Haloperidol plus promethazine for psychosis-induced aggression

— THE LEADERS GUIDE

Produced by the Editorial base of the Cochrane Schizophrenia Group
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from

Background explanation

Thank you for giving this guide a go. The idea behind this is to make things easier for you when you lead the journal club.

Journal clubs are often difficult to conduct and far removed from clinical life. Even if the leaders do prepare well, those turning up may be more in need of lunch, coffee or a social time than practical academic stimulation and the implicit pressure to read a difficult paper.

This suggested design is an attempt to allow for those needs, whilst getting the very best out of the session.

This journal club design should really help those attending see that this research may have some clinical value.

What you will need to do is:

☑ Have a good read of this
☑ Then read the review to which this is attached.
☑ Distribute the review to those attending well before the club
☑ Make more copies for those turning up on spec
☑ Do not really expect many to have read the review

The three parts

Part 1. Set the clinical scene (5 mins)
Be clear, but really make the participants feel the pressure of the situation...just like you would in clinical life

Part 2. Critical appraisal of the review (20 mins)
Get participants to list what is needed from the review before the Board members arrive, get them to talk, split into groups - with a feeling of urgency.

Part 3. Use of evidence in clinical life (20 mins)
Having distilled the evidence use role play to see how the participants would use what they have learned in everyday life.
Part 1.1 Setting the scene – The ward round

Introduce participants in the journal club to their scenario

There has been a problem with the supply of Lorazepam to your hospital. Local guidance favours Lorazepam although you realise that supporting evidence is absent. Shortage of supply affords an opportunity to reappraise alternatives.

Use of Olanzapine IM is being heavily marketed but you are aware that the older combination of Haloperidol plus Promethazine is used in many countries and settings.

Part 1.2 Setting the scene – the Journal club

Complicate the scenario by adding the need to attend this journal club

You have not had time to read the paper and need some lunch. Nevertheless, you are compelled to attend journal club.

By a stroke of luck the paper for discussion focuses on the value of Haloperidol plus Promethazine for psychosis-induced aggression.

Part 2.1 Critical appraisal of the review

For every review there are only three important questions to ask:

1. Are the results valid?
2. What are the results?
3. Are the results applicable to the situation?

You now have only 20 mins to get participants though this large review. To do this quickly is not easy, especially as many will not have read the paper in preparation.

Suggestion: Ask participants what salient facts they want to know - especially considering their tight time-scale.

Remind them that the meeting now will be in about 20 mins.

You should be able to fit most of the suggestions supplied by participants into the three categories of question outlined above.

Questions for participants:

Q 1. If you had not had this paper fall into your lap where might you have gone for reliable information?

A 1. There are now lots of answers to this - The Cochrane Library, Clinical Evidence, NICE Technology Appraisals.

Anything that has a reproducible method by which results are obtained.

Read 2.2 as this give more detail of the issues that will, in some shape or form, be supplied by the participants.

If they are not lively - give them a hand.

Do not panic. Bright journal club attendees will come up with all the answers - your job is to help focus their efforts and categorise their answers.

Do not be worried by silence.

Questions for participants:

Q 1. What do you think the Board members may ask?

A 1. [Suggestion] “Is the combination of Haloperidol plus Promethazine more effective at putting patients asleep than Olanzapine alone?”

Q 2. “Would these patients require restraint after taking the medication?

A 2. List the suggestions from participants as these are what we will come back to in the role play.

LIST 1:

1. 
2. 
3. 
4. 
5.

LIST 2:

1. 
2. 
3. 
4. 
5.

Participants will think of most of the issues - you just need to catch them and write them on a board or flip chart.
Part 2.2 The three parts of appraising a review

1. Are the results valid?
   There is no point looking at the result if they are clearly not valid.
   a. Did the review address a clearly focused issue?
      Did the review describe the population studied, intervention given, outcomes considered?
   b. Did the authors select the right sort of studies for the review?
      The right studies would address the review’s question, have an adequate study design
   c. Do you think the important, relevant studies were included?
      Look for which bibliographic databases were used, personal contact with experts, search for unpublished as well as published studies, search for non-English language studies
   d. Did the review’s authors do enough to assess the quality of the included studies?
      Did they use description of randomization, a rating scale?

2. What are the results?
   a. Were the results similar from study to study?
      Are the results of all included studies clearly displayed?
      Are the results from different studies similar?
      If not, are the reasons for variations between studies discussed?
   b. What is the overall result of the review?
      Is there a clinical bottom line?
      What is it?
      What is the numerical result?
   c. How precise are the results?
      Is there a confidence interval?

3. Can I use the results to help the Board meeting?
   a. Can I apply the results to my patients?
      Are your patients so different from those in the trial that the results don’t apply?
   b. Should I apply the results to my patients?
      How great would the benefit of therapy be for my patients?
      Is the intervention consistent with the patients’ values and preferences?
      Were all the clinically important outcomes considered?
      Are the benefits worth the harms and costs?

Part 2.3 Doing the appraisal

Having managed the interactive session with the participants - acquiring the three questions that need to be addressed by those appraising a review and some idea of how to answer each of those questions - now divide the room into three.

Apportion one of the questions per group and ask each group to get a feel for the whole review (1 min) but to focus on answering their particular question for the rest of the participants (5 mins or so).

Encourage talking to each other.

Move round the room to help the groups if they seem to need it.

Have your copy of the review marked up with where they may look for answers - although in a good review it should be obvious.

Stop the flow after about 10 minutes and ask each group to report in turn.

Do Group 1 really think that the review uses valid methods? Why?

After the first group’s report you may want to ask everyone to vote whether to proceed or not.

If they agree to proceed - see if you can get Group 2 to give you the clinical bottom line.

We suggest that the Graph 3.3 providing data for ‘Not asleep’ best fits the Board’s request of information about the effectiveness of Haloperidol plus Promethazine on putting patients asleep.

And from Group 3 get some feel of how applicable the findings are.
Part 2.4 A quick and dirty way to work out NNT

COMPARISON 3: HALOPERIDOL + PROMETHAZINE vs OLANZAPINE
Outcome 3.3 Not asleep

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Halop. + p’methazine</th>
<th>Olanzapine</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>3.3.1 by 15 mins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TREC-Vellore-II</td>
<td>64</td>
<td>150</td>
<td>85</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>64</td>
<td>150</td>
<td>85</td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable
Test for overall effect: Z = 2.39 (P = 0.02)

| 3.3.2 by 30 minutes |           |           |           |           | 0.65 [0.46, 0.93] | 0.65 [0.46, 0.93] |
| TREC-Vellore-II    | 30        | 150       | 36        | 150       | 100.0%   |                      |                      |
| Subtotal (95% CI)  |           |           |           |           | 0.59 [0.40, 0.87] | 0.59 [0.40, 0.87] |
| Total events       | 30        | 150       | 36        | 150       | 100.0%   |                      |                      |

Heterogeneity: Not applicable
Test for overall effect: Z = 2.35 (P = 0.02)

| 3.3.3 by 1 hour    |           |           |           |           | 0.59 [0.40, 0.87] | 0.59 [0.40, 0.87] |
| TREC-Vellore-II    | 30        | 150       | 30        | 150       | 100.0%   |                      |                      |
| Subtotal (95% CI)  |           |           |           |           | 0.59 [0.40, 0.87] | 0.59 [0.40, 0.87] |
| Total events       | 30        | 150       | 30        | 150       | 100.0%   |                      |                      |

Heterogeneity: Not applicable
Test for overall effect: Z = 2.67 (P = 0.008)

| 3.3.4 by 2 hours   |           |           |           |           | 0.61 [0.44, 0.86] | 0.61 [0.44, 0.86] |
| TREC-Vellore-II    | 14        | 150       | 14        | 150       | 100.0%   |                      |                      |
| Subtotal (95% CI)  |           |           |           |           | 0.24 [0.14, 0.41] | 0.24 [0.14, 0.41] |
| Total events       | 14        | 150       | 14        | 150       | 100.0%   |                      |                      |

Heterogeneity: Not applicable
Test for overall effect: Z = 5.25 (P = 0.0001)

| 3.3.5 by 4 hours   |           |           |           |           | 0.61 [0.44, 0.86] | 0.61 [0.44, 0.86] |
| TREC-Vellore-II    | 36        | 150       | 36        | 150       | 100.0%   |                      |                      |
| Subtotal (95% CI)  |           |           |           |           | 0.61 [0.44, 0.86] | 0.61 [0.44, 0.86] |
| Total events       | 36        | 150       | 36        | 150       | 100.0%   |                      |                      |

Heterogeneity: Not applicable
Test for overall effect: Z = 2.87 (P = 0.004)

64 people out of 150 given Haloperidol + Promethazine were not asleep by 15mins(43%) compared to 85 people out of 150 (57%) given Olanzapine. So because a few people would be asleep by 15 minutes without Haloperidol + Promethazine, the proportion of benefit attributable to taking these drugs, according to the above results, is the difference between the group (57% minus 43% = 14%). Just round it up or down to make it easy. Let's say, in this case, 15%.

So 15% of people in the above trial are asleep by 15 minutes - or put another way, about 1 in 7, or put another way NNT = 7.

Part 3. Ward round time

This is the most important part of the journal club - the practical application of what knowledge you have gained.

This is one way of doing it. Set out chairs in Board meeting style. Do not call for volunteers - just nominate people to be the clinician and you be the Board member.

Make sure that the clinician feels they can have time to ask their [relieved for not being singled out] colleagues for help [remember - this has got to be a combination of practical and fun].

Back on page 2 there are suggestions for what the Board member may ask - use them.

"Is the combination of Haloperidol plus Promethazine more effective at putting patients asleep than Olanzapine alone?"

See if they can put across in a supportive way the best evidence as they understand it.

There is no perfect way to do this - but perhaps something like this: "The best evidence we have is from a small Cochrane systematic review. Data does indicate that the combination of Haloperidol plus Promethazine is more effective at putting patients asleep than giving Olanzapine alone."

"Would these patients require restraint after taking the medication?"

As has been said - there is no right answer but think about how to put into words what the research outcome really means.

If it is going well, there are other questions that you may ask - see Page 5.
Box 1. Additional questions

☑ But we are interested in being tranquil not just asleep

You could be numerical here - the case for Haloperidol + Promethazine is not so convincing. Can you put Relative Risk into words?

COMPARISON 3: HALOPERIDOL + PROMETHAZINE vs OLANZAPINE
Outcome 3.5: Never tranquil or asleep during first 4 hours

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Halop. + p’methazine</th>
<th>Olanzapine</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>TREC-Vellore-II</td>
<td>1</td>
<td>150</td>
<td>0.25 [0.03, 2.21]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td>150</td>
<td>0.25 [0.03, 2.21]</td>
</tr>
<tr>
<td>Total events</td>
<td>1</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable
Test for overall effect: $Z = 1.25$ ($P = 0.21$)

☑ Does giving Olanzapine mean we have more people become aggressive again?

This could well be possible - see 'requiring additional drugs' or 'additional visit of doctor'. It does look as if Olanzapine increases risk of the aggressive episode revving up again.

COMPARISON 3: HALOPERIDOL + PROMETHAZINE vs OLANZAPINE
Outcome 3.8.1: Requiring additional drug during initial phase

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
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<th>Olanzapine</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>TREC-Vellore-II</td>
<td>31</td>
<td>65</td>
<td>0.48 [0.33, 0.69]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td>150</td>
<td>0.48 [0.33, 0.69]</td>
</tr>
<tr>
<td>Total events</td>
<td>31</td>
<td>65</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable
Test for overall effect: $Z = 4.00$ ($P < 0.0001$)

☑ What about the nasty side effects, Doc?

These are not common but it looks like there are less if the haloperidol + promethazine combination is used, please refer to Graph 3.6.1

COMPARISON 3: HALOPERIDOL + PROMETHAZINE vs OLANZAPINE

<table>
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<tr>
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<th>Halop. + p’methazine</th>
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<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>TREC-Vellore-II</td>
<td>1</td>
<td>3</td>
<td>0.33 [0.04, 3.17]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td>150</td>
<td>0.33 [0.04, 3.17]</td>
</tr>
<tr>
<td>Total events</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable
Test for overall effect: $Z = 0.96$ ($P = 0.34$)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Halop. + p’methazine</th>
<th>Olanzapine</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>TREC-Vellore-II</td>
<td>0</td>
<td>1</td>
<td>0.33 [0.01, 8.12]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td>150</td>
<td>0.33 [0.01, 8.12]</td>
</tr>
<tr>
<td>Total events</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
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Heterogeneity: Not applicable
Test for overall effect: $Z = 0.67$ ($P = 0.50$)
Haloperidol plus Promethazine for psychosis-induced aggression
- HANDOUT FOR PARTICIPANTS

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from

Board members are arriving soon
What do you think the Board members may ask?
List:
1. 
2. 
3. 
4. 
5. 

Special points of interest:
- The idea of this is to lead you from the clinical situation, through the research and back to the real-world clinical situation again
- You may or may not have read the paper - but even if you have not that does not mean that you cannot get something out of this

What key points do you need to know to see if this review can help?*
1. 
2. 
3. 
4. 
5. 

*Board members arrive in 30 mins

If you had not had this paper fall into your lap where might you have gone for reliable information?
After discussion do you want to change the key points you need to know to see if this review can help?*

1.

2.

3.

*Board members are arriving in 10 mins

Can you extract numbers that will be useful to you and the Board?
Clue: focus on what you think the Board members may ask - main effects and adverse effects - graph 3.3 may be a good one to use

1. Can you put relative risk into words?

2. Can you work out the proportion of improvements *attributable* to use of Haloperidol plus Promethazine?

3. Can you work out the number needed to treat?

4. Can you put that into words?

**Board meeting**
Is there a good use of words you would want to use?
Haloperidol plus Promethazine for psychosis-induced aggression
- PARTICIPANTS’ CRIB SHEET

The three parts of appraising a review

1. Are the results valid?
   There is no point looking at the result if they are clearly not valid.
   a. Did the review address a clearly focused issue?
      Did the review describe the population studied, intervention given, outcomes considered?
   b. Did the authors select the right sort of studies for the review?
      The right studies would address the review’s question, have an adequate study design
   c. Do you think the important, relevant studies were included?
      Look for which bibliographic databases were used, personal contact with experts, search for unpublished as well as published studies, search for non-English language studies
   d. Did the review’s authors do enough to assess the quality of the included studies?
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2. What are the results?
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A quick a dirty way to work out NNT (Graph 3.3)

64 people out of 150 given Haloperidol + Promethazine were not asleep by 15 mins (43%) compared to 85 people out of 150 (57%) given Olanzapine.

So because a few people would be asleep by 15 minutes without Haloperidol + Promethazine, the proportion of benefit attributable to taking these drugs, according to the above results, is the difference between the group (57% minus 43% = 14%).

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Haloperidol plus Promethazine for psychosis-induced aggression

FEEDBACK

Date and place of journal club

1. How many attended?

About

2. What was the background of the people attending? (please tick)

Health care professionals

Consumers

Policymakers

Undergraduate

Postgraduate

Others

3. Marks out of ten compared with usual journal club

(10=much better, 5=same, 0 = much worse)

Free text feedback

Thank you

This is one of 40 Cochrane Schizophrenia Group Guides for Journal Clubs

A full list is found on

http://szg.cochrane.org/journal-club