Pharmacology Fact: To Use a SYNTHETIC anything is an Insult to the Body
Those who do not remember the past are condemned to repeat it.

Those who forget history are doomed to repeat it.
Birth defects blamed on unapproved morning sickness treatment 2014

Canadian women with severe morning sickness are being prescribed a powerful anti-nausea drug that is suspected of birth defects, side-effect reports show severe risk of birth defects.

Thalidomide 1960s - 70s

Thalidomide: The Tragedy of Birth Defects and the Effective Treatment of Disease

Abstract

WINDOWS OF EXPOSURE AND DOSE

MECHANISMS OF ACTION

THE CONTINUED USE OF THALIDOMIDE

CURRENT AND FUTURE CHALLENGES

References

SHADOW OF DOUBT WIPES OUT BENDECTIN 1980s

Bendectin and birth defects: I. A meta-analysis of the epidemiologic studies

Teratology

Abstract

Medical uses

Medical organizations’ position

Safety in pregnancy

Adverse effects

History

Society and culture

See also

References

Daubert v. Merrell Dow Pharmaceuticals

Over the drug Benedictine

Facts

Majority opinion

Prior law

The standard governing expert testimony

Aftermath
Birth defects blamed on unapproved morning sickness treatment 2014

Canadian women with severe morning sickness are being prescribed a powerful anti-nausea drug that is suspected of birth defects, side-effect reports show severe risk of birth defects.

Dr. Gideon Koren, director of the Motherisk resource centre at Toronto’s Hospital for Sick Children, said the side-effect reports suspecting ondansetron of causing birth defects are a “signal that should be looked into.” Health Canada says it hasn’t reviewed the cases.
Canadian women with severe morning sickness are being prescribed a powerful anti-nausea drug suspected of causing deformities in some babies, a Toronto Star investigation has found.

The drug, ondansetron, is approved by Health Canada to treat nausea and vomiting in chemotherapy and surgery patients. It is not approved to treat pregnant women, but some doctors prescribe it “off label” without hard proof it is safe for expectant mothers.

So little is known about how ondansetron affects pregnant women that the drug manufacturer says such use is “not recommended” for these vulnerable patients.

At least 20 Canadian women treated with ondansetron for vomiting in pregnancy experienced serious suspected side-effects, including two infant deaths and multiple cases of newborns with heart defects and kidney malformations, according to a Star analysis of 2012 records.

Curiously, information about these unapproved treatments is not publicly available from Health Canada. The Star discovered this crucial information after analyzing a massive trove of data found in the U.S. Food and Drug Administration’s public side-effect report database.

This database holds thousands of publicly available records of side-effects suffered by Canadian patients. (Read more about what they reveal in tomorrow’s Star).

Ondansetron is just one of several powerful drugs being prescribed to Canadians for unapproved uses.

The controversial and common practice is known as an “off-label” use of a drug. Off label means a drug is used for a condition or age group for which it hasn’t been approved.

There is no law or regulation stopping doctors from prescribing drugs off label. And, the Star has found, they are doing so with little oversight.

There are innovative off-label uses of drugs that have helped patients, but many off-label prescriptions are written with no solid scientific proof that the drug will be safe or effective.

In 2012, a Senate committee told Health Canada officials it was concerned about whether the regulator was monitoring the effect of off-label prescriptions on vulnerable Canadians, especially pregnant women.

Yet Health Canada, which was criticized by the auditor general in 2011 for poor drug safety monitoring, says it has not reviewed these reported birth defects. The regulator has issued no warnings to prescribers or the public about pregnant women taking ondansetron for morning sickness.

Four of the Canadian babies featured in the FDA side-effect reports reviewed by the Star were born weighing as little as four-and-a-half pounds. In six cases, a suspected side-effect of ondansetron was listed as “fetal growth restriction.”

The Star looked at Canadian side-effect reports filed in the FDA database between 2010 and 2013. Each report is the opinion of the doctor, pharmacist or patient that a particular drug has caused a reaction. Patients’ names are taken out of the reports to protect their privacy.

All the ondansetron cases are from 2012. They include:

• A baby born with a “musculoskeletal anomaly.”
A doctor reported that ondansetron was the suspected cause of a baby’s mouth deformity, jaundice, heart murmur and two heart defects, including “atrial septal defect,” otherwise known as a hole in the heart.

Because most women experience nausea and vomiting during the first trimester, they would be taking the drug at the same time the fetus is most vulnerable to developing malformations and deformities.

Roughly 10 to 15 per cent of pregnant women receive drugs to treat morning sickness, according to a recent U.S. study.

In the Canadian cases found in the FDA database, doctors prescribed ondansetron to treat “hyperemesis gravidarum,” an extreme form of morning sickness marked by relentless vomiting causing significant weight loss and dehydration. Left untreated, the condition puts both the mother and fetus at risk.

GlaxoSmithKline makes a brand-name version called Zofran and several other companies manufacture generics.

The Star contacted the companies mentioned in the side-effect reports.

Glaxo said “the safety of ondansetron for use in human pregnancy has not been established. . . . (The company) monitors and reports all adverse event reports . . . and works closely with regulatory authorities in Canada to include relevant safety information for physicians and patients within our product labels.”

Generic maker Mylan Inc. refused to comment. India-based Ranbaxy Pharmaceuticals also declined to comment.

Last year, Ranbaxy USA pleaded guilty and paid a $130-million criminal fine, admitting it distributed adulterated drugs and made fraudulent statements to the FDA. Ondansetron was not one of the drugs named in the indictment, though Amir Attaran, a University of Ottawa law professor who has studied drug regulations, says Health Canada should not trust any products from the company.

On its website, Health Canada says Ranbaxy’s version of ondansetron is approved for sale.

The controversial use of ondansetron in pregnant women has been the subject of several studies in the last decade, with conflicting results and scientists from Toronto to Denmark saying more research is needed. A 2011 study suggested the drug doubles the chance of babies being born with cleft palate. Concerns about ondansetron’s safety were briefly placated after a study regarding the risk of adverse outcomes was published in the Feb. 28, 2013, issue of the prestigious New England Journal of Medicine.

The researchers tracked more than 600,000 Danish births using national birth and prescription registries, and found the drug was not associated with a significant increased risk of spontaneous abortion, stillbirth or defect. But the same day the study was presented at a drug safety conference in Montreal, another group of Danish doctors introduced contradictory findings based on the same national registries.

Those researchers, looking at nearly 900,000 births, detected a two-fold increase in heart defects in babies whose mothers received ondansetron. They have since expanded the study to include more births and arrived at the same conclusion; they recently submitted their results to an academic journal, the lead researcher told the Star.
Medical practice guidelines, including those approved by the Society of Obstetricians and Gynaecologists of Canada, urge caution, saying ondansetron should be used only after exhausting other medications that have been tested in pregnant women and are approved to treat morning sickness.

Meanwhile, confusion spreads among pregnant women.

On online message boards, some mothers readily recommend the drug to others, raving about how it quelled their nausea. At the Hospital for Sick Children in Toronto, the Motherisk program, a leading source of information and advice for expectant mothers, gets several calls a week from women asking about their ondansetron prescriptions. In 2012, staff fielded 194 such calls.

Motherisk call takers and counsellors track these patients and their babies’ health but have little hard information about the drug to share with anxious mothers.

“Here is a drug not meant for pregnancy, given in pregnancy, with no data. So how do you know it’s safe for a baby? It’s an extrapolation that doctors do,” says Motherisk director Dr. Gideon Koren. “They think it’s the last chance for your patient. They think that there’s an edge for that drug compared to other drugs.”

For Christina Salvatori, ondansetron was the only drug that relieved her hyperemesis gravidarum. In late 2012, about four weeks into her pregnancy, she was crippled with violent vomiting.

Her symptoms were so severe she lost about 20 per cent of her body weight over the next two months. Salvatori spent 10 weeks of her pregnancy in hospital, six of them hooked up to a tube pumping 2,000 calories and nutrients into her each day.

“As all mothers, I wanted a drug-free pregnancy,” she said from her home in British Columbia. “When you’re in that state — you can’t sleep, you can’t eat, you can’t drink, you just physically can’t do anything — you know it’s not sustainable for your body or the baby. You have to take something.”

During an early hospitalization, doctors tried a battery of anti-nausea medications. Nothing worked until ondansetron.

Her husband researched the drug. The couple grew troubled about conflicting findings on its safety. She continued taking ondansetron right up to the day she gave birth to a healthy girl.

Ten months later, Salvatori said she would take ondansetron again. It was the only thing that got her through the pregnancy, she said.

But she said doctors and women should be cautious of using a drug with so much uncertainty surrounding its off-label use. She thinks Health Canada should track women like her. “If someone has to go on these medications, follow it and see what the effects are — monitor it.”

It is a drug regulator’s job to watch for signals that a drug may be harming the public.

Health Canada and other drug regulators began collecting side-effect reports in the 1960s in the wake of the thalidomide tragedy. The sedative, prescribed to treat the symptoms of morning sickness, caused thousands of serious birth malformations across the world.

Side-effect reports detailing cases of sick, vulnerable women taking a powerful drug and giving birth to babies with defects are a “signal that should be looked into,” Koren said.
Ondansetron is already on Health Canada’s radar: it has issued alerts concerning an increased risk of heart arrhythmias and possibly fatal reactions for patients on the drug for approved treatments.

The regulator, however, says there is no reason to probe the reported birth deformities.

“Currently, no emerging safety issues requiring further assessment related to ondansetron use in pregnant women have been identified,” a spokesperson said in a statement.

The Star found that Health Canada has not shared recent reports of birth defects showing women were given ondansetron to treat morning sickness. When pressed, Health Canada released some of this information to the Star, but has not released the information to the public.

“All the information should be provided by Health Canada in this database for the benefit of all the physicians who treat pregnant women,” said Mercedes Benegbi, executive director of Thalidomide Victims Association of Canada. “The only way to prevent a tragedy is the sharing of information.”

Doctors can learn of potential off-label uses of drugs from a range of sources, including published medical research and by word-of-mouth from other doctors.

It is illegal for drug companies to promote off-label uses to doctors. In 2012, the U.S. Department of Justice reached a $3-billion settlement with GlaxoSmithKline after the government alleged the company promoted the off-label uses of several drugs, including Zofran, the company’s brand-name version of ondansetron.

Court documents alleged the company gave doctors kickbacks to prescribe the drug for morning sickness and disseminated false information about Zofran’s safety and effectiveness.

The company told the Star that as part of the settlement it admitted no wrongdoing “in connection with physician prescribing of Zofran in the U.S.”

North of the border, where Glaxo says its sales reps do not promote off-label uses of ondansetron or other products, Health Canada has never investigated or even asked the company about its ondansetron sales practices.

**Thalidomide 1960s - 70s**

*Pair of artificial arms for a child, Roehampton, England, 1964*

**View Object**
The thalidomide disaster is one of the darkest episodes in pharmaceutical research history. The drug was marketed as a mild sleeping pill safe even for pregnant women. However, it caused thousands of babies worldwide to be born with malformed limbs. The damage was revealed in 1962. Before then, every new drug was seen as beneficial. Now there was suspicion and rigorous testing.

**The development and sale of thalidomide**

Thalidomide was developed in the 1950s by the West German pharmaceutical company Chemie Grüenthal GmbH to expand the company’s product range beyond antibiotics. It was an anticonvulsive drug, but instead it made users sleepy and relaxed. It seemed a perfect example of newly fashionable tranquillisers.

During patenting and testing, scientists realised it was practically impossible to achieve an LD$_{50}$ level, or deadly overdose, of the drug. Animal tests did not include tests looking at the effects of the drug during pregnancy. The apparently harmless thalidomide was licensed in July 1956 for prescription-free over-the-counter sale in Germany and most European countries. The drug also reduced morning sickness, so it became popular with pregnant women.

**First suspicions and the disaster**

By 1960 doctors were concerned about possible side effects. Some patients had nerve damage in their limbs after long-term use. Grüenthal did not provide convincing clinical evidence to refute concerns. In the United States, the Food and Drug Administration (FDA)’s drug examiner Frances Oldham Kelsey did not approve the drug for use.

There was an increase in births of thalidomide-impaired children in Germany and elsewhere. However, no link with thalidomide was made until 1961. The drug was only taken off the market after the German Widukind Lenz and the Australian William McBride independently suggested the link. Over 10,000
children were born with thalidomide-related disabilities worldwide. Well-known people in the UK affected by thalidomide include actor and writer Mat Fraser.

The aftermath and thalidomide's controversial rehabilitation

There was a long criminal trial in Germany and a British newspaper campaign. They forced Grünenthal and its British licensee, the Distillers Company, to financially support victims of the drug. Thalidomide led to tougher testing and drug approval procedures in many countries, including the United States and the United Kingdom.

In 1964 a leprosy patient at Jerusalem’s Hadassah University Hospital was given thalidomide when other tranquillisers and painkillers failed. The Israeli doctor Jacob Sheskin noticed the drug also reduced other leprosy symptoms. Research into thalidomide’s effects on leprosy resulted in a 1967 World Health Organisation (WHO) clinical trial. Positive results saw thalidomide used against leprosy in many developing countries. It is also used successfully to control some AIDS-related conditions, and its effects on various cancers are under investigation.

Thalidomide: The Tragedy of Birth Defects and the Effective Treatment of Disease

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Abstract

Thalidomide was a widely used drug in the late 1950s and early 1960s for the treatment of nausea in pregnant women. It became apparent in the 1960s that thalidomide treatment resulted in severe birth defects in thousands of children. Though the use of thalidomide was banned in most countries at that time, thalidomide proved to be a useful treatment for leprosy and later, multiple myeloma. In rural areas of the world that lack extensive medical surveillance initiatives, thalidomide treatment of pregnant women with leprosy has continued to cause malformations. Research on thalidomide mechanisms of action is leading to a better understanding of molecular targets. With an improved understanding of these molecular targets, safer drugs may be designed. The thalidomide tragedy marked a turning point in toxicity testing, as it prompted United States and international regulatory agencies to develop systematic toxicity testing protocols; the use of
thalidomide as a tool in developmental biology led to important discoveries in the biochemical pathways of limb development. In celebration of the Society of Toxicology’s 50th Anniversary, which coincides with the 50th anniversary of the withdrawal of thalidomide from the market, it is appropriate to revisit the lessons learned from the thalidomide tragedy of the 1960s.

Thalidomide

Thalidomide was first marketed in the late 1950s as a sedative and was used in the treatment of nausea in pregnant women (Fig. 1). Within a few years of the widespread use of thalidomide in Europe, Australia, and Japan, approximately 10,000 children were born with phocomelia, leading to the ban of thalidomide in most countries in 1961. Some countries continued to provide access to thalidomide for a couple of years thereafter (Lenz, 1988). In addition to limb reduction anomalies, other effects later attributed to thalidomide included congenital heart disease, malformations of the inner and outer ear, and ocular abnormalities (Miller and Strömland, 1999). The thalidomide tragedy was averted in the United States because of the hold on its approval by Dr Frances Kelsey of the U.S. Food and Drug Administration, who was recognized by President John F. Kennedy as a recipient of the Gold Medal Award for Distinguished Civilian Service. Dr Kelsey’s decision to hold the approval of thalidomide was not because of the birth defects, which had not yet been attributed to thalidomide, but because of her concerns about peripheral neuropathy (sometimes irreversible) in the patient and the potential effects a biologically active drug could have after treatment of pregnant women. The thalidomide tragedy also brought into sharp focus the importance of rigorous and relevant testing of pharmaceuticals prior to their introduction into the marketplace (Kelsey, 1988). Dr Kelsey was awarded an honorary membership to the Society of Toxicology in celebration of its 50th Anniversary in 2011.

![Structure of thalidomide.](image)

**FIG. 1.** Structure of thalidomide.
Josef Warkany, one of the founders of the Teratology Society, doubted in April of 1962 that thalidomide was responsible for the epidemic of limb defects (Warkany, 1988). His reasoning was that rat experiments had not produced comparable malformations and that malformations in humans were inconsistent (i.e., some mothers who were exposed to thalidomide had normal children and some malformations occurred in children whose mothers did not knowingly take thalidomide) (Warkany, 1988). The thalidomide episode led to the adoption of requirements for the systematic testing of pharmaceutical products for developmental toxicity prior to marketing. The adoption of these requirements is sometimes considered a benefit of the thalidomide tragedy. The legacy of thalidomide extends further than the creation of detailed testing protocols. With thalidomide came, the widespread recognition that differences in sensitivity between species required consideration. As a consequence, developmental toxicity testing for pharmaceuticals is conducted in two species, one of which is not a rodent. It is not clear, however, that the routine use of the second species (usually rabbit) has resulted in better testing, and it has been suggested that a more thorough understanding of results in a single species may be preferable (Janer et al., 2008).

In order to address potential developmental and reproductive toxicities of pharmaceuticals, the U.S. FDA (1966) laid the foundation for the development of the segment I (fertility and general reproduction), II (teratogenicity), and III (perinatal) testing protocols in 1966. Prior to the development of the segment I, II, and III testing protocols, toxicology testing was more hypothesis driven rather than a systematic bioassay testing strategy that is in place today. The segment I, II, and III studies, or their International Conference on Harmonisation and Organisation for Economic Co-operation and Development equivalents, are performed in addition to routine short-term, subchronic, and chronic toxicity assays and have been in place with little change for over 40 years.

An examination of the PubMed literature database revealed a bimodal pattern (Fig. 2) in the number of citations containing thalidomide as a keyword. As a direct result of the thalidomide tragedy in the early 1960s, not surprisingly, there was a steady number of publications in that decade. Because of the ban in its use, interest in thalidomide waned in the 1970s and 1980s. For reasons that will be described below, the number of thalidomide publications began increasing in the latter half of the 1990s and have increased dramatically in the last 10 years. Though its use in pregnant women was banned in 1961, thalidomide continues to be used in the treatment of leprosy because of its immunomodulatory properties. The World Health Organization still does not recommend thalidomide for the treatment of leprosy because of its use in areas of poor medical surveillance resulting in a number of thalidomide–affected children (http://www.who.int/lep/research/thalidomide/en/).
In 1998, thalidomide was approved by the U.S. Food and Drug Administration for the treatment of leprosy and, subsequently, for multiple myeloma. Studies are ongoing to evaluate the effectiveness of thalidomide in the treatment of other diseases. Thalidomide inhibits angiogenesis and could be used to treat human diseases that are dependent on angiogenesis. Inhibition of angiogenesis is one of the proposed mechanisms of action for thalidomide’s teratogenic properties (discussed below).

As a "model" teratogen, thalidomide is also being used as a tool to evaluate the predictivity of alternative testing methods such as in vitro assays.

Toxicologists have long held dear the tenet of Paracelsus that “All substances are poisons; there is none which is not a poison. The right dose differentiates a poison from a remedy.” (Gallo, 2008). For developmental and reproductive toxicology, this tenet needs to be modified with a consideration of the exposure period. In the early 1960s, it was recognized that the timing of exposure was as important as the dose for teratogenic effects (Lenz, 1962; Nowack, 1965). Based on the literature, Miller and Strömland (1999) and Miller et al. (2009) constructed a timetable of critical exposure periods for thalidomide embryopathy. For example, the window of exposure in humans for upper limb malformations is days 24–32 postfertilization; the window for lower limb malformations is days 27–34 postfertilization (Miller and Strömland, 1999). Other endpoints include external ear malformations (days 20–24), inner ear malformations (days 24–34), thumb hypoplasia (days 21–28), and triphalangism of the thumbs (days 32–36). The sensitive period during pregnancy for thalidomide effects in humans is approximately days 20–34 after fertilization (Miller and Strömland, 1999; Miller et al., 2009). A summary of these windows of critical exposures and limb defects is presented in Figure 3.

**FIG. 2.**

Number of PubMed entries for thalidomide publications by year (searched on 12/27/2010).

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**FIGURE 2.**

Number of PubMed entries for thalidomide publications by year (searched on 12/27/2010).
FIG. 3.

Critical exposure periods for thalidomide embryopathy during human development.

Miller and Strömland (1999) also listed other findings in thalidomide-exposed children: kidney malformations, ventricular septal defects, dental malformations, autism and mental retardation, ocular anomalies, and Duane syndrome (lack of the sixth nerve and aberrant innervation of ocular muscles by the third cranial nerve) (Miller et al., 2009). Autism and mental retardation, ocular anomalies, and Duane syndrome are not always accompanied by limb anomalies.

Previous SectionNext Section

MECHANISMS OF ACTION

A diverse collection of thalidomide mechanisms of action has been proposed (Hansen and Harris, 2004; Stephens, 1988). Hansen and Harris (2004) noted over 30 hypotheses for the mechanism of thalidomide teratogenicity from 1966 to 2003, including: (1) acylation of macromolecules, (2) ascorbic acid synthesis, (3) downregulation of adhesion receptors, (4) alteration of cytokine synthesis, (5) folic acid antagonism, (6) inhibition of DNA synthesis, (7) DNA oxidation, (8) interference of glutamate metabolism, and (9) mesonephros-stimulated chondrogenesis. As described below, more recent research has focused on hypotheses involving (1) oxidative stress/damage, (2) DNA intercalation, (3) inhibition of angiogenesis, and (4) cereblon (CRBN) binding.

Thalidomide has been reported to increase the production of oxygen radicals and induce oxidative stress (Hansen and Harris, 2004). For example, rabbits treated with 400 mg/kg/day thalidomide on gestational day (GD) 8–12 produced litters with phocomelia (Parman et al., 1999). For DNA oxidation studies, the rabbits were treated 6 h before sacrifice with a single dose of 400 mg/kg (Parman et al., 1999). Levels of DNA oxidation in maternal tissues (liver, lung, kidney, brain, and placenta) and in embryos were decreased when the rabbits were pretreated (by 15 min) with 40 mg/kg phenyl N-tert-butylnitrone (PBN; a spin-trapping agent). Cotreatment of the rabbits with PBN also reduced the incidences of phocomelia (Parman et al., 1999).

Using in vitro whole embryo culture techniques, rat (thalidomide-resistant Sprague-Dawley) and rabbit (thalidomide-sensitive New Zealand White) embryos were exposed to thalidomide (0, 5, 15, and 30μM), and changes in glutathione were assessed (Hansen et al., 1999). The rabbit embryo cultures exhibited glutathione depletion (to 50% of control values) at 15μM, about twice the peak concentration achieved in humans on therapy, whereas rat embryo cultures did not. Glutathione depletion was also observed in the rabbit but not rat visceral yolk sacs at 15μM thalidomide. These experiments suggested a species-specific role for oxidative stress in thalidomide teratogenesis, though the mechanism still needs exploration. Hansen and Harris (2004) have proposed that nuclear factor kappa-B (NF-κB) mediates the redox regulation of limb outgrowth. Pregnant rabbits, which are thalidomide-sensitive, were treated with thalidomide (70 mg/kg bw/day) on GD 8–12 and pregnant rats, which are thalidomide insensitive, were treated with thalidomide (300 mg/kg bw/day) on GD 9–13. Limb buds were harvested on the last day of treatment, and green fluorescent protein (GFP) reporter vectors containing NF-KB-binding promoter sites...
were transfected into the cells for expression experiments (Hansen et al., 2002). GFP expression was decreased in thalidomide-exposed rabbit limb bud cells, whereas rat limb bud cells did not exhibit such a decrease. In situ hybridization of rabbit embryos (maternal rabbits treated with 400 mg/kg/day thalidomide) demonstrated decreased expression of genes (Twist, fibroblast growth factor [FGF]-8, FGF-10) involved in the proposed pathway (Hansen and Harris, 2004). Decreased GFP expression in the transfected limb bud cells and decreased expression of Twist, FGF-8, and FGF-10 could be prevented by cotreatment with the free radical spin-trapping compound PBN. Mutant mice that are deficient in antioxidant enzymes (i.e., glucose-6-phosphate dehydrogenase) or glutathione or that have inhibition of glutathione peroxidase or reductase are more sensitive to thalidomide embryopathy than are wild-type mice (reviewed by Wells et al., 2005). In addition, p53 knockout mice that are deficient in DNA damage responses and repair are also more sensitive to thalidomide- and radiation-induced embryopathies. Thalidomide has also been observed to induce cell death via upregulation of bone morphogenetic proteins and the Wnt antagonist, Dickkopf1 (Dkk1), resulting in inhibition of Wnt/β-catenin signaling in chicken embryos and human embryo fibroblasts (at about 5 times the maximum human therapeutic concentration) but not in mouse embryo fibroblasts (Knobloch et al., 2007). Perturbation of signaling pathways via oxidative stress has been hypothesized to result in apoptosis of key progenitor cells in limb development (Knobloch and Ruther, 2008; Knobloch et al., 2008).

As early as 1986, Koch and Czejka (1986) reported the intercalation by thalidomide of DNA of various specimens. Stephens et al. (2000) demonstrated that thalidomide binds to GC-rich promoter sites by intercalation and thereby decreases the transcription of insulin-like growth factor (IGF-1) and FGF-2. These gene products are known to stimulate transcription of α5- and β3-integrin subunit genes, resulting in stimulation of angiogenesis in the limb bud and proper limb growth. This theory is consistent with thalidomide exerting its teratogenic effects by inhibiting angiogenesis (Stephens et al., 2000; Stephens and Fillmore, 2000). To investigate a hypothesis that thalidomide interferes with genes regulated by GC-rich promoters by blocking the binding of SP-1, Druckeret al. (2003) reported this same observation while studying the mechanism of thalidomide in the treatment of multiple myeloma. Inhibition of angiogenesis may be a mechanism of thalidomide action common to teratogenicity and utility against multiple myeloma (Drucker et al., 2003; Stephens et al., 2000).

D’Amato et al. (1994) demonstrated in a rabbit cornea micropocket assay that FGF-induced angiogenesis could be inhibited by thalidomide. Pellets containing basic fibroblast growth factor and sucralfate were implanted into the micropockets of both corneas of rabbits to stimulate angiogenesis. Thalidomide (200 mg/kg) administered by gavage on the same day as pellet implantation resulted in inhibited angiogenesis. Therapontos et al. (2009) reported that those thalidomide analogs that were anti-angiogenic but not anti-inflammatory could induce limb defects in chicken embryos. Thalidomide caused temporary blockage of mature blood vessels but caused complete obliteration of immature blood vessels in the chicken embryo, resulting in the hallmark limb defects (Therapontos et al., 2009).

A recent publication by Ito et al. (2010) reported that CRBN is a thalidomide-binding protein. CRBN normally forms an E3 ubiquitin ligase complex with damaged DNA binding protein 1 (DDB1) and Cullin-4A (CUL4A). DDB1 and CUL4A are important for the expression of FGF-8 and limb development. Ito et al. (2010) used zebrafish as a model to evaluate CRBN function in vivo. Zebrafish have a CRBN ortholog (zCRBN) that is 70% identical to human CRBN. Zebrafish injected with an antisense morpholino oligonucleotide for zCRBN exhibited a phenotype (defects in fin and otic vesicle development) similar to that found in zebrafish treated with very high concentrations of thalidomide (0, 200, or 400μM); coinjection with zCRBN messenger RNA rescued the embryos from those antisense-induced defects. More compelling was the observation that zebrafish expressing zCRBN mutant proteins (with low thalidomide binding affinity) were resistant to thalidomide effects; in addition, normal zebrafish embryos that are thalidomide sensitive were rescued when the zCRBN mutant protein was overexpressed. These antisense experiments were repeated using the zebrafish ortholog to CUL4A, resulting in similar observations. The zebrafish knockdowns for zCRBN and zCUL4A also exhibited decreased FGF-8 expression. Chick embryos were used to confirm the findings. Thalidomide-induced limb defects were
attenuated by overexpression of the mutant human CRBN protein possessing low thalidomide-binding affinity.

There is evidence to support all the hypotheses for the mechanisms of action of thalidomide limb teratogenicity: (1) oxidative stress/damage, (2) DNA intercalation, (3) inhibition of angiogenesis, and (4) CRBN binding, although the use in some experiments of very high concentrations of thalidomide raises questions about more clinically relevant exposure levels. The proposed mechanisms are not mutually exclusive. It is quite possible that several of the proposed mechanisms are working in parallel or synergistically to result in the hallmark thalidomide-associated limb anomalies.

Previous Section Next Section

THE CONTINUED USE OF THALIDOMIDE

Thalidomide appears to operate through anti-inflammatory and anti-angiogenesis mechanisms (Calabrese and Fleischer, 2000; Matthews and McCoy, 2003). These properties of thalidomide have been used as the basis for the treatment of leprosy (Calabrese and Fleischer, 2000; Sheskin, 1965, 1980) and multiple myeloma (Calabrese and Fleischer, 2000; Miller and Strömland, 1999). Leprosy patients with erythema nodosum leprosum exhibit vasculitic nodules and sometimes severe neuritis, conditions that cause extreme pain. Thalidomide administration to these patients is useful in suppressing these reactions. Thalidomide has also been used to treat the wasting syndrome of advanced HIV infection (Calabrese and Fleicher, 2000; Matthews and McCoy, 2003). This syndrome is marked by increased tumor necrosis factor-α, the synthesis of which can be inhibited by thalidomide. Other diseases proposed to benefit from the anti-inflammatory properties of thalidomide include systemic lupus erythematosus, nodular prurigo, Behçet syndrome, erythema nodosum, Langerhans cell histiocytosis, and graft versus host disease (Calabrese and Fleischer, 2000; Matthews and McCoy, 2003).

As an anti-angiogenic drug, thalidomide inhibits tumor hypervascularity, growth, and metastasis (Calabrese and Fleisher, 2000). Because of these properties, thalidomide has been demonstrated to be useful in the treatment of multiple myeloma.

The FDA has mandated a strict surveillance program to prevent the availability of thalidomide to pregnant women. The Celgene Corporation (the maker of thalidomide) has developed a program called System for Thalidomide Education and Prescribing Safety (STEPS) to safeguard against potential exposure of pregnant women (Public Affairs Committee [PAC], 2000). The STEPS program requires that physicians prescribing thalidomide in the United States be registered with the program and that both male and female patients adhere to mandatory contraceptive plans. STEPS is a three-step program: (1) physicians must educate patients on the potential benefits and side-effects of thalidomide, (2) patients must receive contraceptive counseling and regular pregnancy testing, and (3) patients must provide informed consent and continued participation in mandatory surveys. Prescribers of thalidomide that do not comply with any of these steps will not have prescriptions honored at registered pharmacies (PAC, 2000). The STEPS program also has the following strict requirements to decrease the possibility of exposure to pregnant women: (1) only a 4-week supply can be prescribed with no automatic refills and (2) female patients must use two forms of birth control. The STEPS program has so far been successful in managing the risks of thalidomide teratogenicity in the United States (Uhl et al., 2006). However, the availability of thalidomide has not been restricted in other areas of the world for the treatment of leprosy; access to thalidomide has likely resulted in cases of thalidomide-associated phocomelia on many continents but has been particularly well documented in South America (Castilla et al., 1996; Schuler-Faccini et al., 2007).

A recent publication by Johnson et al. (2011) investigated the association of thalidomide-associated peripheral neuropathy with single nucleotide polymorphisms (SNP) in 1495 multiple myeloma patients. This study reported that the risk of developing peripheral neuropathy was mediated by polymorphisms in genes involved in repair and inflammation of the peripheral nervous system. Though the mechanism of
thalidomide-associated peripheral neuropathy is unclear, this report illustrates the continued interest in understanding thalidomide’s effects.

Lenalidomide is a thalidomide analog currently used in the treatment of multiple myeloma. An evaluation of lenalidomide developmental toxicity in rabbits concluded that embryo-fetal effects were only manifested at maternally toxic doses (Christian et al., 2007). This finding contrasts with thalidomide studies, in which teratogenesis is observed at nonmaternally toxic doses. Lenalidomide possesses antineoplastic activities that are important for its therapeutic use but does not appear to have the developmental toxicity associated with thalidomide. However, more research is needed to understand the mechanistic differences between the two compounds.
Thalidomide Children, the tragedy of SINthetic drugs
CURRENT AND FUTURE CHALLENGES

As a result of the thalidomide tragedy of the 1960s, the following lessons were learned:

- Pharmaceutical products should be systematically tested for developmental effects prior to marketing.
- There are differences in species sensitivity and manifestations of developmental toxicity.
Use of a second species or more thoroughgoing interpretation of results in a single species (taking pharmacokinetics into consideration) are important considerations in drug testing.

Because thalidomide is useful in the treatment of serious diseases, it is likely that this product will continue to be used in therapeutics until safer alternatives become available. Prevention of inadvertent exposure of pregnant women to this drug is a continuing challenge, particularly in parts of the world where access to the drug is less restricted than in the United States.

The development of thalidomide analogs that retain the therapeutic benefits of the drug without its teratogenic liability is a second challenge. The goal of a safe thalidomide analog may be elusive if the therapeutic mechanisms of action and the teratogenic mechanisms of action are closely related or even identical.

Research into mechanisms of action remains a priority for a better understanding of whether and how safer alternatives can be developed. Toward this end, significant advances over the last two decades in molecular techniques and alternative test species have provided unique methodologies to test hypotheses on thalidomide’s mechanisms of action. Technologies such as the *in vitro* whole embryo culture test and zebrafish have been used to gain insight into mechanisms of action. The recent publication by *Ito et al. (2010)* exemplifies the use of advanced molecular techniques and an alternative test species (zebrafish) for facile phenotypic evaluations to understand mechanisms. Advances in gene expression analysis (pathway analysis, SNP) and omics technologies within the last 10–15 years now allow a rapid collection of information to further our understanding of embryonic development and perturbation of key developmental pathways. Hopefully, technological advances will also provide opportunities to investigate the less frequently encountered endpoints associated with thalidomide (e.g., autism, mental retardation, ocular anomalies, Duane syndrome) on which literature is limited.

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Can medical researchers prove that a drug is safe during pregnancy? Assuming they can, does an official green light mean all pregnant women can use the drug freely?

Years after the horrors of thalidomide, amid arguments over whether an expectant mother can drink a glass of wine, smoke one cigarette or take a single aspirin without endangering her baby's health, these questions still have not been satisfactorily resolved.

The current debate surrounds the decision of Merrell Dow Pharmaceuticals just over a week ago to stop selling Bendectin, a prescription drug designed to combat so-called morning sickness. According to manufacturer estimates, in the 27 years during which Bendectin has been sold more than 33 million pregnant women throughout the world have used it to curb their nausea and vomiting. It is the only drug approved in the United States for treating this condition, and last year one in 10 pregnant women here used it.
In the last five years, however, Bendectin has become the imputed cause of a host of birth defects. More than 300 lawsuits are pending against the manufacturer claiming damages for deformed babies born to mothers who took the drug. The company withdrew it from the market 13 days after a Washington, D.C. jury awarded $750,000 to the family of one such child.

According to Merrell Dow, the decision was made not because the drug has been proved hazardous, but because the company's insurance premiums have soared to $10 million a year, only $3 million less than income from the sale of the drug. "We were forced for business reasons to take a safe and effective medication off the market," said William Donaldson, the director of professional communications.

For most women, the symptoms of morning sickness are short-lived and of little or no medical significance. They usually diminish following simple changes of habit, such as eating dry crackers or drinking very cold or very hot water immediately after awakening. Occasionally, however, the nausea and vomiting are so severe or prolonged that the mother's or baby's well-being may be jeopardized. For such women - a small fraction of Bendectin's market - the American College of Obstetricians and Gynecologists said the drug's withdrawal will leave "a significant therapeutic gap."

The case against Bendectin is unclear. The Food and Drug Administration admitted as much in 1980, after an intensive two-day review of available data. The review panel said no association between Bendectin and birth defects had been demonstrated. It added, however, that because there was no way to prove the absolute safety of any drug in all women under every circumstance, there must remain a "residual uncertainty" about how this drug affects an unborn child.

The research on Bendectin has been inconclusive and contradictory. Questionable scientific methods have raised doubts about the validity of some findings. For example, several studies that linked Bendectin use to an increased risk of birth defects compared mothers of malformed babies with those who had normal children. Psychologists have shown, however, that people are more likely to recall factors associated with an abnormal event than with a normal one. Thus, mothers of defective babies may have been more likely than mothers of normal children to remember and report that they took Bendectin during pregnancy. Several studies that tried to counteract this bias found no increased risk of defects associated with Bendectin use.
Other doubts about Bendectin's risks stem from the range of defects attributed to it. While the largest number of complaints involve limb and other musculoskeletal deformities, the list also includes facial and brain damage; defects of the respiratory, gastrointestinal, cardiovascular and genital-urinary systems; blood disorders and cancer. Doctors know of no teratogen - an agent that causes birth defects - that produces anything resembling this variety of problems. Nearly all teratogens act at specific times during fetal development and affect the organs then forming.

There is another complication. About 5 percent of babies born in the United States each year have some type of birth defect, and about half of those have serious abnormalities. It is inevitable, then, that some Bendectin users would have given birth to defective children if they hadn't taken the drug.

Still, there is that "residual doubt" that while Bendectin is not a high-risk teratogen, such as thalidomide, it may affect some women under some circumstances. One study suggested that babies were at greater risk if their mothers also smoked cigarettes during pregnancy.

Proceed With Caution

Dr. Hugh R.K. Barber, director of obstetrics and gynecology at Lenox Hill Hospital in New York, said "If there is a lesson to be learned from the Bendectin story, it is that no drug or drug-like substance - even vitamins - can be assumed to be completely safe during pregnancy. In pregnant women with chronic illnesses that require medication, a drug's benefits must be weighed against the possible risks."

At least four factors suggest that pregnant women should proceed with extreme caution when it comes to medication. First, only 20 percent of drugs now marketed have been tested for prenatal effects, and some of those tests are far from scientifically sound. Second, it is difficult, if not impossible, to detect interactions between substances that alone may have no effect on a fetus. Third, it is equally difficult to determine whether metabolic or other peculiarities in some women can turn an otherwise harmless drug into a hazard. Finally, substances long thought safe, such as alcohol, have only recently been proved harmful to an unborn child.

Most birth-defect specialists now recommend that a pregnant woman take no drug that is not essential to her health and prescribed by a physician who knows she is pregnant. This does not guarantee a healthy baby, but it greatly reduces the chances of a drug-induced abnormality.
Bendectin and birth defects: I. A meta-analysis of the epidemiologic studies

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Teratology

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Abstract

“Bendectin”¹ (Doxylamine/Dicyclomine/Pyridoxine) was widely used for the treatment of nausea and vomiting of pregnancy until 1983, when production was discontinued in the face of lawsuits alleging that the drug caused congenital malformations. We have conducted a meta-analysis of the 16 cohort and 11 case-control studies that report birth defects from Bendectin-exposed pregnancies. This meta-analysis provides an estimate of the relative risk of malformation at birth in association with Bendectin exposure. The pooled estimate of the relative risk of any malformation at birth in association with exposure to Bendectin in the first trimester was 0.95 (95% CI 0.88 to 1.04). Separate analyses were undertaken for cardiac defects, central nervous system defects, neural tube defects, limb reductions, oral clefts, and genital tract malformations. In these categories, the pooled estimates of relative risk ranged from 0.81 for oral clefts to 1.11 for limb reductions, with all 95% confidence intervals enclosing unity. With the exception of studies for oral clefts and for pylorostenosis, tests for heterogeneity of association indicated for each table that all studies were estimating the same odds ratio. These studies, as a group, showed no difference in the risk
of birth defects between those infants whose mothers had taken Bendectin during the first trimester of pregnancy and those infants whose mothers had not. It is unlikely that Bendectin exposure contributed to the prevalence of congenital malformations in the population.© 1994 Wiley-Liss, Inc.

**Pyridoxine/doxylamine** (Returning to the US market as Diclegis; formerly Bendectin in the US; Debendox in the UK; Lenotan and Merbental in other countries and currently available in Canada as Diclectin) is a combination of pyridoxine (vitamin B₆) and doxylamine prescribed for the management of nausea and vomiting of pregnancy or morning sickness.

### Medical uses

The combination of pyridoxine, more commonly referred to as vitamine B6, and doxylamine, an anti-histamine, is prescribed in Canada (as Diclectin) for the management of nausea and vomiting of pregnancy. No epidemiological studies have found any teratogenic effect.[1] Doxylamine and pyridoxine are classified as a Risk Factor A drugs. This classification system is used in Drugs in Pregnancy and Lactation (8th edition),[2] and utilizes the same definitions as the FDA pregnancy category drug classification.

A randomized, double-blind, placebo-controlled study demonstrated that the combination of 10 mg of pyridoxine and 10 mg of doxylamine in a delayed-release tablet is effective in reducing symptoms of nausea and vomiting of pregnancy.[3]

### Medical organizations’ position

The American College of Obstetricians and Gynecologists states that the recommendation of “taking Vitamin B6 or Vitamin B6 plus doxylamine is safe and effective and should be considered a first-line treatment” is based on consistent scientific evidence.[4] These recommendations have been evaluated by the US Department of Health and Human Services’ Agency for Healthcare Research and Quality, who concur that the benefit of implementing the guideline recommendations would be a reduction on nausea and vomiting of pregnancy.[5] The Society of Obstetricians and Gynaecologists of Canada published a Clinical Practice Guideline on the management of nausea and vomiting of pregnancy in which it states that the “doxylamine/pyridoxine combination should be the standard of care, since it has the greatest evidence to support its efficacy and safety.”[6] The Motherisk Program, an internationally recognized teratogen information centre located at the Hospital for Sick Children in Toronto, published a Current Practice Update for the treatment of nausea and vomiting of pregnancy. This updated algorithm recommends the combination of 10 mg of doxylamine and 10 mg of pyridoxine as first-line therapy for the management of nausea and vomiting of pregnancy.[7]

### Safety in pregnancy
Due to the extensive scientific evidence demonstrating that there is no difference in the risk for birth defects or other adverse pregnancy outcomes between infants whose mothers take pyridoxine/doxylamine during pregnancy and those infants whose mothers do not take this drug combination, the two ingredients of the drug are considered Pregnancy Category A drugs.\[^{6}\]

Since the mid-1950s, over 33 million women have used the combination drug of pyridoxine/doxylamine in pregnancy, and scientific analysis on more than 200,000 exposed pregnancies has been conducted to determine if the combination of pyridoxine and doxylamine is harmful to the unborn baby.\[^{8}\][9\] No epidemiological studies have found any teratogenic effect.\[^{9}\]

Two separate meta-analyses have been conducted that have assessed pregnancy outcomes following the use of a combination of pyridoxine and doxylamine with or without dicyclomine during the first trimester of pregnancy.\[^{10}\][11\] The initial meta-analysis, published in 1988, combined data from 12 cohort and 5 case-control studies,\[^{10}\] and the subsequent meta-analysis, published in 1994, combined data from 16 cohort studies and 11 case control studies.\[^{11}\] These studies included over 200,000 Bendectin-exposed pregnancies and did not observe an increased risk for major malformations.\[^{10}\][11\] Separate analyses were conducted for specific defects including cardiac defects, limb reduction defects, oral clefts, and genital tract malformations; no increased risks for these defects were found.\[^{11}\]

In 1989, a report on the safety of the drug combination of pyridoxine/doxylamine for use in the management of NVP was prepared by a panel of Canadian and American experts for the Special Advisory Committee on Reproductive Physiology to the Health Protection Branch of Health Canada (currently called the Health Products and Food Branch).\[^{12}\] These scientific experts concluded that “numerous studies in animals and in humans that have been reported in the scientific and medical literature demonstrate that Bendectin is not a teratogen…The safety of Bendectin/Diclectin in the management of nausea and vomiting of pregnancy has been established by its use in many thousands of pregnant women”.\[^{12}\]

A study was conducted to determine whether the combination drug of pyridoxine and doxylamine had an effect on the neurodevelopment of children exposed in utero. Results from this study observed no difference in intelligence quotient scores between children who were exposed to pyridoxine/doxylamine in utero and children who were not exposed.\[^{13}\]

**Adverse effects**

Pyridoxine is a water-soluble vitamin and is generally recognized as having no adverse effects.\[^{14}\][15\] The most commonly reported side effect of doxylamine is drowsiness.\[^{15}\] Other adverse drug reactions associated with doxylamine succinate may include: vertigo, nervousness, epigastric pain, headache, palpitation, diarrhea, disorientation, irritability, convulsions, urinary retention or
insomnia. Caution should be used when combining doxylamine with other anti-cholinergic or anti-histamine drugs.

**History**

The combination of doxylamine and vitamin B6 was first introduced to the US market as Bendectin in 1956. At that time, Bendectin was a 3 ingredients prescription medication. The third one, dicyclomine, a Pregnancy Category B antispasmodic, was omitted from the formulation starting in 1976 due to its lack of efficacy. Bendectin (doxylamine/vitamin B6) was voluntarily removed from the market in 1983 by its manufacturer, Merrell Dow Pharmaceuticals, following numerous lawsuits alleging that it caused birth defects, although an FDA panel concluded that no association between Bendectin and birth defects had been demonstrated. In litigation, Bendectin was supposed to cause all kinds of fetal malformations and problems including limb and other musculoskeletal deformities, facial and brain damage, defects of the respiratory, gastrointestinal, cardiovascular and genital-urinary systems, blood disorders and cancer. The most famous case involving the drug is *Daubert v. Merrell Dow Pharmaceuticals* (1993). These suits were led by celebrity plaintiff attorney Melvin Belli. The star witness for the case against Bendectin, William McBride, was later found to have falsified research on teratogenic effects of the drug, and was struck off the medical register in Australia.

An extensive review of the evidence submitted in legal proceedings regarding Bendectin has been summarized and found no evidence that the drug in clinical use was linked to birth defects.

The FDA, in 1999, published a statement in the *Federal Register* that summarized their opinion regarding the safety of pyridoxine/doxylamine during pregnancy: “The FDA has determined that the drug product Bendectin, a tablet composed of pyridoxine hydrochloride 10 mg, and doxylamine succinate 10 mg, for the prevention of nausea during pregnancy was not withdrawn from sale for reasons of safety or effectiveness”

On Monday April 8, 2013 the FDA approved the return of Bendectin under the new trademark name of Diclegis. The medication will be produced by Duchesnay Inc. The Canadian based manufacturer has made a generic version, Diclectin, for many years. Per media reports the medication will be available for sale in the U.S. market in late May 2013.

**Society and culture**

The Bendectin case, and the subsequent removal of the drug from the US market, has had a number of consequences. Firstly, there was an immediate increase in the rates of hospitalization for nausea and vomiting in pregnancy. Secondly, to-date a safe medication that alleviates morning sickness in pregnant women - not a trivial matter as the most severe form of nausea and vomiting of pregnancy, called hyperemesis gravidarum can be life-threatening or cause women to terminate
their pregnancy. The lack of availability of a safe and effective drug for the treatment of nausea and vomiting of pregnancy has resulted in the use of other, less studied drugs in pregnancy. Thirdly, it has been claimed that subsequent to the Bendectin experience drug companies stayed away from developing medications for pregnant patients. As a result only two medications (oxytocin, cervidil) were approved between 1962 and 2010 for obstetrical indications by the FDA. Lastly, the perception that all medications are teratogenic increased among pregnant women and healthcare professionals. The unfounded fear of using medications during pregnancy has orphaned many women from receiving the appropriate treatment they require. Leaving medical conditions untreated during pregnancy can result in adverse pregnancy outcomes or significant morbidity for both the mother and baby. Ongoing education of physicians and the general public has resulted in improvements in the perception of medication use in pregnancy; however, further advances are required to overcome the devastating effects of the Bendectin saga.


See also

- Daubert v. Merrell Dow Pharmaceuticals
- Daubert standard

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The Federal Rules of Evidence govern the admission of scientific evidence in a trial held in federal court. They require the trial judge to act as a gatekeeper before admitting the evidence, determining that the evidence is scientifically valid and relevant to the case at hand.
**Case opinions**

**Majority**
Blackmun, joined by White, O'Connor, Scalia, Kennedy, Souter, Thomas

**Concur/dissent**
Rehnquist, joined by Stevens

**Laws applied**
Federal Rules of Evidence 104(a), 702, 703

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**Daubert v. Merrell Dow Pharmaceuticals**, 509 U.S. 579 (1993) is a United States Supreme Court case determining the standard for admitting expert testimony in federal courts. The Daubert Court held that the enactment of the Federal Rules of Evidence implicitly overturned the Frye standard; the standard that the Court articulated is referred to as the Daubert standard.

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**Facts**

Jason Daubert and Eric Schuller had been born with serious birth defects. They and their parents sued Merrell Dow Pharmaceuticals Inc., a subsidiary of Dow Chemical Company, in a California state court, claiming that the drug Bendectin had caused the birth defects. Merrell Dow removed the case to federal court, and then moved for summary judgment because their expert submitted documents showing that no published scientific study demonstrated a link between Bendectin and birth defects. Daubert and Schuller submitted expert evidence of their own that suggested that Bendectin could cause birth defects. Daubert and Schuller's evidence, however, was based on in vitro and in vivo animal studies, pharmacological studies, and reanalysis of other published studies, and these methodologies had not yet gained acceptance within the general scientific community.

The district court granted summary judgment for Merrell Dow, and Daubert and Schuller appealed to the Ninth Circuit. The Ninth Circuit found the district court correctly granted summary judgment because the plaintiffs' proffered evidence had not yet been accepted as a reliable technique by scientists who had had an opportunity to scrutinize and verify the methods used by those scientists. Furthermore, the Ninth Circuit was skeptical of the fact that the plaintiffs' evidence appeared to be generated in preparation for litigation. Without their proffered evidence, the Ninth Circuit doubted that the plaintiffs could prove at a trial that the Bendectin had, in fact, caused the birth defects about which they were complaining. The plaintiffs asked the Supreme Court to review the Ninth Circuit's decision, and it agreed to do so.

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**Majority opinion**

**Prior law**

In a 1923 case, Frye v. United States, 293 F. 1013 (D.C. Cir. 1923), the D.C. Circuit held that evidence could be admitted in court only if "the thing from which the deduction is made" is "sufficiently established to have gained general acceptance in the particular field in which it belongs." Frye dealt with a systolic blood pressure deception test, a "crude precursor" to the polygraph. In 1923, this blood pressure test was not widely accepted among scientists, and so the Frye court ruled it could not be used in court. Over the years, scholars disputed the proper scope and application of the Frye test.
The plaintiffs successfully argued that after Congress adopted the Federal Rules of Evidence in 1975, Frye was no longer the governing standard for admitting scientific evidence in trials held in federal court. The Supreme Court agreed and had already ruled that where common law rules conflicted with provisions of the Rules, the enactment of the Rules had the effect of supplanting the common law. Frye was certainly part of the federal common law of evidence because it was decided almost 50 years before the Rules were enacted. But the text of the Rules did not suggest that Congress intended to keep the Frye rule, and so the Court reasoned that Frye was no longer the rule.

Rule 702 of the Federal Rules of Evidence provides (in part):

If scientific, technical, or other specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue, a witness qualified as an expert by knowledge, skill, experience, training, or education, may testify thereto in the form of an opinion or otherwise...

The text of Rule 702 did not make admissibility of expert testimony depend on general acceptance, and there was no evidence that Congress intended to incorporate a general acceptance standard into Rule 702. "Given the Rules' permissive backdrop and their inclusion of a specific rule on expert testimony that does not mention 'general acceptance,' the assertion that the Rules somehow assimilated Frye is unconvincing. Frye made 'general acceptance' the exclusive test for admitting expert testimony. That austere standard, absent from, and incompatible with, the Federal Rules of Evidence, should not be applied in federal trials."[1]

The standard governing expert testimony

Three key provisions of the Rules governed admission of expert testimony in court. First, scientific knowledge, meaning that the testimony must be scientific in nature and must be grounded in "knowledge." Of course, science does not claim to know anything with absolute certainty; science "represents a process for proposing and refining theoretical explanations about the world that are subject to further testing and refinement." The "scientific knowledge" contemplated by Rule 702 had to be arrived at by the scientific method.

Second, the scientific knowledge must assist the trier of fact in understanding the evidence or determining a fact in issue in the case. The trier of fact is often a jury or a judge; but other fact finders may exist within the contemplation of the federal rules of evidence.[2] To be helpful to the trier of fact, there must be a "valid scientific connection to the pertinent inquiry as a prerequisite to admissibility." For example, although it is within the purview of scientific knowledge, knowing whether the moon was full on a given night does not typically assist the trier of fact in knowing whether a person was sane when he or she committed a given act.

Third, the Rules expressly provided that the judge would make the threshold determination[3] regarding whether certain scientific knowledge would indeed assist the trier of fact in the manner contemplated by Rule 702. "This entails a preliminary assessment of whether the reasoning or methodology underlying the testimony is scientifically valid and of whether that reasoning or methodology properly can be applied to the facts in issue." This preliminary assessment can turn on whether something has been tested, whether an idea has been subjected to scientific peer review or published in scientific journals, the rate of error involved in the technique, and even general acceptance, among other things. It focuses on methodology and principles, not the ultimate conclusions generated.

The Court stressed that the new standard under Rule 702 was rooted in the judicial process and intended to be distinct and separate from the search for scientific truth. "Scientific conclusions are subject to perpetual revision. Law, on the other hand, must resolve disputes finally and quickly. The scientific project is advanced by broad and wide-ranging consideration of a multitude of hypotheses, for those that are incorrect will eventually be shown to be so, and that in itself is an advance." Rule 702 was intended to resolve legal disputes and, thus, had to be interpreted in conjunction with other rules of evidence and with other legal means of ending those disputes.
Cross examination within the adversary process is adequate to help legal decision makers arrive at efficient ends to disputes. "We recognize that, in practice, a gatekeeping role for the judge, no matter how flexible, inevitably on occasion will prevent the jury from learning of authentic insights and innovations. That, nevertheless, is the balance that is struck by Rules of Evidence designed not for the exhaustive search for cosmic understanding but for the particularized resolution of legal disputes."

Aftermath

Main article: Daubert standard

After Daubert, it was expected that the range of scientific opinion evidence used in court would be expanded. However, courts have strictly applied the standards in Daubert, and it has generally been successful in excluding "junk science" or "pseudoscience", as well as new or experimental techniques and research that the decision might have been expected to deem admissible.

Discerning between science and "pseudoscience" was the theme of a book by Karl Popper whose summary was quoted in Daubert: "the criterion of the scientific status of a theory is its falsifiability, or refutability, or testability." The book, "Conjectures and Refutations: The Growth of Scientific Knowledge (5th ed. 1989), pp. 34-57, explains how psychology is more like astrology than astronomy because it does not make predictions about an individual which are falsifiable. He wrote that "the impressive thing about" Einstein's predictions "is the risk involved...If observation shows that the predicted effect is definitely absent, then the theory is simply refuted." But "it was impossible to describe a human behaviour" which would be accepted as proving psychology false.

The considerations in Daubert do not all have to be met for the evidence to be admitted. It is necessary only that the majority of the tests be substantially complied with.

The principle in Daubert was expanded in Kumho Tire Co. v. Carmichael, where the evidence in question was from a technician and not a scientist. The technician was going to testify that the only possible cause of a tire blowout must have been a manufacturing defect, as he could not determine any other possible cause. The Court of Appeal had admitted the evidence on the assumption that Daubert did not apply to technical evidence, only scientific evidence. The Supreme Court reversed, saying that the standard in Daubert could apply to merely technical evidence, but that in this case, the evidence of the proposed expert did not meet the standard.

Pronunciation of Daubert

While not a matter of law, discussions, corrections, and recriminations on this point from time to time vex attorneys and others among whom the subject of this case arises. Michael H. Gottesman, Jason Daubert's attorney reports that Daubert and his family do not affect the French pronunciation, which would be sounded similar to "dough-bear" /ˈdɔʊ bɛər/. Rather, they pronounce their family name in the same manner as Dow-Burt /ˈdaʊ ˈbɜr/. The popular use of the French pronunciation may have arisen from Gottesman refraining from correcting the justices during oral argument before the Supreme Court.

See also

- Bendectin
- Daubert Standard
- Expert witness
- Kumho Tire Co. v. Carmichael
- Merrell Dow Pharmaceuticals Inc. v. Thompson
- List of United States Supreme Court cases, volume 509
List of United States Supreme Court cases by the Rehnquist Court

References


Further reading


External links

- Text of the opinion, findlaw.com
- Text of the opinion, LII, Cornell University
- Amicus brief of Atlantic Legal Foundation in support of Merrell Dow
- Daubert Institute for Science & Law
- Daubert-The Most Influential Supreme Court Decision You've Never Heard of
- Project on Scientific Knowledge and Public Policy (SKAPP) website, a collection of original documents and commentary on the Daubert standard and the use of science in public policy
Daubert v. Merrell Dow Pharmaceuticals

For years, the admissibility of expert scientific evidence was subject to the Frye test, based on Frye v. United States (1923). Under Frye, only expert scientific evidence based on "generally accepted" principles in the scientific community was admissible. In 1973, the Federal Rules of Evidence were adopted. The Federal Rule of Evidence 702, however, stated the following, in contrast to Frye:

If scientific, technical, or other specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue, a witness qualified as an expert by knowledge, skill, experience, training, or education, may testify thereto in the form of an opinion or otherwise.

The Supreme Court determined in Daubert whether the Federal Rules of Evidence superseded the Frye test.

Summary

Daubert was a product liability action in which the plaintiffs, in essence, sought to establish that the ingestion of a prescription drug caused birth defects. The Court limited its analysis to "scientific" knowledge. The Court found that expert testimony must possess scientific validity to establish evidentiary reliability. Further, the Court found that "all relevant evidence is admissible" and that relevant evidence must "assist the trier of fact to understand the evidence or determine a fact in issue."

While the Court did not adopt "a definitive checklist or test" to determine the reliability of expert scientific testimony, it articulated four important factors:

1. whether the theory or techniques can be (and has been) tested;
2. whether the techniques or theory has been subjected to peer review and publication;
3. whether the techniques employed by the expert have a known or potential rate of error and standards controlling the technique's operations; and
4. whether the theory or technique employed by the expert has been generally accepted by the scientific community.

It is important to note that Daubert emphasizes that testimony may be admissible even where one or more of these factors are unsatisfied. For example, publication "is not a sine qua non [essential condition] of admissibility," and "does not necessarily correlate with reliability," according to the Court. Daubert emphasizes, however, that two
criteria must be met: (1) the evidence must be relevant, as required under Rule 702; and (2) the testimony must be "derived by the scientific method" and "supported by appropriate validation."

A study Obstetrics and Gynecology shows that one gram per day of ginger root can help control morning sickness, characterized by nausea and vomiting in the first few months of pregnancy. For more than 20 years, a drug called Benedictine was the only effective remedy for morning sickness. Lawyers who know nothing about medicine or statistics, do know about the value of intimidation; so many filed suits, even though there is no evidence anywhere that Benedictine causes birth defects. As far as I know, Merrill-Dow, the manufacturer of Benedictine, never lost a case, but they withdrew the drug anyway. For the last 10 years, women with morning sickness have had no medication to help them. But this recent study shows that one gram per day of ginger root effectively controlled morning sickness of pregnancy.

"You Can't Patent anything
Natural only SINthetic"

"Patents only Last for 19 years then ya got to make it slightly different and Bribe them to make a new Patent, it's easy"
Actions done in the name of protecting and encouraging innovation actually cause its destruction.
Counterclock
And all your health problems can be solved with these little patented pills.

Quack!

Patents protect the pharmaceutical company profits but not the People.
“Those who don’t study history are doomed to repeat it. Yet those who do study history are doomed to stand by helplessly while everyone else repeats it.”