TITLE: Abuse and Misuse Potential of Dimenhydrinate: A Review of the Clinical Evidence

DATE: 01 December 2015

CONTEXT AND POLICY ISSUES

Dimenhydrinate (marketed as Gravol in Canada and Dramamine in the United Kingdom and the United States) is an over-the-counter (OTC) antihistamine indicated for the prevention and relief of nausea and vomiting from a number of causes. It is an H1 receptor antagonist that demonstrates anticholinergic activity. Abuse of dimenhydrinate has been reported, and often involves ingestion of high doses to induce psychotropic effects, including hallucinations and euphoria. Psychiatric patients may also abuse dimenhydrinate to achieve an anti-anxiety effect. In addition to frank abuse, OTC medications, including dimenhydrinate, may be misused when taken in higher doses or for a longer duration than indicated on the product monograph. Potential for drug dependence is also a concern in situations of dimenhydrinate abuse or misuse. Given these potential risks, some jurisdictions have chosen to store and sell dimenhydrinate under pharmacist supervision; however, it is available without any restrictions in other jurisdictions. The purpose of this report is to identify the recent clinical evidence on the potential misuse or abuse of dimenhydrinate, in order to inform decision making regarding appropriate access to this drug within the pharmacy.

RESEARCH QUESTION

What is the clinical evidence for the potential misuse or abuse of dimenhydrinate?

KEY FINDINGS

One cross-sectional questionnaire-based study regarding the potential misuse or abuse of antihistamines, including dimenhydrinate, was identified. No cases of misuse or abuse of dimenhydrinate were reported in this study.
METHODS

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2005 and November 5, 2015.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

<table>
<thead>
<tr>
<th>Table 1: Selection Criteria</th>
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<tbody>
<tr>
<td><strong>Population</strong></td>
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<td><strong>Intervention</strong></td>
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<td><strong>Comparator</strong></td>
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<td><strong>Outcomes</strong></td>
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<tr>
<td><strong>Study Designs</strong></td>
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Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2005.

Critical Appraisal of Individual Studies

The included non-randomized study was critically appraised using the Centre for Evidence Based Medicine’s critical appraisal tool for surveys. Summary scores were not calculated for the included study; rather, a review of the strengths and limitations were described.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 360 citations were identified in the literature search. Following screening of titles and abstracts, 338 citations were excluded and 22 potentially relevant reports from the electronic search were retrieved for full-text review. One potentially relevant publication was retrieved from the grey literature search. Of these potentially relevant articles, 22 publications were excluded for various reasons (15 studies did not specifically address dimenhydrinate, four were review articles, two were case reports, and one was a clinical practice guideline). One publication met
the inclusion criteria and was included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

Study Design

One cross-sectional, questionnaire-based pilot study was included in this report. The objective of the pilot study was to assess the feasibility of a pharmacy-led method for monitoring patient-reported abuse and misuse of OTC medications for psychoactive effects. The study was conducted in community pharmacies over the course of two months.

Patient Population

The study was conducted in 74 community pharmacies in France. Adult patients visiting the participating community pharmacies who requested one of the studied drugs were offered a questionnaire. No other inclusion or exclusion criteria were reported.

Interventions and Comparators

Patients were asked about the use of medications from four drug classes known for their abuse potential and psychoactive effects: codeine in analgesics, dextromethorphan, pseudoephedrine and sedative antihistamines. Dimenhydrinate was one of the included antihistamines addressed by the questionnaire. Patients were also asked about the abuse or misuse of antacid drugs as a control group.

Outcomes

Outcomes assessed by the questionnaire were: abuse (defined as the “recurrent and excessive use of a drug leading to clinically significant impairment or distress”), misuse (excessive or regular use), non-medical use (use with the intent of achieving a psychoactive effect), and drug dependence (negative consequences of drug use and continued use of drug despite these consequences, as well as significant time spent on acquiring the drug). Excessive use meant use of a dose higher than the maximum recommended dose, and regular use meant use for longer than 10 days in the past month.

Additional details regarding study characteristics are provided in Appendix 2.

Summary of Critical Appraisal

The study design and objectives were clearly presented, but a sample size calculation was not performed to ensure enough patients were recruited to identify a difference between groups, should a true difference exist. All patients who requested the studied drugs from the pharmacist were offered the questionnaire, and the reasons for refusal to participate in the study were provided. However, 32% of patients who accepted the questionnaire did not complete it, and the reasons for this are unclear. It is also unclear how valid and reliable self-report of drug abuse or misuse on this questionnaire was.
Additional critical appraisal points are provided in Appendix 3.

Summary of Findings

A total of 817 patients were offered a questionnaire, 778 accepted, 530 completed the questionnaire, and 491 responses were analyzed (39 questionnaires were excluded due to irrelevant drug use and patient age under 18 years). Of the 491 analyzed patients, 99 reported use of antihistamines, and 60 patients reported use of antihistamines in the past month. The types of antihistamines used were not reported; therefore, it is unclear how many patients, if any, reported the use of dimenhydrinate. One case of non-medical antihistamine use was identified: one patient reported using oxomemazine for sleep aid. No reports of dimenhydrinate misuse, abuse, non-medical use, or dependence were identified.

Additional details regarding study findings are provided in Appendix 4.

Limitations

Given that the identified cross-sectional study was designed to be a pilot study with a short duration, it had a limited set of results for antihistamine use, and it is unclear whether any patients used dimenhydrinate at all. Furthermore, the types of patient-reported results that were received may be biased due to the potential for stigma associated with OTC medication abuse or misuse. Some patients may have chosen not to return the questionnaire for the same reason. Both cases could have led to underreporting of OTC drug abuse or misuse.

No eligible studies regarding the abuse or misuse of dimenhydrinate in children or adolescents were identified for inclusion in this report.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

One cross-sectional study evaluating the abuse or misuse of OTC medications, including dimenhydrinate, was identified. No cases of dimenhydrinate abuse or misuse were reported in this study; however, these results should be interpreted with caution due to the small sample size and potential for bias in patient self-reporting. Another study that evaluated the abuse and misuse potential of dimenhydrinate and other antihistamines demonstrated that there is some evidence of this problem for this drug class; however, results specific to dimenhydrinate were not reported separately. Additional references regarding abuse or misuse of antihistamines that do not specify inclusion of dimenhydrinate are provided in Appendix 5. No additional information was identified to inform decisions on access to dimenhydrinate in pharmacies to limit abuse or misuse of this drug.

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REFERENCES


APPENDIX 1: Selection of Included Studies

360 citations identified from electronic literature search and screened

338 citations excluded

22 potentially relevant articles retrieved for scrutiny (full text, if available)

1 potentially relevant report retrieved from other sources (grey literature, hand search)

23 potentially relevant reports

22 reports excluded:
- irrelevant intervention (15)
- other (review articles, guidelines, case reports, editorials) (7)

1 report included in review
## APPENDIX 2: Characteristics of Included Publications

**Table A1: Characteristics of Included Clinical Studies**

<table>
<thead>
<tr>
<th>First Author, Publication Year, Country</th>
<th>Study Design</th>
<th>Patient Characteristics</th>
<th>Intervention(s)</th>
<th>Comparator(s)</th>
<th>Clinical Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orriols 2009, France</td>
<td>Cross-sectional study</td>
<td>Adult patients requesting one of the drugs from the five studied drug classes Offered questionnaire: n = 817; completed questionnaire: n = 491</td>
<td>Questionnaire assessing use of codeine in analgesics, dextromethorphan, pseudoephedrine and sedative antihistamines (including dimenhydrinate)</td>
<td>Assessment of use of antacid drugs</td>
<td>Misuse, abuse, non-medical use, dependence</td>
</tr>
</tbody>
</table>
APPENDIX 3: Critical Appraisal of Included Publications

| Table A2: Strengths and Limitations of Surveys using the CEBM Critical Appraisal Tool
<table>
<thead>
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<tbody>
<tr>
<td><strong>Strengths</strong></td>
<td><strong>Limitations</strong></td>
</tr>
<tr>
<td>Orriols 2009’</td>
<td></td>
</tr>
<tr>
<td>• The study addressed a clearly focused question</td>
<td>• Sample size calculation not performed</td>
</tr>
<tr>
<td>• The study design was appropriate for answering the research question</td>
<td>• Low patient response rate of 65%</td>
</tr>
<tr>
<td>• Method of patient selection described</td>
<td>• Unclear validity and reliability of patient-reported drug abuse or misuse data</td>
</tr>
<tr>
<td>• All patients who requested the studied drugs were offered the questionnaire</td>
<td>• Confidence intervals not presented</td>
</tr>
<tr>
<td>• Reasons for refusal to participate (by pharmacies and patients) provided</td>
<td>• Unclear confounding factors</td>
</tr>
<tr>
<td>• Statistical significance of results compared with the control antacid group presented</td>
<td>• Details of specific drugs reported for cases of abuse or misuse but not for any use</td>
</tr>
</tbody>
</table>

CEBM = Centre for Evidence Based Medicine
APPENDIX 4: Main Study Findings and Author’s Conclusions

<table>
<thead>
<tr>
<th>Table A3: Summary of Findings of Included Studies</th>
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<tbody>
<tr>
<td><strong>Main Study Findings</strong></td>
</tr>
<tr>
<td>------------------------</td>
</tr>
<tr>
<td><strong>Orriols 2009</strong></td>
</tr>
<tr>
<td>• 491/817 questionnaires were completed and analyzed, mean age 45.8 ± 15.1 years (range 19 – 85 years), 64.8% female</td>
</tr>
<tr>
<td>• 99/491 patients reported use of antihistamines, mean age 49.0 years ± 16.0 years (range 19 – 83 years), 76.8% female</td>
</tr>
<tr>
<td>• 60/99 antihistamine users reported use in the past month</td>
</tr>
<tr>
<td>• 1/60 patients reported non-medical use of an antihistamine in the past month (oxomemazine)</td>
</tr>
<tr>
<td>• No abuse, misuse, non-medical use of, or dependence on dimenhydrinate reported</td>
</tr>
</tbody>
</table>

OTC = over-the-counter.
* standard deviation
APPENDIX 5: Additional References of Potential Interest

Case Reports


Abuse and Misuse of Antihistamines (Not Specific to Dimenhydrinate)


Clinical Practice Guidelines


See Literature Review: Dimenhydrinate: Acute Exposures in Patients 6 Years of Age and Older; Dimenhydrinate: Chronic Exposures in Patients 6 Years of Age and Older, page 213