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# Application of the Bradford Hill Criteria to Assess the Causality of Cisapride-Induced Arrhythmia

## A Model for Assessing Causal Association in Pharmacovigilance

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## Abstract

**Introduction:** The Bradford Hill criteria are a widely used, useful tool for the assessment of biomedical causation. We have examined their application to pharmacovigilance using the example of cisapride-induced QTc interval prolongation/arrhythmia.

**Methods:** A literature search was conducted using MEDLINE, EMBASE, Reactions Weekly and regulatory websites to identify evidence for the association between cisapride and QTc interval prolongation/arrhythmia that had been published in the English language. Two hundred and five publications were identified as being potentially suitable for the study. After excluding irrelevant articles, studies on high-risk populations and review articles, 70 publications were assessed using the Bradford Hill criteria. These included 24 case reports, case series or spontaneous report summaries; eight epidemiological studies; 22 clinical studies; and 16 experimental (*in vivo* and *in vitro*) publications.

**Results:** The most compelling evidence for an association between cisapride use and QTc interval prolongation/arrhythmia came from case/spontaneous reports and biological plausibility. Considering the rare incidence of serious cardiac events, these criteria formed the basis for the strength of the association. The number of reports from different populations showed consistency. Specificity was supported by clinical and cardiographic characterisation of the events. There were temporal relationships between the events and the initiation of cisapride treatment, increases in the dosage and the receipt of interacting medications. The relationships between the adverse events and the latter two factors exhibited biological gradients. Experimental evidence could be found from biological models, as well as reports of positive dechallenge and/or rechallenge found in individual patients. Cisapride was found to bind the human ether-a-go-go-related gene (HERG) potassium channel, which provides a plausible mechanism for QTc interval prolongation/arrhythmia. Other QTc interval-prolonging/arrhythmic drugs that also bind to HERG provided an analogy for cisapride causing QTc interval prolongation/arrhythmia via this mechanism. The evidence provided by clinical studies was inconsistent, and epidemiological studies failed to demonstrate an association. Nevertheless, this did not prevent the assessment of causation.

**Discussion:** This study showed how different types of evidence found in pharmacovigilance can be evaluated using the Bradford Hill criteria. Further work is required to examine how the criteria can be applied to different types of adverse events and how they may be applied to pharmacovigilance.

## Introduction

The Bradford Hill criteria for causal association were first described in a lecture given in 1965 by Sir Austin Bradford Hill to the Section of Occupational Medicine of the Royal Society of Medicine.[1] In the lecture he considered nine criteria that may be used in the assessment of causation: strength, consistency, specificity, temporality, biological gradient, plausibility, coherence, experimental evidence and analogy.[1] Recent publications by Shakir and Layton[2] and Shakir[3] have put forward some thoughts on the application of the Bradford Hill criteria in pharmacovigilance and pharmacoepidemiology.

Cisapride is a gastrointestinal prokinetic agent (launched in the UK in early 1989) that was withdrawn from the UK market in 2000 because of safety concerns.[4] It was found to increase the risk of QTc interval prolongation and cause serious cardiac arrhythmias (torsade de pointes), particularly in patients who used contraindicated medications that increased its plasma concentration. Despite warnings to avoid the concomitant use of contraindicated medications, it continued to be inappropriately prescribed.[5-10] A prolonged QTc interval is a risk factor for the development of torsade de pointes, which is a serious ventricular tachyarrhythmia characterised by 'twisting of the points' at the cardiac axis.[11-13] QTc interval prolongation is defined as a QTc interval (QT interval 'corrected' for heart rate) of >440ms in males and >460ms in females. However, arrhythmias tend to be associated with values of ≥500ms.[11] In this study, we identify published evidence for the association between cisapride and QTc interval prolongation/arrhythmia and examined how the Bradford Hill criteria could be used in the assessment of causation. Using the association between the use of cisapride and serious cardiac arrhythmias as a model, we assess the suitability of applying the criteria to the types of evidence that may be available for the assessment of causation.

## Method

A literature search was conducted using free text and index terms related to cisapride and QTc interval prolongation/arrhythmia and general adverse event terms (terms available on request) in MEDLINE (1965 to October 2005) and EMBASE (1974 to October 2005). Further searches were conducted in the Cochrane Library (2005, Issue 4), Reactions Weekly (1990 to October 2005) and regulatory websites (the European Agency for the Evaluation of Medicinal Products [EMEA], the Medicines and Healthcare products Regulatory Agency [MHRA], the US Food and Drug Administration [FDA], Health Canada, the Australian Therapeutic Goods Administration and New Zealand's Medsafe). We sought to identify evidence published in the English language of the association between cisapride and QTc interval prolongation/arrhythmia. Specific review articles and systematic reviews were examined for any further publications, as were the reference sections of all articles identified by the literature search.

Publications were excluded from this analysis if they were non-English articles; studies or review articles that did not specifically examine cardiac effects associated with cisapride; drug utilisation studies; or experimental studies using cisapride as a reference compound for validation tools to detect QTc interval-prolonging drugs (to ensure that only the evidence relevant for the assessment of causation was included). Clinical studies conducted in high-risk populations, e.g. premature neonates, infants aged <3 months or subjects undergoing dialysis, were initially obtained but subsequently excluded from the study, because of possible effects of these conditions on cardiac findings. Case reports involving overdose or poisoning were also excluded, as were those where it was uncertain whether cisapride was involved. Where the same results were published more than once, only the publication containing the results most relevant for this investi-

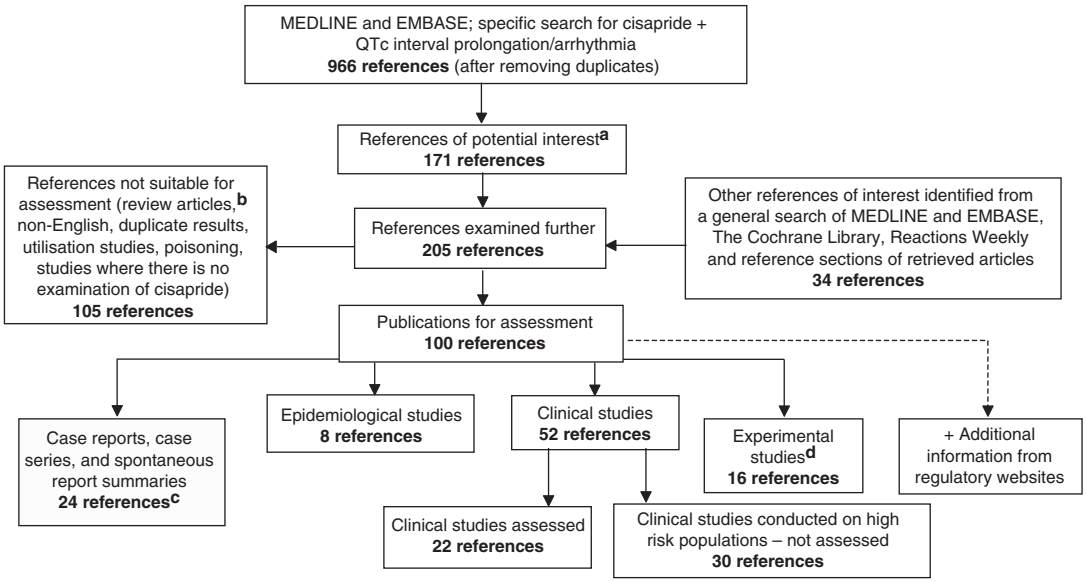


**Fig. 1.** Summary of the selection process used to identify articles for inclusion in the study. **a** References of potential interest were those that appeared to investigate and/or provide evidence for the association between the cisapride and QTc interval prolongation/arrhythmia. **b** A review article that provided a summary for an initially proposed biological mechanism for cisapride-induced tachycardia was included, because it would be unfeasible for all of the individual studies reporting the biological evidence of this sort to be included. **c** A paper containing a case report also included a clinical study conducted in a high-risk population. **d** A case series provided details of a potential biological mechanism.

gation was assessed. Validation was undertaken by a second review of the search results to ensure that no articles had been missed and that the inclusion criteria had been applied consistently.

Relevant information from the articles was extracted into a database, by one of the authors (MP). Each piece of evidence was assessed using the following Bradford Hill criteria: strength (numerical measure of the association); consistency (was the same trend observed across studies); specificity (specific event caused by a specific mechanism); temporality (drug taken prior to event, time to onset); biological gradient (evidence of a dose response); plausibility (biologically plausible mechanism); coherence (coherent with drug causing the effect); and experimental evidence (biological/clinical experiments, dechallenge/rechallenge). Analogy was assessed separately, using information from the main articles as well as additional references. The evidence was classified by MP according to the criteria met, and any uncertainties were discussed with the other authors. We noted that there was considerable overlap between several of the criteria. This led us to group some of the criteria together, and in particular we considered plausibility, coherence and experimental evidence under one heading. We subsequently found that this is similar to the description of causal criteria in the US Surgeon General's report on the association between smoking and lung cancer.[14,15]

## Results

Figure 1 shows the selection of publications for inclusion in the study. The initial literature search of MEDLINE and EMBASE identified 1148 references. After removing 182 duplicates, 966 references remained. Of those references, 171 were examined further, as were 34 references from other sources. A total of 70 publications, including experimental studies, were assessed using the Bradford Hill criteria. Evidence identified from regulatory websites was also examined, as were other relevant publications for background or additional information. Figure 2 shows the study types identified in this investigation and what criteria were fulfilled by the different types of evidence.

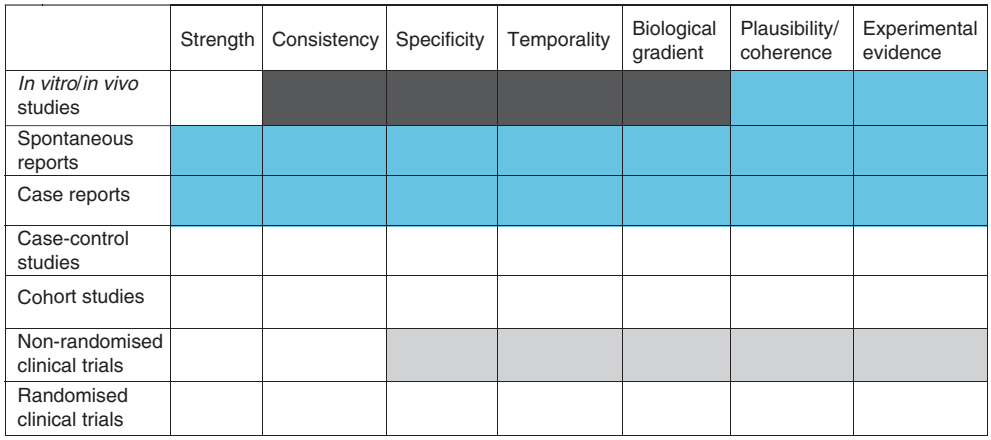


**Fig. 2.** Summary of the type of evidence used in the causal assessment of cisapride-induced QTc interval prolongation/arrhythmia using the Bradford Hill criteria. The filled squares show the type of evidence identified that allowed the assessment of causation. The blue shading indicates where a study type contributed clear evidence to fulfil a particular criterion. The grey cells are considered to partly contribute to the evidence. The black cells show where the biological basis of this criteria was demonstrated by *in vitro* and *in vivo* studies. For blank squares, no evidence was identified that could be considered to fulfil the criteria.

### Strength of the Association

No clinical or observational studies provided evidence of the strength of the association. Two cohort studies both showed relative risks of 1.6, but neither result was statistically significant (95% CIs 0.9, 2.9[16] and 0.67, 3.82,[17] respectively). Other population studies were unable to provide sufficient evidence for an association.[18-21] Case-control studies had also estimated the risk of QTc interval-prolonging drugs, including cisapride, for arrhythmia[22] and sudden cardiac death (non-cardiac drugs only).[23] In an overall assessment of all QTc interval-prolonging drugs, the adjusted odds ratios (ORs) were 1.2 (95% CI: 0.8, 1.9)[22] and 2.7 (95% CI: 1.6, 4.7),[23] respectively. In only one of these studies was a separate analysis carried out for cisapride (OR 1.2 [95% CI: 0.8-1.9]). However, there were only four cases and 29 controls included in that analysis.[23] The limitations of some of the observational studies for the assessment of cisapride-induced arrhythmia have been discussed in a previous publication,[24] with the major factor being the rarity of the event, making it impractical for studies of a sufficient size to be conducted.[24] In pharmacoepidemiology, it is rare to find a relative risk >2 for serious adverse events,[3] but, as this example demonstrates, a lack of strength, and more importantly a lack of an association (in terms of measures of association such as relative risks), does not necessarily rule out causation. However, caution must be taken to ensure that this is not used to promote false associations.

### Consistency

Evidence for the consistency of the association between cisapride and QTc interval prolongation/arrhythmia is supported by the large number of cases reported both spontaneously to regulatory authorities/manufacturers and in the published literature. Conversely, there were few reports of arrhythmia submitted for drugs prescribed for similar indications to those treated with cisapride.[25] At the time of the withdrawal of cisapride in the UK, there were 386 reports of arrhythmia (125 fatalities) and 50 reports of sudden unexplained death related to cisapride worldwide.[26] Additional publications have also summarised spontaneous report information.[25,27-29] The case reports described in the literature have come from a number of populations and in patients with different levels of risk and susceptibility.[30-49] Risk factors included the use of interacting medications, cardiovascular conditions, prematurity in children and renal failure. Very few of the events occurred in patients without any risk factors, and a spontaneous report summary showed that only 11% of cases were not associated with known risk factors or contraindications.[25,50]

In our analysis, we identified 15 case reports/series involving 24 adult patients from nine countries.[30,31,33,35,39-49] Patients were aged between 18 and 83 years, with a median age of 52 years (interquartile range 40–65 years). There were ten reports of cardiac events associated with cisapride in children from three countries (age range 11 days to 8 years). Nine children were aged <3 months, including seven who had also been born prematurely, both of which are risk factors for QTc interval prolongation and arrhythmia.[32,34,36-38] It is of interest that the majority of cardiac events reported in adult patients were in older individuals (14 of 24 case reports were from patients aged ≥50 years) and females (16 of 24 case reports), which is consistent for these also being risk factors for arrhythmia and torsade de pointes.[11-13] However, it must also be considered that the limitation of spontaneous report data is that it does not provide a denominator, and that reports are not normally submitted showing the absence of an event in a patient.

Clinical studies were identified in the literature search if they had assessed the QTc interval or adverse cardiac effects in patients taking cisapride. After the exclusion of clinical studies conducted in high-risk populations (these were non-randomised studies), 22 clinical studies were examined. Studies were included if they contained a mixed population of patients with and without these risk factors, as long as these two patients subgroups had been analysed separately. The results from the included clinical studies were inconsistent, and although some studies provided the suggestion of an association,[51-60] others did not.[61-72] Effects of cisapride on the QTc interval were observed in a number of studies.[54-60] In only one of these studies did an increase in QTc interval prolongation lead to torsade de pointes.[56] Other clinical studies showed that cisapride had an effect on heart rate.[51-53] Most of the studies that could be used either to support or disprove the association could not be described as definitively providing evidence either way. In some of the studies, events were observed in individual patients who were receiving cisapride, but this was not significantly different compared with a control group not taking medications in one study,[56] and another lacked a control group.[58] Only one of the studies was a randomised, controlled trial,[67] and this did not provide evidence for an association between cisapride use and QTc interval prolongation. In another study, it was not clear whether the effect on QTc interval prolongation was solely due to cisapride.[54] Therefore, it can be considered in this example that clinical studies provided inconclusive evidence of a consistent association, mainly because of the rarity of the event.

### Specificity

When Bradford Hill[1] came to describe the specificity of the association, he related it to effects being observed in specific workers and at particular sites and types of disease. Others have argued that the specificity category is not useful for the assessment of causation, mainly because of interventions being able to cause multiple effects.[73] As with all the criteria, Bradford Hill stated that caution should be taken in excluding an association because the criterion was not fulfilled, noting: "… if it is not apparent, we are not thereby necessarily left sitting irresolutely on the fence".[1] However, when specificity does exist, it can aid the assessment of causation. In pharmacovigilance, specificity is important, because drugs cause adverse drug reactions by specific mechanisms.[2,3] In assessing a causal association between an adverse event and a suspected drug, specificity can be supportive of causation, and the lack of specificity weakens a hypothesis of causation. Initial reports linked cisapride to the development of tachycardia.[30] However, tachycardia can be caused by a number of mechanisms. Subsequent reports documented that cisapride prolonged the QTc interval and could lead to the development of torsade de pointes,[27] and this was found to be caused by blockade of the human ether-a-go-go-related gene (HERG) potassium channel.[74,75] In this example, having an understanding of the biological mechanism helped to define the specificity of the association, which was supported by the adverse cardiac events reported spontaneously. Although there are other causes for prolongation of the QTc interval, such as congenital long QT syndrome, the use of drugs is a major cause.[11] This does not make the relationship with the drug certain, but it reduces the number of other likely causes.

### Temporality

It is important to know whether a suspected drug was taken before the onset of the adverse event, and whether the event was consistent with the timing of exposure to the medication.[2,3] Moreover, the timing of the event in relation to the pharmacokinetic and pharmacodynamic characteristics of the drug can support or weaken a hypothesis of causation. It is important to note that the half-life of cisapride is 10 hours, and there is no accumulation or change in its metabolism with repeated doses.[26] Where information was available from case reports, the median time to onset after starting cisapride, increasing the dose or starting an interacting medication was 4.5 days (range 1–15 days).[30,31,33-35,37-41,43-45,47] These reports described 20 cases of potentially cisapride-associated QTc interval prolongation or cardiac adverse events and all had a time to onset that indicated causation by cisapride was feasible. However, for six case reports and one case series, the time to onset was not assessable, because of a lack of information.[30,32,33,36,42,48,49]

It can be difficult to assess the time to onset using observational and clinical studies, as the time between taking the drug and the event is not normally stated. Another problem can be determining compliance, which is a particular problem for observational studies. In pharmacovigilance it is important to assess the time to onset, and, sometimes, detailed information on this may only be available from case reports.

### Biological Gradient

Several reports have found that patients experienced QTc interval prolongation after being exposed to a higher-than-usual dose of cisapride. In one individual, QTc interval prolongation occurred after increasing the dose of cisapride, and it returned to normal once the dose was decreased.[31] In another case report, an increase in cisapride dosage after the patient was admitted to hospital was potentially related to the development of arrhythmia.[44] Use of high-dose cisapride in infants and neonates has been associated with QTc interval prolongation,[32,36,37] and in some of these cases a reduction in dose has led to normalisation of the QTc interval.[36]

Although some publications have demonstrated a clear temporal relationship between plasma cisapride concentrations and the QTc interval,[34,55] other studies have failed to demonstrate any association.[57,66,68,72] In another study, a statistically significant increase in the QTc interval from baseline was found only in the high-dose group.[60]

The most compelling evidence of a dose-response relationship for cisapride-induced QTc interval prolongation has come from studies reporting drug interactions. Cisapride is mainly metabolised by the cytochrome P450-3A4 (CYP3A4) enzyme, and coadministration with other medications that are known to inhibit the activity of CYP3A4 increases the bioavailability of cisapride.[50,76-78] Such circumstances have been associated with a large proportion of the spontaneously reported cases of cisapride-induced QTc interval prolongation.[25-29,78] From the case reports identified in the published literature, 12 involved potential drug interactions and provided information on 15 patients. The most likely potentially interacting medications were all CYP3A4 inhibitors and included erythromycin (six reports),[31,33,35,41,47] clarithromycin (four),[39,43,44] paroxetine,[45] diltiazem,[42] itraconazole,[49] ketoconazole,[41] and fluconazole and/or erythromycin.[34]

Cisapride drug interactions have also been demonstrated in some clinical studies. Cisapride levels were increased 3-fold when it was coadministered with clarithromycin.[55] In another study, two individuals who developed arrhythmia whilst receiving cisapride were subsequently found to have been taking macrolides.[56] A clinical survey of drug interactions found that a combination of cisapride and erythromycin significantly increased the QTc interval by 113ms (95% CI 0.3, 226).[59] Another study showed that coadministration of cisapride and sparfloxacin increased the QTc interval by 7.8%.[54] However, there was no assessment of the effects of cisapride alone (sparfloxacin can also prolong the QTc interval).

The mechanism of action of cisapride on the HERG potassium channel is dose dependent, and potassium currents are inhibited to a greater extent as the dose is increased.[74,75,79-82] This provides a plausible explanation for cardiac adverse events

tending to be associated with higher doses of cisapride.

### Plausibility, Coherence and Experimental Evidence

We considered that, with regard to assessing causation in pharmacovigilance, there was sufficient overlap between the categories of plausibility, coherence and experimental evidence to consider these criteria under one heading. We selected references where the effect of cisapride in relation to QTc interval prolongation/arrhythmia was examined. To limit repetition and the retrieval of unnecessary references, articles were not retrieved if cisapride was used as a reference compound in biological models of QTc interval prolongation.

Cisapride-induced arrhythmia is an example where different theories about the mechanism of the adverse effect were proposed before the currently accepted mechanism was identified. At the time of the first report of cisapride-related tachycardia, it was suggested that cisapride may exert a procainamide-like effect.[30] An alternative explanation was that it involved the serotonin 5-$HT_4$ receptor,[83] and cisapride was proposed to cause arrhythmia via this receptor through a pathway involving atrial fibrillation.[84] However, subsequent studies and reports demonstrated that cisapride led to ventricular arrhythmia,[85,86] and that the $5HT_4$ receptor was not involved.[87] Subsequently, the mechanism of cisapride-induced arrhythmia was found to be caused by blockade of the HERG inwardly rectifying potassium channel.[74,75] Further research has provided a more detailed understanding of the mechanism.[79-82,88-92] In these studies, the effect of cisapride was observed in a number of animal models, including guinea pigs, cats, dogs and rats.[86,88,92] It must be noted that this is not a comprehensive list, because studies using cisapride as a reference compound were not retrieved. From a biological perspective, the finding that cisapride causes these effects in a number of biological models adds to the consistency of the association.

Experimental evidence can be found in case reports if dechallenge and/or rechallenge has taken place. It also adds further evidence to support the temporal relationship between use of the drug and the onset of the event. Amongst the case reports and case series describing cisapride-induced QTc interval prolongation, 32 of 34 cases provided information that patients recovered or were improved when cisapride was withdrawn, the dosage was decreased or an interacting medication was discontinued.[30,31,33-35,39-49] The remaining two cases lacked information on the effect of dechallenge[30,42] Five of the 34 cases from case series or reports documented rechallenge,[30,38,39] and there was a positive rechallenge in all but one of them.[39] However, this patient has resumed treatment with cisapride at a lower dosage and discontinued use of an interacting medication. In one patient, rechallenge occurred on three occasions and all of these had positive results.[30] An early spontaneous report summary found two cases where rechallenge occurred,[29] and another provided details of a male who had positive dechallenges and rechallenges on two separate occasions.[25] In a clinical study, 18 of 22 patients taking cisapride had evidence of tachycardia, and when it was withdrawn the heart rate normalised in 14 individuals.[53] Twelve of these 14 individuals were rechallenged and in all of these patients the heart rate increased again.

### Analogy

There are many analogous examples of other drugs that can cause QTc interval-prolonging and arrhythmogenic effects through the HERG channel.[93-96] We considered an important analogy to be that with terfenadine, because it facilitated the identification of the biological mechanism. In the 1980s, there were a large number of reports of syncope, QTc interval prolongation and torsade de pointes associated with terfenadine, and it was subsequently discovered that the effect was mediated through the HERG channel.[97,98] The product of the *HERG* gene, IKr, was investigated because of its known involvement in the hereditary long QT syndrome.[99] Other analogous examples of drug-induced cardiac effects mediated through the HERG channel that were known at the time of the identification of cisapride binding to the HERG receptor included dofetilide-induced cardiac effects[100] and astemizole-induced cardiac effects.[98] As this example demonstrates, using analogous examples such as these can make it easier to understand the biological plausibility of an association between an adverse

event and drug administration, which, in turn, can aid the assessment of causation. However, some analogies can be more useful than others, and, where analogy does not exist, this does not rule out causation.

### Summary

In this study, we have examined the application of the Bradford Hill criteria to assess the causal relationship between cisapride administration and QTc interval prolongation/arrhythmia. The evidence that contributed to the assessment of causation is summarised in table I.

In understanding and interpreting the criteria for causation, it is also important to consider other variables, such as the type of event (incidence, immediate versus delayed effects and seriousness), the medication of interest (frequency of use, formulation and other medications with the same effects on certain parameters), the quality of the evidence, potential bias (including publicity bias) and confounding, and whether there is a more likely causal explanation. However, as the aim of our study was to examine the application of the Bradford Hill criteria using this example as a case study, we felt that a full pharmacovigilance benefit/risk assessment of the relationship between cisapride and QTc interval prolongation/arrhythmia was beyond the scope of this study.

## Discussion

The evaluation of benefit/risk is inconsistent, even when considering important drug safety issues such as product withdrawal,[101] and although there are guidelines for benefit/risk evaluation in pharmacovigilance (e.g. the CIOMS IV report),[101] there is a clear need for consistent and scientifically robust methods to examine the causal association of drugs with the occurrence of serious adverse effects. The aim of our study was to use the relatively recent drug safety issue of cisapride-induced QTc interval prolongation/arrhythmia as a case study to examine the application of the Bradford Hill criteria in the assessment of causal relationships in pharmacovigilance.

Published case reports and spontaneous reports provided the most useful information for assessing causation. In epidemiology, the strength of an association is conventionally based on a numerical finding, but considering the rare incidence of serious cardiac events with cisapride, the strength of the association was provided by case reports, spontaneous reports and biological plausibility. These reports provided evidence for the consistency of association, as they were reported from different populations. The specificity was supported by clinical and cardiographic characterisation of the reported events. Temporality was shown by the event occurring soon after initiation of the drug, an increase in its dosage or the coadministration of an interacting medication. A biological gradient was demonstrated, as events occurred in patients taking higher doses of the drug or using interacting medications. Experimental evidence could be found in reports when dechallenge and/or rechallenge were documented.

The evidence from experimental studies helped to establish the plausibility, coherence, experimental evidence and specificity of the event. They also provided the biological basis for temporality and the dose response, as well as helping to form the basis of the strength of the association. This example has demonstrated that, in the absence of strong evidence from clinical or observational studies, characterisation of the biological mechanism can facilitate the assessment of causation. However, caution must be taken in other situations, as the plausibility could be misleading or unclear. The preclinical assessment for QTc interval prolongation by new drugs[102] shows how biological plausibility is used for decision-making in the drug development process. In this context, the surrogate marker (the effect of the drug on the length of the QTc interval) is used to predict whether new chemical entities have the potential to cause arrhythmia, and therefore perturb further clinical development of those compounds considered to be potentially arrhythmogenic. However, it must be noted that the relationship between QTc interval prolongation and the development of torsades de pointes is complex, and that torsades de pointes can occasionally occur without any substantial prolongation of the QTc interval.[11] Further investigation and evaluation of the assessment of biological plausibility is required,[103] and in particular of whether a strong biological plausibility should

**Table I.** Descriptive summary of the evidence used in the assessment of causation of cisapride-induced QTc interval prolongation/arrhythmia using the Bradford Hill criteria

| Strength | Consistency | Specificity | Temporality | Biological gradient | Plausibility/coherence/experimental evidence | Analogy |
|---|---|---|---|---|---|---|
| ***In vitro*/*in vivo* studies** | | | | | | |
| | The effect of cisapride was observed in a number of animal models and *in vitro* systems | Cisapride exerts its effect through specific binding of the HERG potassium channel | In experimental models, the addition of cisapride was temporally related to adverse cardiac events | Cisapride binding to the HERG receptor caused dose-dependent inhibition of potassium currents | Cisapride binding to the HERG receptor is plausible and coherent, leading to QTc interval prolongation and arrhythmia. Experimental models demonstrated that cisapride inhibited the HERG receptor and could cause cardiac effects in animals | Other QTc interval-prolonging drugs that bind to the product of the HERG gene (e.g. terfenadine) and long QT syndrome |
| **Spontaneous reports and case reports** | | | | | | |
| Number and nature of the reports (and strong biological plausibility) | Number of reports from different populations. Events were consistent with QT interval prolongation/ arrhythmia | The events that were observed were caused by cisapride specifically inhibiting the HERG potassium channel, although some early reports were for tachycardia and the link to HERG had not been established at the time | The development of QT interval prolongation / arrhythmia was temporally related to starting the medication, increasing the dose or starting an interacting medication | In some instances, events were observed after increasing the dose of cisapride, or after taking a concomitant CYP3A4 inhibitor | The events observed in human subjects are plausible and coherent with the known biological mechanism of cisapride. Most of the case reports described a successful dechallenge. There were several examples where rechallenge was also observed | |
| **Clinical trials (most of the studies were non-randomised and lacked a comparator group)** | | | | | | |
| | Results were inconsistent, which is not surprising given the rarity of the event | Some of the events could be considered specific to HERG potassium channel inhibition (e.g. prolonged QTc interval), whereas others were less specific (e.g. tachycardia) | The clinical nature of the study meant that the outcome could be temporally related to taking cisapride | Inconsistency between prolonged QTc interval and increased doses of cisapride. Some evidence was provided by drug interaction studies | The events observed in human subjects are plausible and coherent with the known biological mechanism of cisapride. One clinical study showed dechallenge and rechallenge. Other studies showing the effect of the drug in human subjects also provided some experimental evidence | |

**CYP3A4** = cytochrome P450 3A4; **HERG** = human ether-a-go-go-related gene; **QTc interval** = corrected QT interval.

allow smaller relative risks to be accepted when establishing causation.[3]

In this analysis, there was a lack of evidence from epidemiological studies, some of which were validation studies conducted in order to assess the association between cisapride use and QTc interval prolongation.[16,17] This was mainly because of the rarity of the event making it unfeasible to conduct studies of sufficient size, as well as biases in the study designs making it hard to demonstrate an association.[24] The only available quantitative estimates of the association were therefore risk estimates based on spontaneous reports and utilisation data.[27]

Most of the clinical studies that provided evidence for the association were considered, in evidence-based medicine terms, to be poor quality as they tended to be non-randomised, have no comparator groups and/or be conducted in very small numbers of individuals. Thus, most studies did not account for possible bias or confounding, nor did they have the power to detect an association between cisapride use and the cardiac adverse effects.[104] Although it may be argued that if better-quality randomised, controlled trials had been available they may have added to the strength of the association, the rarity of the event means that the feasibility of conducting randomised, controlled trials capable of demonstrating a clear association is low. The hierarchy of evidence[104] (which serves well in assessing efficacy) is not always useful and can even lead to confusion in examining the safety of medicines, because most of the evidence available for evaluation is derived from non-randomised studies.[105] Although this calls for enhancement of the evidence used to address safety questions,[106] double-blind, randomised, controlled trials may not always be the best method for this purpose, because of problems such as the small numbers of patients studied and the exclusion of patients at high risk for the development of adverse drug reactions. However, notwithstanding these limitations, there is a place for randomised clinical trials in studying the safety of medicines.

It is apparent that current procedures in pharmacovigilance do use elements of the Bradford Hill criteria for the assessment of causation. The CIOMS I reporting form for individual case reports asks about dechallenge and rechallenge.[107] The WHO criteria for the assessment of individual case reports have a number of terms that are similar to the Bradford Hill criteria.[3] The FDA uses an adapted version of the Bradford Hill criteria for the assessment of birth defects.[108] Although not a pharmacovigilance issue, the Department of Health in the UK has used the Bradford Hill criteria for the assessment of the link between alcohol and breast cancer.[109] There have been several other published examples where drug safety issues have been assessed using the Bradford Hill criteria.[110-114] However, in some of these examples it is unclear whether the literature was selected in a systematic manner or what evidence has been used to fulfil a particular criterion. These publications also appeared to treat the criteria as a checklist and did not consider their limitations.

The criteria are open to interpretation and there are no guidelines regarding the implication of not meeting one or more of the criteria and how this affects the value of the other evidence. When a particular criterion is not met questions should be asked, for example, whether there is a reason why this criterion has not been met and whether the association could still be considered causal. Otherwise, there is the danger that causal associations may be disregarded despite evidence to the contrary, or vice versa. As the example we have used demonstrates, pharmacoepidemiological studies (because of their limitations) fail to indicate a true association under some circumstances.

Studies have also found that the Bradford Hill criteria are used inconsistently by investigators, with certain criteria being excluded without explicit reasons being given for their exclusion.[115,116] In our analysis, we realised that it was hard to consider all of the criteria independently and that there was overlap between some of the categories. We discovered that our grouping of plausibility, coherence and experimental evidence was similar to the use of causal criteria in the US Surgeon General's report on smoking.[14,15,115] Other instances where there could be overlap include strength and consistency, as well as temporality being related to the biological gradient and experimental evidence (particularly when considering dechallenge and/or rechallenge).

In this example, because of the nature of the event that we studied, most of the evidence came

from spontaneous reports even though we conducted an extensive literature search. However, this does not diminish the importance of evaluating all types of evidence from the published literature and other sources in the assessment of causation in drug safety. Spontaneous reports were sufficient to demonstrate a causal association in this example, because torsades de pointes is rare and occurs only in a few instances,[11] whereas an event such as myocardial infarction occurs commonly and would require additional evidence. This pertains to different types of evidence having different weightings under different circumstances, which would be an important point to consider when adapting the Bradford Hill criteria for use as a global pharmacovigilance tool.

Future work should also try to establish how causation can be assessed for events with different levels of incidence and characteristics, as well as considering the baseline rate of the event in the population being studied.[117] Further evaluation may also be warranted to determine what aspects of the different types of pharmacovigilance data can be assessed using the Bradford Hill criteria, and whether modification of the criteria is required to accommodate the nature of the evidence used in pharmacovigilance, such as the predominance of spontaneous and literature case reports and the paucity of randomised clinical trials. The creation of clear guidelines may help enable the assessment of causation with more scientific rigour in the future.

We acknowledge the limitations of applying the Bradford Hill criteria to a drug safety issue retrospectively. Our objective was to examine the application of the Bradford Hill criteria for decision-making in pharmacovigilance, using cisapride as a case study. Cisapride is a good example for a case study, because there was a good body of evidence in the public domain about its cardiac safety. Furthermore, the use of past drug safety issues as examples may help to educate and improve the systems that are in place for the assessment of causation in the future. In this work, the exclusion of non-English articles, clinical studies conducted in high-risk populations, and experimental studies using cisapride as a reference compound has meant that we have not evaluated every single piece of published evidence. However, by searching the reference sections of retrieved articles we ensured that all the most important references were evaluated. We identified several reports that summarised spontaneous report data (we did not evaluate individual spontaneous reports). Therefore, reanalysing individual cases was considered to be unnecessary for the purpose of this study. The evidence we identified by systematically searching the medical literature is consistent with the cited evidence used to support the withdrawal of cisapride.[105]

## Conclusion

To summarise, we have used the example of cisapride-induced QTc interval prolongation/arrhythmia to examine how the Bradford Hill criteria can be used for assessing causal associations in pharmacovigilance. This example has shown that it is important to consider all types of data in the assessment of causation. It was possible, in the case of cisapride-induced QTc interval prolongation/arrhythmia, to attribute causality in pharmacovigilance on the basis of biological evidence and individual case reports. This calls for broadening the data sources used in the assessment of causation in pharmacovigilance and for all data sources to be given proportionate and appropriate emphasis. Further work is needed to examine what evidence is required to establish causation for different types of adverse events and to establish how this information can be applied to the practice of pharmacovigilance.

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Contribution of each author: Dr Michael Perrio was responsible for helping to design the study, searching the literature, analysing the results, validating the data and writing the paper; Dr Simon Voss helped to design the study, provided advice on the analysis of the results and contributed to the final paper; Professor Saad AW Shakir proposed the concept of the study, helped to design it, provided guidance and contributed to the final paper.

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