

# Reporting rate of adverse drug reactions to the French pharmacovigilance system with three step 2 analgesic drugs: dextropropoxyphene, tramadol and codeine (in combination with paracetamol)

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## WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Three 'weak' opioid analgesics are marketed in France and other European countries in association with paracetamol.
- They are very largely used, but to our knowledge there is no large study comparing the reporting rate of adverse drug reactions (ADRs) between these different step 2 analgesic combinations to determine the safest one.

## WHAT THIS STUDY ADDS

- The aim of this study was to compare reporting rate of ADRs with three step 2 combinations according to their consumption in France.
- The results show that among these combinations, reporting rate and 'seriousness' of reported ADRs are the highest with tramadol/paracetamol (TRM+P) and the lowest with codeine/paracetamol.
- The safety of TRM+P needs to be urgently investigated with more methodologically rigorous studies.

## AIMS

Three 'weak' opioid analgesics in association with paracetamol are marketed in France as step 2 analgesics: dextropropoxyphene, tramadol and codeine. These combinations are involved in several adverse drug reactions (ADRs), but no data are available about their comparative reporting rate. The aim was to compare the reporting rate of ADRs between tramadol/paracetamol (TRM+P), codeine/paracetamol (COD+P) and dextropropoxyphene/paracetamol (DXP+P).

## METHODS

All spontaneous reports submitted to the French Pharmacovigilance Database from 1 January 1987 to 31 December 2006 suspected to be induced by one of the three step 2 analgesic combinations (DXP+P, TRM+P, COD+P) were extracted. Their consumption for the same period was obtained from the French Drug Agency. The number of ADRs, serious ADRs and different organ classes of ADRs were compared according to their consumption. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for each variable using DXP+P as reference.

## RESULTS

The reporting rate of ADRs was calculated as 24.9/100 000 person-years for DXP+P, 44.5/100 000 person-years for TRM+P and 12.5/100 000 person-years for COD+P. The reporting rate (OR 0.56, 95% CI 0.50, 0.63) and 'seriousness' (OR 0.65, 95% CI 0.53, 0.80) of ADRs were significantly higher with TRM+P than with DXP+P. However, hepatobiliary ADRs were significantly more frequent with the DXP+P combination (OR 2.62, 95% CI 1.59, 4.37). In contrast, the reporting rate (OR 1.99, 95% CI 1.82, 2.18) and 'seriousness' (OR 2.64, 95% CI 2.24, 3.11) of ADRs were significantly higher with DXP+P than with COD+P.

## CONCLUSIONS

Among the three step 2 analgesic combinations, reporting rate and 'seriousness' of ADRs are the highest with TRM+P and the lowest with COD+P. Our study suggests that the safety profile of DXP+P is worst than that of COD+P.

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## Keywords

adverse drug reactions, analgesic drugs, codeine, dextropropoxyphene, pharmacovigilance, tramadol

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## Introduction

Three 'weak' opioid analgesics are marketed in France in association with paracetamol as step 2 analgesics (according to the World Health Organization (WHO) classification) [1]: dextropropoxyphene, tramadol and codeine (Table 1). Their level of consumption is very high, especially dextropropoxyphene/paracetamol (DXP+P) (20 801 997 160 units in 2006), which belongs to the top 10 drugs in France [2].

Dextropropoxyphene is a 'weak' opioid analgesic, structurally related to methadone, acting through activation of  $\mu$ -opioid receptors and producing analgesia and other central effects similar to those seen with other morphine-like compounds [3]. The association DXP+P has been marketed in France since 1974. It is involved in several serious adverse drug reactions (ADRs) (i.e. hepatic reactions, hallucinations, abuse, withdrawal symptoms, hypoglycaemia...) [1]. Moreover, plasma elimination half-life of dextropropoxyphene is long (15–34 h), in contrast to paracetamol (2 h), which increases the risk of accumulation in patients with renal failure or in elderly people [3]. Overdoses of dextropropoxyphene could lead to fatal respiratory depression or cardiac ADRs (such as severe bradycardia or atrioventricular dysfunction) [3, 4]. These observations have led some European countries (Switzerland, Sweden, UK, ...) to remove approval of products containing DXP [5, 6]. In 2008, the European Medicines Agency decided to review all fixed combination analgesics containing DXP+P to determine whether they should have their product information changed to reflect safety concerns or be taken off the market altogether [7]. Recently, the Food and Drug Administration (FDA) review committee has voted against the Darvon (paracetamol + propoxyphene) combination, and it remains to be seen whether or not the FDA will implement a total ban [8].

Tramadol and codeine are two other 'weak' opioid analgesics also used in combination with paracetamol as step 2 analgesics. The combination of tramadol/paracetamol (TRM+P) has been marketed in France since 2002 and the combination of codeine/paracetamol (COD+P) since 1983.

They have the same ADR profile as opioid analgesics in general [3]. To our knowledge, there is no large study comparing the reporting rate of ADRs between these different step 2 analgesic combinations.

Thus the aim of this study was to compare the rate of ADRs reported with TRM+P, COD+P and DXP+P according to their consumption in France.

## Methods

The French Pharmacovigilance System was first established in 1973 and consists of a network of 31 Regional Centres. The French Pharmacovigilance Database (FPD) was established in 1985 to record spontaneous reporting of ADRs [9, 10]. Furthermore, reporting 'serious' or 'unlabelled' ADRs to the French Regional Centres has been mandatory for any drug prescriber, physician, dentist or midwife in France since 1995 [11]. A 'serious' ADR is defined as any untoward medical occurrence that at any dose results in death, requires hospital admission or prolongation of existing hospital stay, results in persistent or significant disability/incapacity, or is life threatening [12]. An 'unlabelled' (or 'unexpected') ADR is defined as an ADR whose nature or severity is not consistent with data contained in domestic labelling or market authorization or expected from characteristics of the drug [12]. Case causality assessment is performed for all ADRs registered in the FPD according to the French method, which contains five intrinsic causality levels: I0, excluded; I1, dubious; I2, plausible; I3, likely; I4, very likely [13].

Spontaneous reports submitted to the FPD from 1 January 1987 to 31 December 2006, in which the products containing the combination of DXP+P, TRM+P or COD+P (whatever the dosage forms) were 'suspected' (I1, I2, I3 and I4 levels of causality assessment), were extracted. Consumption of the same products in France for the same period was obtained from the French Drug Agency [Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSaPS)]. The number of ADRs, 'serious' ADRs and different organ classes of ADRs were compared according to their consumption expressed in person-years using the

**Table 1**

Dosage forms and defined daily doses (DDDs) of dextropropoxyphene, tramadol and codeine, in combination with paracetamol

| Combination                    | Main commercial products  | Opioid dosage | Paracetamol dosage | DDDs                     |
|--------------------------------|---|---------------|--------------------|--------------------------|
| Dextropropoxyphene/paracetamol | Dextroref; Di-Dolko; Diadupsan; Dialgirex; Di-Antalvic; Propofan  | 27–30 mg      | 400 mg             | 4 pharmaceutical units   |
| Tramadol/paracetamol           | lxprim; Zaldiar   | 37.5 mg       | 325 mg             | 4 pharmaceutical units   |
| Codeine/paracetamol            | Algicalm; Algisedal; Claradol Codeine; Codoliprane; Compralgyl; Dafalgan Codeine; Efferalgan Codeine; Gaosedal Codeine; Gelumaline; Klipal Codeine; Lindilane; Migralgine; Panadol Codeine; Prontalgine; Salgydal; Sedarene; Supadol; Vegadeine | 10–30 mg      | 250–600 mg         | 3–6 pharmaceutical units |

1 defined daily dose of combination products according to  
2 the WHO (Table 1) [14].

### 3 *Statistical analysis*

4 Categorical variables were expressed as counts per  
5 100 000 person-years and compared using the  $\chi^2$  test (if  
6 frequency  $<5$ , Fisher's exact test was performed). Adjusted  
7 odds ratios (ORs) and 95% confidence intervals (CIs) were  
8 calculated for each variable using DXP+P as reference.  
9 Statistical analyses were performed using EPI-INFO. The  
10 significance threshold was 5%.  
11

## 12 **Results**

13 Consumption was 14 247 943 person-years for DXP+P  
14 from 1 January 1987 to 31 December 2006, 655 746  
15 person-years for TRM+P from 1 January 2003 to 31 Decem-  
16 ber 2006 and 4 575 058 person-years for COD+P from 1  
17 January 1987 to 31 December 2006 in France according to  
18 data provided by AFSSaPS. A total number of 4418 spon-  
19 taneous notifications (i.e. 3553 with DXP+P, 292 with  
20 TRM+P and 573 with COD+P) were registered in the FPD  
21 during the same period. Thus, the rate of reported ADRs  
22 was calculated as 24.9/100 000 person-years for DXP+P,  
23 44.5/100 000 person-years for TRM+P and 12.5/100 000  
24 person-years for COD+P.

25 Comparison between DXP+P and TRM+P shows that  
26 rate and 'seriousness' of reported ADRs were significantly  
27 higher with the TRM+P combination (Table 2). However,  
28 the rate of deaths related to ADRs was not significantly  
29 different between the two groups ( $P = 1.000$ ). The combi-  
30 nation of TRM+P was involved in significantly more  
31 gastrointestinal, vascular, neurological, psychiatric and  
32 cutaneous ADRs ( $P < 0.001$ ). Nevertheless, hepatobiliary  
33 ADRs were significantly more frequent with the DXP+P  
34 combination.  
35

36 Results with DXP+P and COD+P are also shown in  
37 Table 2. Rate and 'seriousness' of reported ADRs were sig-  
38 nificantly higher with the DXP+P combination. The rate of  
39 deaths due to ADRs was more marked with DXP+P, even  
40 though not reaching the level of significance ( $P = 0.082$ ).  
41 Gastrointestinal, neurological, hepatobiliary, cutaneous  
42 and metabolic ADRs were significantly more frequent with  
43 the DXP+P combination ( $P < 0.001$ ). Among metabolic  
44 ADRs, it should be emphasized that no case of hypergly-  
45 caemia was reported with COD+P, contrary to a reporting  
46 rate of 0.8/100 000 person-years and 0.6/100 000 person-  
47 years with DXP+P and TRM+P, respectively.  
48

## 49 **Discussion**

50 This study shows that between the three step 2 analgesic  
51 combinations, rate and 'seriousness' of reported ADRs are  
52 the highest with TRM+P and the lowest with COD+P. The

53 rough number of ADRs is the highest with DXP+P and the  
54 lowest with TRM+P. However, TRM+P has been marketed  
55 in France since 2003, whereas DXP+P and COD+P were  
56 marketed between 1970 and 1985.  
57

58 To our knowledge, no large study has compared the  
59 safety profile of these three step 2 analgesics. However, a  
60 few studies have compared the efficacy and reporting rate  
61 of ADRs between two step 2 analgesics in some indications  
62 during short periods of use. For example, Mullican com-  
63 pared TRM+P and COD+P combinations in a 4-week,  
64 randomized, double-blind, multicentre trial for the man-  
65 agement of nonmalignant low back pain or osteoarthritis  
66 pain in adults. The overall incidence of ADRs was compa-  
67 rable between the two groups [15]. Boissier *et al.*, in a  
68 double blind, randomized, parallel group trial, compared  
69 the acceptability and efficacy of COD+P and DXP+P for 1  
70 week in 141 outpatients with active osteoarthritis of the  
71 knee or hip. They show that acceptability of COD+P was  
72 significantly worse than that of DXP+P: 53% failure with  
73 COD+P vs. 29% failure with DXP+P ( $P = 0.005$ ) [16]. Never-  
74 theless, in another study comparing DXP+P and COD+P  
75 in post-partum pain after episiotomy and/or rupture of  
76 perineum, the COD+P combination was shown to cause  
77 fewer ADRs than DXP+P [17]. Thus, study results differ  
78 according to the type of pain treated by analgesics.  
79 However, results from these small studies can not be  
80 extrapolated to the general population using step 2 anal-  
81 gesics in different indications. The present study is the first  
82 to compare the three step 2 analgesics in the general  
83 population, in all types of pain and in real life.  
84

85 Comparison of different types of ADRs showed that for  
86 most organ classes, the TRM+P combination was signifi-  
87 cantly associated with the highest reporting rate. However,  
88 the reporting rate of hepatobiliary ADRs was significantly  
89 higher with DXP+P. These data are in accordance with pre-  
90 vious studies. For example, Bergeron *et al.* reported four  
91 cases of hepatitis with the DXP+P combination [18]. They  
92 also found 29 cases of hepatic injuries in patients treated  
93 with dextropropoxyphene in international publications.  
94 It was suggested that the active dextropropoxyphene  
95 metabolite, norpropoxyphene, could induce these hepatic  
96 ADRs via an immunoallergic mechanism [19, 20].  
97

98 Our study suffers from some unavoidable limitations.  
99 The first one is underreporting of ADRs to a national phar-  
100 macovigilance system. The reporting rate of ADRs in France  
101 was estimated to be about 5–10% for 'serious' ADRs [21].  
102 However, Pierfitte *et al.*, in a study based on the FPD data,  
103 demonstrated that the magnitude of reporting rates is the  
104 same for several drugs from the same therapeutic, support-  
105 ing the methodology used in the present study and the  
106 results with three drugs belonging to the same pharmaco-  
107 therapeutic class (step 2 analgesics) [22]. Second, the com-  
108 bination TRM+P was launched much more recently (2002).  
109 Healthcare professionals are probably much more likely to  
110 submit reports of suspected ADRs arising with new, unfa-  
111 miliar agents, thus accounting for the differences in rates.

**Table 2** Frequency of ADRs registered in the French Pharmacovigilance Database with dextropropoxyphene, tramadol and codeine in combination with paracetamol between 1 January 1987 and 31 December 2006

| Parameters             | DXP+P                  |   |                        | TRM+P                                       |                        |   | COD+P               |          |                      |
|------------------------|------------------------|---|------------------------|---|------------------------|---|---------------------|----------|----------------------|
|                        | Number of case reports | Frequency per 10 <sup>5</sup> patient-years | Number of case reports | Frequency per 10 <sup>5</sup> patient-years | Number of case reports | Frequency per 10 <sup>5</sup> patient-years | OR (95% CI)         | P        | OR (95% CI)          |
| Number of ADRs         | 3553                   | 24.9  | 292                    | 44.5  | 573                    | 12.5  | 0.56 (0.50, 0.63)*  | <0.001*  | 1.99 (1.82, 2.18)*   |
| Number of serious ADRs | 1357                   | 9.5   | 96                     | 14.6  | 165                    | 3.6   | 0.65 (0.53, 0.80)*  | <0.001*  | 2.64 (2.24, 3.11)*   |
| Death due to ADRs      | 42                     | 0.3   | 1                      | 0.2   | 6                      | 0.1   | 1.93 (0.29, 37.82)  | 1.000    | 2.25 (0.92, 5.87)    |
| Gastrointestinal ADRs  | 557                    | 3.9   | 106                    | 16.2  | 120                    | 2.6   | 0.24 (0.20, 0.30)*  | <0.001*  | 1.49 (1.22, 1.82)*   |
| Cardiac ADRs           | 56                     | 0.4   | 6                      | 0.9   | 14                     | 0.3   | 0.43 (0.18, 1.11)   | 0.054    | 1.28 (0.69, 2.41)    |
| Vascular ADRs          | 83                     | 0.6   | 16                     | 2.4   | 19                     | 0.4   | 0.24 (0.14, 0.42)*  | <0.001*  | 1.40 (0.83, 2.39)    |
| Neurological ADRs      | 385                    | 2.7   | 65                     | 9.9   | 80                     | 1.7   | 0.27 (0.21, 0.36)*  | <0.001*  | 1.55 (1.21, 1.98)*   |
| Seizure                | 23                     | 0.2   | 7                      | 1.1   | 2                      | 0.0   | 0.15 (0.06, 0.39)*  | 0.095    | 3.69 (0.85, 22.64)   |
| Peripheral neuropathy  | 16                     | 0.1   | 0                      | 0.0   | 1                      | 0.0   | NA                  | 0.091    | 5.14 (0.72, 103.97)  |
| Abnormal movements     | 33                     | 0.2   | 18                     | 2.7   | 15                     | 0.3   | 0.08 (0.08, 0.16)*  | <0.001*  | 0.71 (0.37, 1.36)    |
| Cephalalgia            | 106                    | 0.7   | 6                      | 0.9   | 19                     | 0.4   | 0.81 (0.34, 2.05)   | 0.640    | 1.79 (1.08, 3.01)*   |
| Psychiatric ADRs       | 222                    | 1.6   | 35                     | 5.3   | 53                     | 1.2   | 0.29 (0.20, 0.42)*  | <0.001*  | 1.35 (0.99, 1.84)    |
| Delirium and confusion | 106                    | 0.7   | 19                     | 2.9   | 12                     | 0.3   | 0.26 (0.15, 0.43)*  | <0.001*  | 2.84 (1.52, 5.41)*   |
| Behavioural disorders  | 58                     | 0.4   | 15                     | 2.3   | 5                      | 0.1   | 0.18 (0.10, 0.33)*  | <0.001*  | 3.72 (1.44, 10.53)*  |
| Hepatobiliary ADRs     | 967                    | 6.8   | 17                     | 2.6   | 79                     | 1.7   | 2.62 (1.59, 4.37)** | <0.001** | 3.93 (3.11, 4.98)*   |
| Cutaneous ADRs         | 852                    | 6.0   | 61                     | 9.3   | 183                    | 4.0   | 0.64 (0.49, 0.84)*  | 0.001*   | 1.50 (1.27, 1.76)*   |
| Metabolic disorders    | 189                    | 1.3   | 12                     | 1.8   | 6                      | 0.1   | 0.72 (0.39, 1.36)   | 0.361    | 10.11 (4.34, 25.22)* |
| Hypoglycaemia          | 118                    | 0.8   | 4                      | 0.6   | 0                      | 0.0   | 1.36 (0.48, 4.31)   | 0.702    | NA                   |

DXP, dextropropoxyphene; ADR, adverse drug reaction; CI, confidence interval; COD, codeine; NA, not accurate; OR, odds ratio; P, paracetamol; TRM, tramadol.

The target population may also have been different. Patients from the 1980s and 1990s who have been taking DXP+P or COD+P may have different comorbidities from those on TRM+P.

## Conclusion

Among the three step 2 analgesic combinations marketed in France (DXP+P, TRM+P, COD+P), the rate and 'seriousness' of reported ADRs were the highest with TRM+P and the lowest with COD+P. However, the rate of deaths due to ADRs did not differ among the three combinations. Concerning the different types of ADRs, TRM+P is associated with the greatest reporting rate of gastrointestinal, vascular, neurological, psychiatric and cutaneous ADRs and DXP+P with the greatest reporting rate of hepatobiliary ADRs. Thus, despite its intrinsic limitations, our study suggests that the safety profile of DXP+P is worst than that of COD+P. It is more difficult to draw conclusions about TRM+P. There is evidence concerning its high reporting rate of ADRs, but further systematic studies are necessary to confirm these results.

## Competing interests

None to declare.

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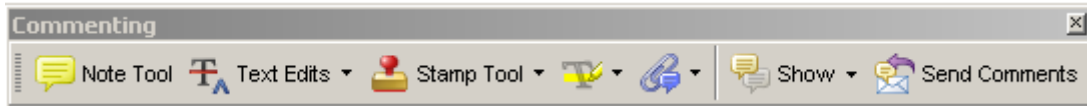
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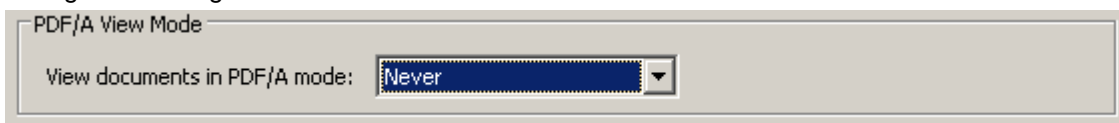
Adobe Acrobat Professional or Acrobat Reader (version 7.0 or above) is required to e-annotate PDFs. Acrobat 8 Reader is a free download: <http://www.adobe.com/products/acrobat/readstep2.html>

Once you have Acrobat Reader 8 on your PC and open the proof, you will see the Commenting Toolbar (if it does not appear automatically go to Tools>Commenting>Commenting Toolbar). The Commenting Toolbar looks like this:



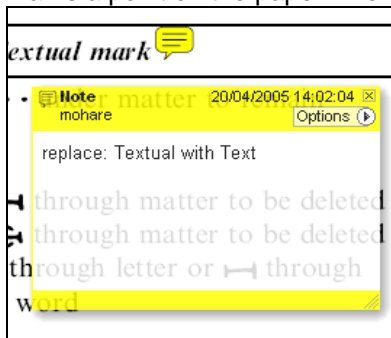
If you experience problems annotating files in Adobe Acrobat Reader 9 then you may need to change a preference setting in order to edit.

In the "Documents" category under "Edit – Preferences", please select the category 'Documents' and change the setting "PDF/A mode:" to "Never".



### Note Tool — For making notes at specific points in the text

Marks a point on the paper where a note or question needs to be addressed.

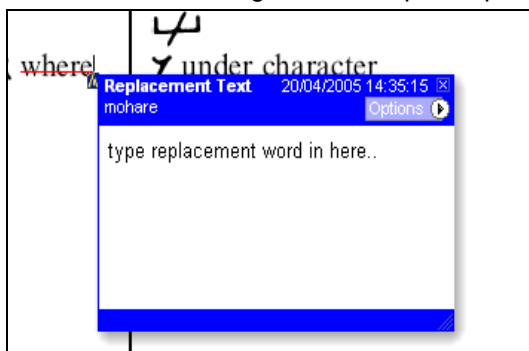


#### How to use it:

1. Right click into area of either inserted text or relevance to note
2. Select Add Note and a yellow speech bubble symbol and text box will appear
3. Type comment into the text box
4. Click the X in the top right hand corner of the note box to close.

### Replacement text tool — For deleting one word/section of text and replacing it

Strikes red line through text and opens up a replacement text box.

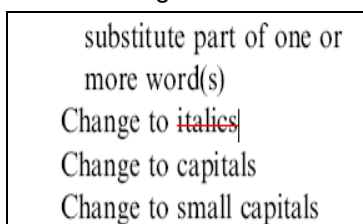


#### How to use it:

1. Select cursor from toolbar
2. Highlight word or sentence
3. Right click
4. Select Replace Text (Comment) option
5. Type replacement text in blue box
6. Click outside of the blue box to close

### Cross out text tool — For deleting text when there is nothing to replace selection

Strikes through text in a red line.



#### How to use it:

1. Select cursor from toolbar
2. Highlight word or sentence
3. Right click
4. Select Cross Out Text

**Approved tool — For approving a proof and that no corrections at all are required.**

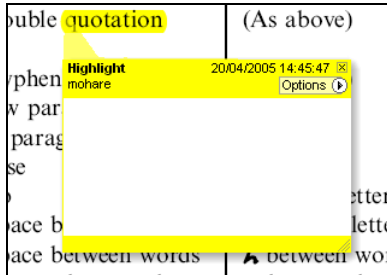


**How to use it:**

1. Click on the Stamp Tool in the toolbar
2. Select the Approved rubber stamp from the 'standard business' selection
3. Click on the text where you want to rubber stamp to appear (usually first page)

**Highlight tool — For highlighting selection that should be changed to bold or italic.**

Highlights text in yellow and opens up a text box.

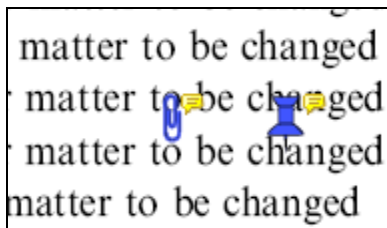


**How to use it:**

1. Select Highlighter Tool from the commenting toolbar
2. Highlight the desired text
3. Add a note detailing the required change

**Attach File Tool — For inserting large amounts of text or replacement figures as a files.**

Inserts symbol and speech bubble where a file has been inserted.

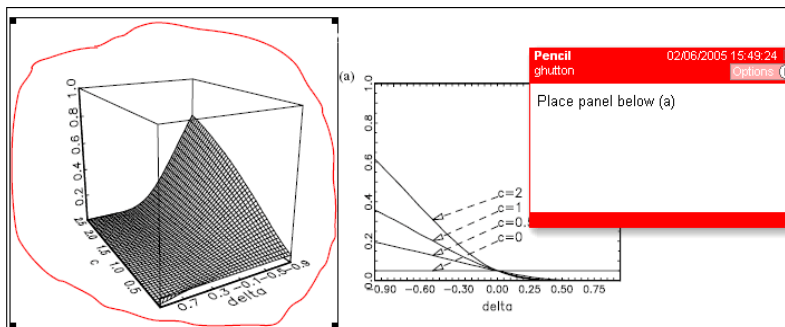


**How to use it:**

1. Click on paperclip icon in the commenting toolbar
2. Click where you want to insert the attachment
3. Select the saved file from your PC/network
4. Select appearance of icon (paperclip, graph, attachment or tag) and close

**Pencil tool — For circling parts of figures or making freeform marks**

Creates freeform shapes with a pencil tool. Particularly with graphics within the proof it may be useful to use the Drawing Markups toolbar. These tools allow you to draw circles, lines and comment on these marks.



**How to use it:**

1. Select Tools > Drawing Markups > Pencil Tool
2. Draw with the cursor
3. Multiple pieces of pencil annotation can be grouped together
4. Once finished, move the cursor over the shape until an arrowhead appears and right click
5. Select Open Pop-Up Note and type in a details of required change
6. Click the X in the top right hand corner of the note box to close.

## Help

For further information on how to annotate proofs click on the Help button to activate a list of instructions:

