on metabolic function of the carnitine in human setting (36), but that study has not directly addressed clinical effect of carnitine. Evidence about pharmacotherapy of obesity have addressed the long-term impact of orlistat, sibutramine and rimonabant on weight loss in people (37,38). Although carnitine has a lower magnitude of weight loss than these drugs, unlike them, it does not suffer from some side-effects such as gastrointestinal issues, rising blood pressure, and pulse rate and increased risk of psychological disorder (39,40). The researchers had some trials, which had relatively heterogenic characteristics. Lack of sufficient data precluded us to assess the impact of the variables on effect size of the study. More investigations would help to have a better assessment of the comparative effect of the anti-obesity drugs in long-term follow-up studies. Multiple-treatments meta-analysis of the drugs and non-pharmacotherapy options might be helpful in this regard.

Conclusions

Carnitine might be an effective drug for weight loss in adults.

Conflict of interest statement

The authors declared that they have no potential conflicts of interest.

Acknowledgements

This review was funded by Tehran University of Medical Sciences. We thank the referees for their valuable comments.

Supporting Information

Additional Supporting Information may be found in the online version of this article, http://dx.doi.org/10.1111/obr.12436

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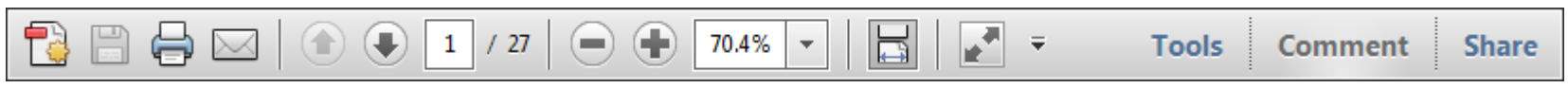
Q1	AUTHOR: Please confirm that given names (red) and surnames/family names (green) have been identified correctly.	
Q2	AUTHOR: Please supply a maximum of four keywords only as per technical style sheet.	
Q3	AUTHOR: The funding agency 'Tehran University of Medical Sciences' matches multiple possible funders. Please confirm which of the following funders is referred here: Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences ,Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences ,Tehran University of Medical Sciences and Health Services ,Tehran University of Medical Sciences and Health Services	
Q4	AUTHOR: Is this the correct definition for PRISMA? Please change if this is incorrect.	
Q5	AUTHOR: Reference "17" is not cited in the text. Please indicate where it should be cited; or delete from the reference list and renumber the references in the text and reference list.	
Q6	AUTHOR: Please provide volume and page number for reference 40.	

WILEY

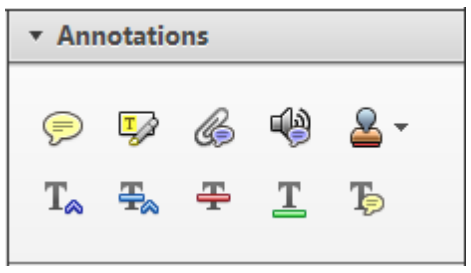
USING e-ANNOTATION TOOLS FOR ELECTRONIC PROOF CORRECTION

Required software to e-Annotate PDFs: Adobe Acrobat Professional or Adobe Reader (version 7.0 or above). (Note that this document uses screenshots from Adobe Reader X)
The latest version of Acrobat Reader can be downloaded for free at: http://get.adobe.com/uk/reader/

Once you have Acrobat Reader open on your computer, click on the Comment tab at the right of the toolbar:



This will open up a panel down the right side of the document. The majority of tools you will use for annotating your proof will be in the Annotations section, pictured opposite. We've picked out some of these tools below:

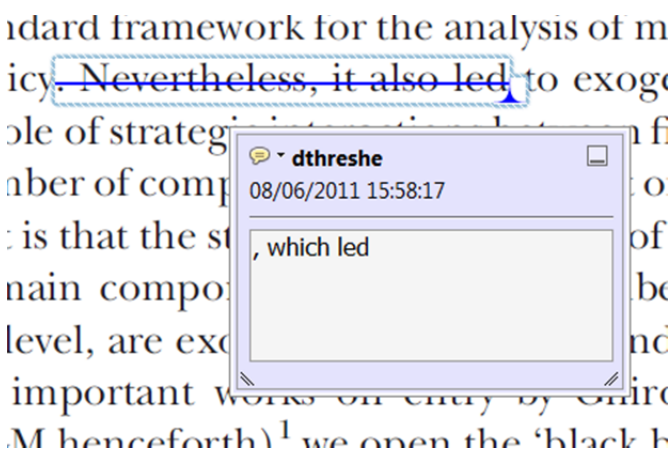


1. Replace (Ins) Tool – for replacing text.

Strikes a line through text and opens up a text box where replacement text can be entered.

How to use it

- Highlight a word or sentence.
- Click on the Replace (Ins) icon in the Annotations section.
- Type the replacement text into the blue box that appears.

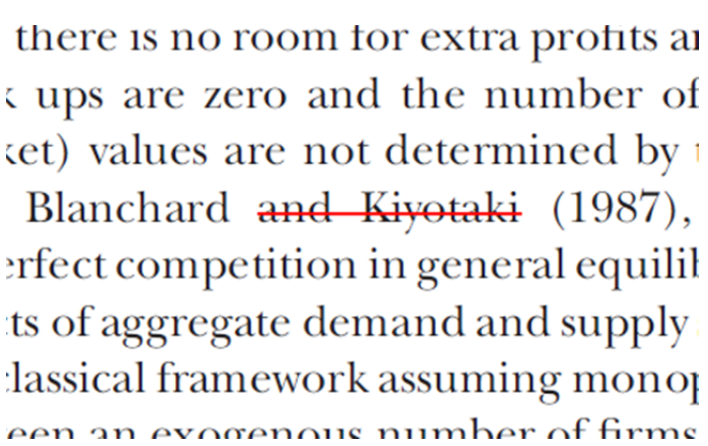


2. Strikethrough (Del) Tool – for deleting text.

Strikes a red line through text that is to be deleted.

How to use it

- Highlight a word or sentence.
- Click on the Strikethrough (Del) icon in the Annotations section.

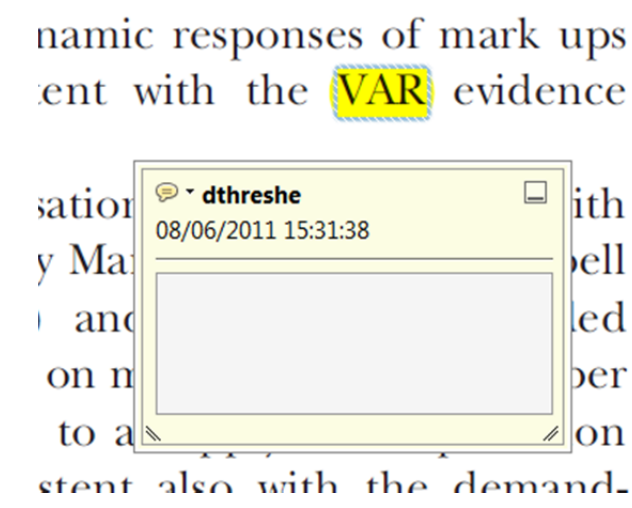


3. Add note to text Tool – for highlighting a section to be changed to bold or italic.

Highlights text in yellow and opens up a text box where comments can be entered.

How to use it

- Highlight the relevant section of text.
- Click on the Add note to text icon in the Annotations section.
- Type instruction on what should be changed regarding the text into the yellow box that appears.

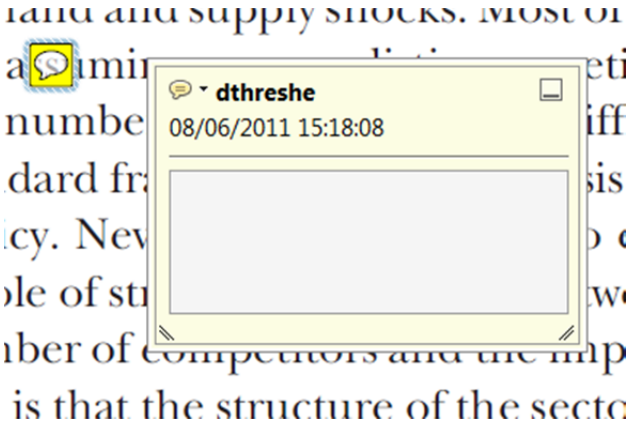


4. Add sticky note Tool – for making notes at specific points in the text.

Marks a point in the proof where a comment needs to be highlighted.

How to use it

- Click on the Add sticky note icon in the Annotations section.
- Click at the point in the proof where the comment should be inserted.
- Type the comment into the yellow box that appears.



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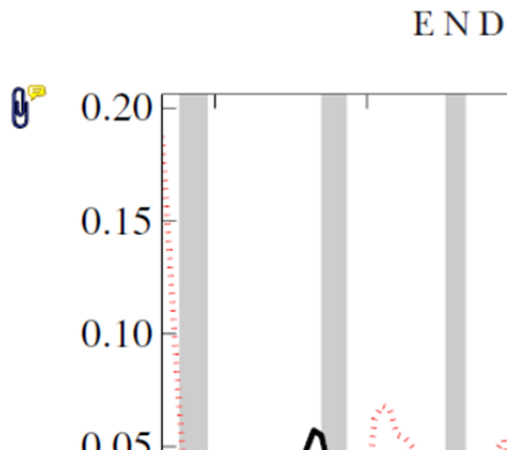
USING e-ANNOTATION TOOLS FOR ELECTRONIC PROOF CORRECTION

5. Attach File Tool – for inserting large amounts of text or replacement figures.

Inserts an icon linking to the attached file in the appropriate pace in the text.

How to use it

- Click on the Attach File icon in the Annotations section.
- Click on the proof to where you'd like the attached file to be linked.
- Select the file to be attached from your computer or network.
- Select the colour and type of icon that will appear in the proof. Click OK.

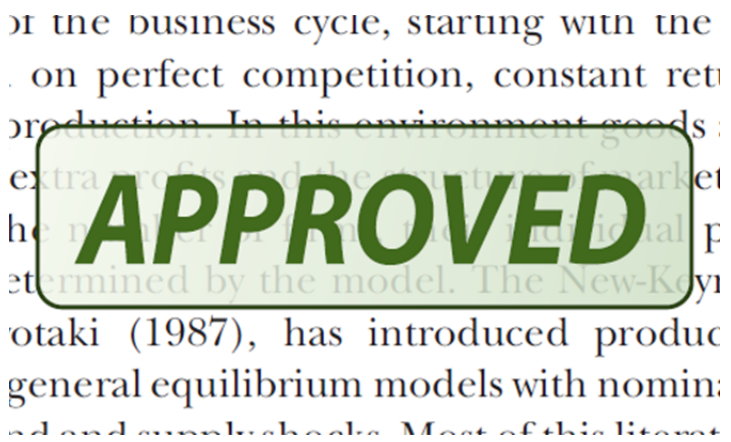


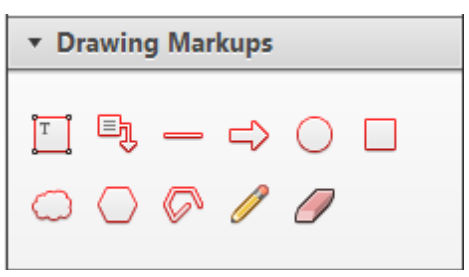
6. Add stamp Tool – for approving a proof if no corrections are required.

Inserts a selected stamp onto an appropriate place in the proof.

How to use it

- Click on the Add stamp icon in the Annotations section.
- Select the stamp you want to use. (The Approved stamp is usually available directly in the menu that appears).
- Click on the proof where you'd like the stamp to appear. (Where a proof is to be approved as it is, this would normally be on the first page).



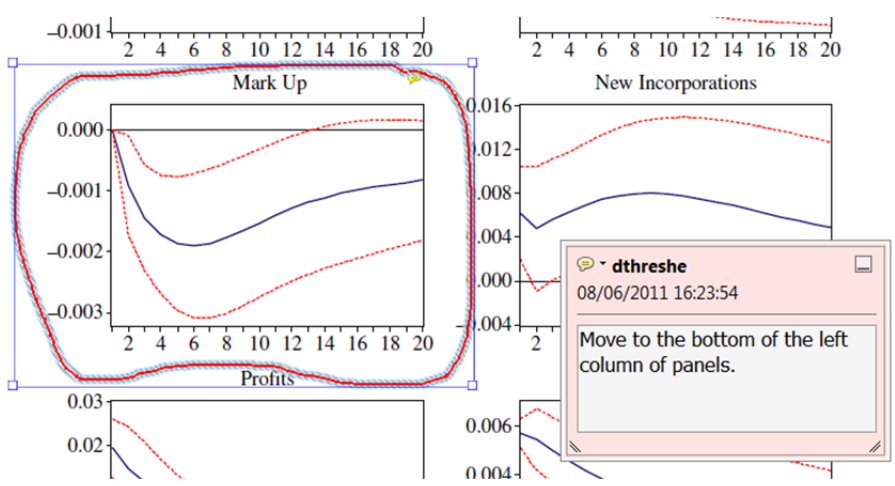


7. Drawing Markups Tools – for drawing shapes, lines and freeform annotations on proofs and commenting on these marks.

Allows shapes, lines and freeform annotations to be drawn on proofs and for comment to be made on these marks..

How to use it

- Click on one of the shapes in the Drawing Markups section.
- Click on the proof at the relevant point and draw the selected shape with the cursor.
- To add a comment to the drawn shape, move the cursor over the shape until an arrowhead appears.
- Double click on the shape and type any text in the red box that appears.



For further information on how to annotate proofs, click on the Help menu to reveal a list of further options: