Thalidomide: The journey from curse to boon
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Abstract
The tragic spectacle of thousands of infants born with deformed arms and legs at the beginning of the 1960s stunned the entire globe. The public's memory has been permanently scarred by the sight of those young people struggling with limb deformities. The medicine thalidomide, which pregnant women use for morning sickness and insomnia, was found to be responsible for the deformities in limbs and other organs.

Thalidomide was sold in over 40 nations and was authorised for prescription usage in Canada from April 1961 to March 1962. Although the true number was likely greater due to spontaneous miscarriages and stillbirths, it resulted in around 115 occurrences of deformities in this country. Due to its expulsion from the medical toolbox, this medication became a term of demeaning for many years. However, thalidomide has emerged from the darkness of unimaginable tragedy. Though under stringent restrictions, it has made a remarkable recovery and entered the current therapeutic regimen. As a result of the discovery that thalidomide and its derivatives have beneficial effects on a variety of cellular functions, they are currently recommended for the treatment of a number of diseases, including leprosy and multiple myeloma. Before returning the medication to the market, the US FDA conducted a number of clinical trials. Additionally, the deaths connected to this agent stimulated legislation that expanded patient informed consent processes, redesigned the FDA regulatory process, and required more openness from pharmaceutical companies.

Keywords: Teratogenicity; Thalidomide; Morning sickness; Pregnant women; Phocomelia; AIDS; Multiple Myeloma; Leprosy

1. Introduction
Thalidomide was created in 1953 by the Swiss pharmaceutical company CIBA and released in 1956 by the German pharmaceutical company Chemic Grunenthal. Thalidomide, which was first sold under the name Converging, was prescribed as a nonbarbiturate hypnotic sedative capable of inducing deep sleep without the risk of dependence or a hangover. The medication was generally thought to be harmless to humans when rodent testing failed to identify a median lethal dose. Formal testing for negative teratogenic effects was not conducted in that era, in contrast to the thorough testing carried out today. The medicine quickly gained popularity due to its ability to treat morning sickness in pregnant women and was soon made available all over the world. The fact that the medication was widely accessible and reasonably priced, as well as being available without a prescription, contributed significantly to its attraction.

Dr. Widukind Lenz, a German physician and geneticist, and Dr. William McBride, an Australian obstetrician, independently published observations in 1961 connecting thalidomide use during pregnancy to congenital abnormalities. Multiple incidents across the globe supported these conclusions, and thalidomide was subsequently taken off the market. Initial reports noted limb and bone abnormalities, including Amelia, phocomelia, syndactyly, and other deformities, as well as undeveloped long bones. Along with heart anomalies, aplasia of the gallbladder and appendix, atresia of the oesophagus, duodenum, and anus were also noted. Even one dose of thalidomide was related
with an elevated risk of abnormalities when taken between 34 and 49 days after the last menstrual period. Within a year, up to 40% of the affected infants died.

Thalidomide was briefly marketed as an investigational drug in the US. Despite being promoted as an anxiety reliever, the drug’s marketing was never authorised. By the end of the decade, thalidomide had been removed from the majority of commercial markets and was completely banned. Thalidomide is an adaptable chemical. It is a glutamic acid derivative with a range of functions that include both targeted and general anti-inflammatory, immune-modulatory, and angiogenesis inhibition. Unfortunately, one of its chiral enantiomers has a well-known connection to teratogenesis. The drug thalidomide is a racemic combination of the optical isomers rectus R and sinister S.

Thalidomide has experienced a spectacular comeback thanks to its pleomorphic immune-system effects, anti-proliferative effects, and anti-angiogenesis qualities. It has now been given FDA approval for at least 13 different diseases or disease states, including Kaposi’s sarcoma, primary malignant glioma, myelodysplastic syndrome, AIDS-wasting syndrome, erythema nodosum leprosum (leprosy), multiple myeloma, recurrent aphthous ulcers and stomatitis in immunosuppressed individuals, graft-versus-host disease, and various...
Taiwan), Distaval (in the UK and Australia), Softenon (in the bulk of Europe), Contergan (in Germany), Kedavon (in Canada), Sedalis (in Brazil) and were only a few of the names that the medication was known by.

In Germany, Australia, and Britain, between 1957 and 1960, there was an extremely large rise in the number of babies born with severe, rarely observed limb abnormalities and organ disorders, which at first confused and concerned physicians. It wasn’t until 1961 that a German physician by the name of Lenz expressed his views that the horrifying abnormalities being seen were connected to the mothers’ consumption of thalidomide during their pregnancies. Soon after, an Australian physician named William McBride independently added support for Lenz’s contention. Thalidomide was taken off the market in late 1961 as a result of the significant association between the medicine and deformed babies that Lenz and McBride had found, but it was too late to undo the harm that had already been done to an estimated 10,000 children worldwide.

![Figure 2 Phacomelic baby](image)

4. Thalidomide today

Since 1965, when leprosy treatment effectiveness was revealed, the medicine has once again found use throughout the world, including in the USA. Thalidomide is used to treat multiple myeloma, a condition where the bone marrow overproduces white blood cells, as well as erythema nodosum leprosum (ENL), a consequence of leprosy, a chronic skin and nerve illness brought on by Mycobacterium leprae. Numerous other illnesses, including as Crohn’s disease, HIV, arthritis, and some malignancies, are also treated with the medication. Thalidomide is undoubtedly a very helpful medication in the clinic.

Tragically, thalidomide embryopathy in children has returned because to the rising use of thalidomide for the treatment of ENL/leprosy in South America and Africa. This demonstrates how hazardous thalidomide still is and how closely its use must be maintained. Finding a therapeutically appropriate, non-teratogenic thalidomide analogue is one way to lessen and ultimately eliminate such terrible side effects. Therefore, creating a secure, non-teratogenic analogue depends on understanding the mechanisms generating thalidomide embryopathy.

5. Mechanism of action

Thalidomide effects’ molecular mechanisms of action are not fully known. Due to its precise control of inflammatory cytokines, thalidomide has immunomodulatory, anti-inflammatory, and angiogenic effects. TNF-α production in human monocytes is selectively inhibited by thalidomide, a result that most likely results from increased TNF-α mRNA degradation. Additionally, it has been demonstrated that thalidomide blocks nuclear factor (NF)-κB activity by preventing IκB kinase activity. A DNA-binding transcription factor called NF-kB controls the expression of genes including TNF-α, interleukin (IL)-8, and IL-12 that are involved in the immune response. Additionally, thalidomide
reduces IL-6 and IL-12 production. Inactivation of Caspase-1, which activates pro-inflammatory cytokines like IL-1, is one of the anti-inflammatory effects of this compound. Thalidomide has a strong stimulatory effect on T cells, preferentially promoting CD8+ T-cell subset proliferation. Additionally, by preferentially stimulating Th2 cytokine production and suppressing Th1 cytokine production in peripheral mononuclear cells, thalidomide is helpful in T helper cell (Th) 152immune modulation. This activity modifies the nature of T lymphocyte-dependent immune responses, increasing the production of IL-4 and decreasing the production of interferon (IFN)-γ.

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7. Phocomelia\textsuperscript{13-14}

The survivors’ phocomelic limbs are perhaps the most remarkable and defining aspect of thalidomide embryopathy. The loss of or significant shortening of the long bones of the limb (upper and/or lower) is known as phocomelia. Most people who have survived thalidomide embryopathy have some kind of limb malformation. According to current theories, phocomelia develops as a result of the early developmental loss of cells that should generate the long bones of the leg. In fact, early chick limbs exposed to X-rays develop without proximal components (humerus). Furthermore, CPS49 results in extensive mesenchymal cell death, vascular loss in the developing chick leg, disruption of limb signalling pathways, and a variety of severely shortened limbs, some of which strikingly resemble phocomelia. The idea is that after thalidomide exposure and the loss of cell populations intended to create the proximal limb elements, signalling between the AER and limb mesenchyme recovers, leaving the surviving cells to pattern distal elements under the control of the AER.

7.1. Toxicity\textsuperscript{15-16}

In addition to its well-known teratogenicity, thalidomide has side effects that can affect up to 30% and 50% of individuals, respectively, in terms of peripheral neuropathies and drowsiness. According to electrophysiologic research, thalidomide-related neuropathies more frequently present as axonal sensory injuries than motor ones. Painful paraesthesia or numbness are common manifestations of polyneuropathies, and these symptoms are correlated with cumulative total exposure to thalidomide. The discovery of a number of single nucleotide polymorphisms (SNPs) linked
to thalidomide-related neuropathy was reported by Johnson and colleagues. These results imply that the risk of neuropathies may be mediated by hereditary variables. Other less severe but more frequent toxicities include interstitial pneumonia, tremor, constipation, and rash. Hypothyroidism, hypercalcemia, and hyperkalaemia are examples of metabolic disorders, particularly in myeloma patients who also have kidney impairment.

8. The revival of thalidomide

Thalidomide was taken off the market in the UK on 2 December 1961, marking 60 years since its introduction. It was finally determined that the medication, which had been sold for five years as a remedy for morning sickness in pregnant women, was to blame for babies being born with undeveloped limbs and legs as well as other birth defects. No other drug has likely had a greater impact on the legal requirements for evaluating new medications for safety before they are administered to humans. The thalidomide tragedy led to the establishment of the Drugs and Medicine Act 1968 and the Committee on the Safety of Drugs in the UK. Thalidomide, according to many who oppose using animals in medical research, is an example of a drug that was initially found to be safe in animal testing before harming people. The real narrative shows that thalidomide did not harm so many newborns because animal testing is inefficient, but rather because the studies that were conducted were not nearly stringent enough: it was never administered to pregnant humans before being tested on animals. The idea that thalidomide was the cause of birth defects was supported when it was finally - and much too late - tested on pregnant rats and rabbits. Damage was detected in their embryos and offspring. Thalidomide caused harm to the foetus in seven other species of small animals and eight species of monkeys over the period of the next ten years.

Figure 6 The revival of Thalidomide

9. Recent advances in thalidomide therapy

9.1. HIV/AIDS

TNF-alpha, a crucial cytokine with various immunologic activities including apoptosis, inflammation, cancer, and viral replication, was shown in 1991 by Dr. Gilla Kaplan of New York's Rockefeller University to be suppressed by thalidomide. This discovery established a theoretical foundation for the use of thalidomide in this disease because it is known that persons with HIV/AIDS have higher levels of TNF-alpha. Further research demonstrated thalidomide's effectiveness against HIV/AIDS-related aphthous ulcers and the wasting syndrome at a period when traditional treatments were largely ineffective. This encouraged the establishment of "buyers' clubs," or clubs of people with HIV/AIDS, who gathered to import the drug into the US, primarily from South America, especially in New York and California. As a result, they came conflict of the US Food and Drug Administration (FDA), which aimed to regulate thalidomide distribution and supply in order to avoid a repeat of the terrible tragedy that occurred in the early 1960s. The main pharmaceutical business having a stake in thalidomide was the New Jersey-based Celgene Corporation, which was granted a patent to produce it in December 1995. There were more notable developments in the thalidomide study while discussions between the FDA and Celgene continued.
9.2. Multiple Myeloma

Cardiologist Dr. Ira Wolmer was diagnosed with multiple myeloma, an untreated plasma cell malignancy, in 1997 and was in critical condition as a result. Dr. Wolmer was given thalidomide treatment by Dr. Bart Barlogie, and his wife attempted to get in touch with him. But after another myeloma patient showed improvement, Dr. Barlogie's team at the University of Arkansas decided to set up a therapeutic trial with 84 patients who had previously received treatment but were still having trouble responding to it. They kept monitors on changes in the bone marrow, blood and urine paraprotein levels, and clinical response.

In 32% of patients, blood and urine paraprotein levels dramatically decreased, and in 81% of those who underwent evaluation, the bone marrow responded similarly. In addition, after a year of follow-up, "58 ± 5% of the 84 patients were still alive and 22.5 ± 5% of the patients remained event-free." When one considers that at the time, refractory multiple myeloma was always deadly in a couple of months, these results might not seem all that spectacular. So, after more than 30 years, thalidomide was the first chemotherapy medication to show effectiveness against myeloma. This study inspired numerous other thalidomide multiple myeloma therapy trials, which demonstrated the great effectiveness of the medication against this condition. Thalidomide has also shown effectiveness in treating a variety of skin disorders, including discoid lupus erythematosus, cutaneous sarcoidosis, prurigo nodularis, and lichen planus.

Lenalidomide (Revlimid), a structural analogue of thalidomide developed by Celgene in 2004, has increased antitumor effectiveness and a lower safety profile. Lenalidomide has shown therapeutic benefit in a few other myelodysplastic syndromes and lymphoma subtypes in addition to multiple myeloma.

9.3. Angiogenesis

In a 1994 study using a rabbit corneal micropocket test, Dr. R. D'Amato, who was working in Dr. Judah Folkman's group, found that thalidomide has anti-angiogenic capabilities. They gave anaesthetized rabbits pellets filled with bFGF (basic fibroblast growth factor, known to induce blood vessel expansion), which they subsequently divided into control and thalidomide groups. The thalidomide group had a marked reduction in this phenomenon, whereas the control group manifested the anticipated corneal neovascularization. Furthermore, they hypothesised that this anti-angiogenic impact of thalidomide was independent of its capacity to reduce production of TNFα by relating other studies to their findings. They believed it to be a thalidomide-related side effect. These results confirmed Dr. Folkman's prior thesis from 1971, which postulated that angiogenesis—a process that results in the formation of new blood vessels—was necessary for the development of cancer. He proposed that the cancer's growth could be stopped if a means could be discovered to halt this process. Perhaps because his concept was so groundbreaking, the medical world originally rejected it. Dr. D'Amato, however, continued to research angiogenesis and its connection to cancer growth as Dr. Folkman's protégé. He proved through experimentation that thalidomide and sulindac (an anti-inflammatory) together significantly reduced the growth of cancer in rabbits by 75%.

9.4. Leprosy

The latest outbreak of thalidomide began in 1964 with Dr. Jacob Sheskin, a dermatologist in Jerusalem treating leprosy patients. Erythema nodosum leprosum (ENL), which causes diffuse red nodular lesions associated with fever, arthritis, weight loss and overall malaise, might occasionally develop in these patients while they are receiving treatment. Dr. Sheskin used some thalidomide to sedate one of these people in order to relieve him, and after just four tablets, he saw a tremendous improvement. He subsequently administered ENL to six more patients, noting the same striking outcome.

Significant responses were seen in subsequent investigations involving much larger numbers of patients, and the WHO conducted a short-term, double-blind study of male lepromatous patients contrasting thalidomide with acetylsalicylic acid (ASA). This trial, which was published in 1971, demonstrated thalidomide's significant superiority over ASA in the treatment of cutaneous lesions but only moderate efficacy in the treatment of brain and interior lesions. Additional research also revealed some effectiveness of thalidomide against graft-versus-host disease and Behcet syndrome.

9.5. Anticancer properties

After thalidomide's teratogenic qualities were discovered in the 1960s, the drug's potential utility in the treatment of cancer was originally hypothesized. Researchers thought that the teratogenic effects could also serve as possible cancer-treatment strategies. However, for a number of reasons, the early clinical trials investigating thalidomide as an anticancer drug did not demonstrate appreciable effectiveness. Recently, castrate-resistant prostate cancer has had some encouraging results. 90% of patients in a phase II trial with 60 patients utilising thalidomide as an alternate anti-angiogenic drug combined to conventional chemotherapy plus bevacizumab experienced a PSA drop of at least 50%. There have been conflicting findings in other solid tumours where angiogenesis is suspected, such as ovarian,
hepatocellular, and renal cell malignancies. Thalidomide is now being investigated in numerous phase II and phase III trials as an adjunctive treatment in a range of solid tumours.

Through the System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.) programme, access to thalidomide has been restricted in order to reduce the risk of teratogenicity. Thalidomide prescribing, dispensing, and use are regulated by the programme, which requires all prescribing physicians, pharmacists, and patients to register with it and adhere to its safety rules. This approach served as a template for other situations in which medication therapy offers appealing benefits but poses deep hazards unless its distribution is properly regulated. It also reduced the possible risk for foetal harm linked with thalidomide therapy.

9.6. Myelodysplastic syndromes

Thalidomide has been used to treat myelodysplastic syndromes due to its anti-cytokine immunomodulatory and anti-angiogenic effects. Patients who require blood transfusions have shown a satisfactory response to erythromycin, although they tolerate effective (higher) doses poorly. Clinical trial dosages of thalidomide ranged from 200 to 1000 mg daily. The conflicting trial outcomes as well as the different toxicities in this situation may be explained by such dose variability.

9.7. Waldenstrom macroglobulinemia

Thalidomide is a highly effective treatment for Walden Strom macroglobulinemia when used alone or in combination with other drugs, according to phase II research. When thalidomide and rituximab were used to treat symptomatic illness in patients who were mostly untreated, Treon and colleagues found a 72% overall response rate. At the time of the best response, median hemacrit increased from 33.0% to 37.6% and median serum IgM dramatically decreased from 3670 to 1590mg/dl (p 140.004); among responders, the median time to progression was 38 months. In non-Hodgkin lymphoma, acute myeloid leukaemia, and chronic lymphocytic leukaemia, thalidomide has only weak anticancer efficacy.

9.8. Myelofibrosis

Myelofibrosis has been successfully treated with thalidomide in the past. According to preliminary statistics, cytopenias and splenomegaly have improved. 28% of patients in a study including 36 individuals and a median follow-up of 25 months showed a sustained response to thalidomide.

10. The potent anti-inflammatory properties of thalidomide

Thalidomide’s significant anti-inflammatory activity, which is made possible by the substantial engagement of both the innate and adaptive immune systems, is one of the most widely used methods of action. The FDA approved the use of thalidomide for the treatment of acute cutaneous symptoms of moderate to severe instances of this disease since its anti-inflammatory qualities were clearly proven in ENL. However, large-scale randomised clinical trials did not demonstrate the efficacy of its anti-inflammatory action in treating autoimmune disorders (such as rheumatoid arthritis, ulcerative colitis, and Crohn’s disease) and some dermatological problems.

11. Current and future challenges

Prior to marketing, pharmaceutical drugs should undergo extensive developmental testing. There are variations in species sensitivity and developmental toxicity symptoms. Important factors in drug testing include the use of a second species or a more detailed interpretation of the data in a single species (taking pharmacokinetics into account). Thalidomide will probably continue to be used in therapies until safer alternatives are developed because it is effective in the treatment of critical disorders. A persistent concern is preventing unintentional exposure of pregnant women to this medication, particularly in regions of the world where access to the medication is less limited than in the United States.

The second challenge is the creation of thalidomide analogues without the drug’s teratogenic potential but with the therapeutic benefits. If the teratogenic mechanisms of action and the therapeutic mechanisms of action are similar or even the same, finding a safe thalidomide counterpart may prove to be difficult.

For a better understanding of whether and how safer alternatives might be produced, research into the mechanisms of action continues to be a focus. To this purpose, substantial developments in molecular techniques over the previous two decades and alternative test animals have enabled special methodologies to investigate theories on the mechanisms
of action of thalidomide. Technologies like zebrafish and the in vitro whole embryo culture test have been utilised to provide information on how some things work. In the past 10-15 years, developments in omics technology and gene expression analysis (pathway analysis, SNP) have made it possible to rapidly gather data to improve our understanding of embryonic development and perturbation of important developmental processes. Hopefully, technical advancements will also make it possible to look into thalidomide-related endpoints that are less common and have less information in the literature, such as autism, mental retardation, ocular defects, and Duane syndrome.

12. Conclusion

Nearly four decades after the discovery of thalidomide's teratogenicity, it is quite likely that no one could have foreseen such a clinical revival of the drug. The horrible experience with thalidomide dramatically demonstrated the risk associated with employing its pharmacological compounds without conducting enough research and testing. It clarified the necessity of ongoing medication monitoring and control, particularly for those with teratogenic potential. Another outcome was that all pharmaceuticals had to go through official testing for teratogenic effects; as a result, the field of teratology has grown quickly. It is a polyneuropathy that worsens with time and is dose-dependent; nevertheless, stopping treatment frequently cures it. Additionally, it is undergoing promising testing in numerous additional solid and haematological cancers. Numerous other non-neoplastic illnesses also require it. Early embryonic exposure to the medication caused significant and a variety of harm never before or since seen all at once. Thalidomide will probably continue to be used in therapies until safer alternatives are developed because it is effective in the treatment of critical disorders. A persistent concern is preventing unintentional exposure of pregnant women to this medication, particularly in regions of the world where access to the medication is less limited than in the United States. The second issue is the creation of thalidomide analogues that maintain the drug's therapeutic benefits without its teratogenic potential. If the teratogenic mechanisms of action and the therapeutic mechanisms of action are similar or even the same, finding a safe thalidomide counterpart may prove to be difficult. Lenalidomide-based combinations’ clinical efficacy in treating advanced solid tumours, hematologic malignancies, and multiple myeloma patients is still being studied by researchers. Therefore, the thalidomide drug provided an important reminder of the terrible consequences that can result from a drug being introduced to the market without adequate research and clinical testing.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors have no conflict of interest to declare.

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