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Commentary

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Was thalidomide a placebo hypnotic?

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Abstract

Six decades ago the world learned that thalidomide, a seemingly non-toxic sedative and hypnotic, caused severe birth defects including the flipper-like deformity of the arms known as phocomelia. When thalidomide was tested against placebo by the trialist Louis Lasagna in 1960 (while the drug was banned from the U.S. marketplace), he found the 100-mg dosage equivalent to placebo, as well as greatly inferior to the 200-mg dosage, in producing sleep. Even as these findings were made known, a 100-mg dose of thalidomide was in general use as a sleep aid for pregnant women. It appears that unbeknownst to themselves, an untold number of pregnant women around the world who were prescribed thalidomide incurred the risks of a teratogen in return for the benefits of a sugar pill.

Keywords

placebo, clinical trial, efficacy, harm, thalidomide

A pharmaceutical favourite

In 1962 the world learned that thalidomide, a supposedly non-toxic drug, caused severe birth defects including the flipper-like deformity of the limbs known as phocomelia. The drug was one of a multitude that poured into the marketplace during the 1950s, before any requirement for testing against placebo existed. It was in direct response to the thalidomide crisis that this requirement was instituted in the United States in 1962.[1] However, the efficacy of thalidomide itself was not an issue at that moment; only its safety was. Perhaps the time has come to look into the reputation for efficacy that drew people to thalidomide to begin with. In 1955, only a few years before thalidomide arrived on the market, Beecher made the argument that many seemingly effective drugs are actually indistinguishable from placebo,[2] and we have reason to believe that thalidomide as commonly used was just that – a placebo, albeit a dangerous one.

In the United States thalidomide was barred from the market by the vigilance of a single officer of the FDA, Frances Kelsey – a circumstance that kept casualties far lower than they would otherwise have been. In West Germany, by contrast, the drug was integrated into daily life.[3] Branded as Contergan, thalidomide was not only sold over the counter as a sedative and hypnotic but combined with aspirin, even given to children in the form of 'cinema-juice' when the parents left for the movies.[4] Whatever the potion did or did not do for the children, evidently it put the minds of the parents at ease. Two factors suggest that Contergan often served as a placebo. First, when consumers use a single remedy for all manner of ills it is probably a placebo, and Contergan was used for everything from migraine to asthma, from nerves to the common cold. Second, the placebo effect thrives on novelty,[5] and the glow of novelty enveloped Contergan, which had emerged from the laboratory only recently. While we are accustomed to thinking of the placebo effect as a benefit without risks or harms, here was a case in which it enhanced the appeal of a dangerous drug.

Beecher's classic article 'The Powerful Placebo' (1955) belongs to the mid-century movement to reform the very procedures of clinical investigation by introducing stringent safeguards against bias, including placebo controls and double blinding, as well as statistical validation of observed differences. A year before, one of Beecher's junior collaborators, Louis Lasagna, published just such a study of sleep drugs, a study considered by some the first randomised clinical trial in psychiatry.[6,7] (Significantly enough, certain drugs and dosages were found to be equivalent to placebo.) Thalidomide underwent no such trials. That is, it was spared the one and only kind of test that could reliably distinguish it from placebo. Grünenthal, the patent holder, simply distributed Contergan to a number of doctors, asked for their impressions, and buried the unfavourable reports.

Usage spread from West Germany around the world, propelled less by actual evidence of efficacy than by

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impression, the unacknowledged power of the placebo, and thalidomide's engineered image as a benign alternative to barbiturates.[8] Sold under dozens of brand names, thalidomide would have been a wonder drug indeed if it had lived up to its own mythology. In the UK thalidomide, branded as Distaval, was advertised as an ideal sedative and hypnotic, not only highly effective but so safe that a child who accidentally swallowed an overdose would not be harmed. Such an ad appeared in the pages of *BMJ* even as letters reporting signs of the coming disaster appeared as well. One can only imagine the halo thalidomide would have worn in the United States had it been cleared for the market. Obviating risk/benefit analysis because it supposedly had no risks, thalidomide gave rise to such exaggeration that its usage may or may not have had something to do with its actual properties.

Placebo dosage

How much thalidomide was to be prescribed? The ad in *BMJ* recommended two or three doses of 25 mg as a 'daytime sedative' and between 50 and 200 mg as a night-time hypnotic, as if Distaval offered a sliding scale of remedies for the troubled consumer. The 50–200 mg range matches the range at which thalidomide was judged an effective hypnotic in German trials without placebo or other controls.[9] However, trials without controls are notoriously unreliable; drugs that appear effective in preliminary testing or indeed regular clinical practice[10] may and often do appear quite otherwise when tested against placebo under conditions of minimal bias.

If only because the placebo effect of giving a drug like thalidomide is not zero, it is one thing to submit it to uncontrolled observation and another to compare it to placebo in a trial with appropriate checks on bias. In his 1958 report of uncontrolled trials of the first antidepressant, Kuhn portrayed imipramine as a miracle drug[11]; 3 years later, a team of investigators presciently cautioned that 'The placebo success rate appears sufficiently high to require antidepressant drug trials of considerable size in order to provide convincing evidence of drug differences'.[12] Also questionably effective when tested against placebo was the most widely used prescription drug in the United States at the time: meprobamate (Miltown). In principle, this anti-anxiety drug offered a chemical solution to the fundamental problem of life in what some have called an age of anxiety. However, a careful review of studies of the celebrated drug after it was already in use by millions found little if anything to differentiate it from placebo for most patients.[13]

Yet as important as it is to distinguish drugs from placebos, we would err to suppose that a medication is either one or the other. The fact is that these categories are not mutually exclusive, and that at a certain dosage, a drug itself – even thalidomide – may be a placebo.

Inasmuch as thalidomide was prescribed to pregnant women as a sleep drug, let us consider its use as a hypnotic In the absence of rigorous tests of the drug, a clinician who kept to the lower end of the recommended range of 50–200 mg (perhaps in the hope of avoiding the side effects that dogged this purportedly innocuous agent) might inadvertently prescribe it at placebo level. The prescription of a calming agent at such a level would not be a thing unknown. 'Many effective anti-anxiety drugs were prescribed both knowingly and unknowingly at placebo dosages – for example, 5 mg of chlordiazepoxide (Librium); 2 mg of diazepam (Valium); 5 mg of prochlorperazine (Compazine)'.[5] After all, the effect of a medication at placebo level does not necessarily vanish and may be considerable. A placebo itself can act like a hypnotic. In a comparative study of hypnotics published in 1956 Lasagna specifically noted a 'surprisingly high placebo rate'.[14] In a 1970 study initially involving 150 subjects with insomnia of at least a year's duration, fully 100 were removed when they fell asleep within 30 min and slept for more than 6 h on a placebo. They were deemed 'placebo reactors'.[15]

Ironically, the first pre-market trial of drug against placebo on record appears to be that of thalidomide.[16] Shortly before the drug's devastating teratogenic effects became known, and while its sale was barred in the United States, Lasagna gave patients in the Johns Hopkins Hospital either 100 or 200 mg of thalidomide or placebo, in random order, as a hypnotic. While 200 mg of the drug outperformed placebo by a wide margin, the lower dosage proved equivalent to placebo, yielding only 6 min more sleep – a difference neither statistically nor clinically significant. Added Lasagna, 'It is . . . somewhat disappointing to have failed to show even a trend in favor of the 100-mg doses over placebo'.[9] (In his seminal study of hypnotic agents in 1954, Lasagna uncovered the same pattern in chloral hydrate; only doubling the 'customary' dosage distinguished the old reliable drug from placebo.) Moreover, chronically poor sleepers slept *over 2.5 h longer* and fell asleep *70 min faster* on the 200 mg than the 100 mg dosage of thalidomide. These chasmal differences, coupled with the indistinguishable performance of 100 mg and placebo, strongly suggest that the drug was indeed an ineffective hypnotic at the 100 mg level.

Because thalidomide was withdrawn from the market in Europe less than 18 months after the publication of this study, there was little time for a literature to form around it, and so we are left to rely on Lasagna – an accomplished trialist and experienced investigator of hypnotics in particular – for our estimate of active and inactive dosages of the now-infamous drug. As it happens, though, a Canadian study of thalidomide against placebo appeared in the interim between Lasagna's study and the withdrawal of thalidomide in late 1961. Although this study used patients whose lengthy sleep (over 8 h on placebo) seems to have muted differences between drugs tested and placebo, 100 mg of thalidomide once again performed notably poorly. Those given 100 mg now fell asleep 5 min faster and slept 4 min longer than the placebo group. It is on the strength of these unimpressive findings, to which no tests of statistical significance are applied, that the authors rate two 50-mg tablets of thalidomide as 'more active' than two placebo tablets, in contrast to Lasagna.[17] Arguably, however, a medication trivially superior to placebo is tantamount to placebo. As Lasagna once said, 'How important is

it to know that a drug is "microscopically" better than no drug at all?'[18]

With all this in mind, let us assume, then, that thalidomide taken at a dosage of 100 mg as a hypnotic was a placebo. Were patients actually prescribed 100 mg of thalidomide, or even less?

Placebo in practice

They were. A 1958 paper in *BMJ* notes that the drug K 17 (i.e., thalidomide) 'has been extensively used on the Continent' as a hypnotic at a dosage of 50–100 mg.[19] The authors' finding that K 17 has an anti-thyroid effect at 200 mg – the level at which it appears active – might have served to reinforce these low dosages.

In essence, placebo levels of thalidomide were grandfathered into British practice. The first publication to sound the alarm on thalidomide, a December 1960 letter to *BMJ* by a GP in Aberdeenshire, reports that four patients complaining of paraesthesia took 100 mg of Distaval (i.e., thalidomide) for sleep and that the author has found it 'a most effective hypnotic'.[20] That this dosage was standard is suggested by a September 1961 report in the same journal on 13 cases of neuropathy following use of Distaval as a hypnotic; the authors note that most of the patients took the 'usual' dose of 100 mg.[21] Five months later, a letter from two doctors in Plymouth reported that a woman who gave birth to a deformed infant (who died within minutes) took 100 mg of thalidomide nightly for the first 5 months of her pregnancy.[22] Investigating a cluster of ten deformed infants born in Stirlingshire in 1961–62, Speirs found that in four cases the mother took 100 mg at night and in a fifth, three 25 mg tablets per day; in two additional cases, the mother took between 100 and 200 mg.[23]

The placebo dosage seems to have travelled with the drug. In a Canadian case reported in 1962, a woman hospitalised during early pregnancy was given 100 mg of thalidomide each evening for 3 days and 200 mg on the fourth. She gave birth to a deformed infant.[24] And in a 1963 study that identified ten thalidomide infants born in British Columbia, in the three instances where the mother's bedtime dose is specified, two of the doses are 100 mg and the third 50 mg.[25]

In the United States, even while the drug was kept off the market, over a thousand doctors conducted 'trials' of thalidomide (branded as Kevadon) which consisted of handing samples to patients, including pregnant women. Presumably many gave the drug at the conventional dosage of 100 mg, although we will never know because records were haphazard at best. We do know, however, that the first to investigate–Ray Nulsen, a Cincinnati obstetrician friendly with the medical director of the drug's American licensee, William S. Merrell–began giving his patients 25 mg but soon 'scaled . . . up to fifty milligrams and one hundred milligrams'.[26] The study reported under Nulsen's name in the *American Journal of Obstetrics and Gynecology* in 1961, which was ghostwritten by Merrell[27] and has the tone of a sales brochure for Kevadon, does not use placebo controls and does not even mention the word 'placebo', but does assert that thalidomide is perfectly safe even if it should pass through the placenta.[28] Nulsen appears linked to more cases of thalidomide birth defects than any other doctor in the United States.

Drug vs placebo

But was 100 mg of thalidomide teratogenic? 'A single dose of 100 mg of thalidomide during the "sensitive" period, which for woman appears to be between 28 and 42 days after conception . . . may cause severe injury to the fetus'.[29] Indeed, in two documented cases in Canada, women gave birth to deformed infants after taking 50 mg doses of thalidomide for insomnia in early pregnancy.[30]

It appears, then, that unbeknownst to themselves an untold number of pregnant women incurred the risks of a teratogen in return for the benefits of a sugar pill. If these patients were relieved by a placebo dosage of thalidomide – and it is hard to see why doctors would regularly prescribe a dosage that patients found unsatisfactory – then they were not in need of thalidomide in the first place; they were in need of a good conductor of the placebo effect. There were other ways for doctors to give reassurance and cultivate the placebo effect than by providing thalidomide. However, because of its reputation for efficacy, thalidomide's dependence on the power of the placebo – at least at lower dosages – seems to have gone unrecognised even after Lasagna's study. Certainly the arrival of drugs like thalidomide did not drive the placebo effect out of existence but gave it an important new field of operation. Doctors at the time who may have imagined that new drugs would render the placebo effect obsolete or insignificant were sadly, and in this instance dangerously, mistaken.

At a historic conference in 1946, Harry Gold, a pioneer of the testing of drug against placebo, argued that to prescribe a placebo 'would be much more legitimate . . . than the practice of loading patients with barbiturates and other sedatives as is the common practice in situations in which the physician is hard pressed for something to prescribe'. Within a decade, thalidomide entered the scene as an all-purpose sedative and alternative to barbiturates. In effect, it served as a pharmaceutical placebo. Gold was highly critical of this sort of hybrid, contending that clinicians would be well advised to administer pure placebos like lactose instead of placebic drugs, or doses of drugs, that can easily deceive doctor and patient alike. 'That danger is real', he warned.[31] In the case of the thalidomide disaster, the danger transcended anything the world had known.

Over the decades since its withdrawal from the market following this catastrophe, thalidomide has seen a revival. This unforeseen renaissance began with Sheskin's 1964 discovery that in each of six unselected cases, thalidomide given as a sedative resolved not only the symptoms but the objective signs of complications of leprotamous leprosy. By contrast, prior placebo treatment over 48 h had no effect on the condition of any of the patients.[32] The inference that the drug was responsible for the stunning improvement was confirmed by a much larger placebo-controlled,

double-blind study by Sheskin, in which 91% of patients with lepra reactions improved on thalidomide, against 27% on placebo.[33] Since then, thalidomide has shown promise as an anti-inflammatory and anti-angiogenic agent, and has been used to treat complications of HIV and, in combination with other drugs, multiple myeloma. Indeed, at this moment thalidomide has 'remarkably many clinical applications'.[34] Does this mean we have returned to the open-ended list of the drug's uses in West Germany in 1960? It does not, because current applications of thalidomide do not free-ride on the placebo effect.

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References

1. Temin P. *Taking Your Medicine: drug Regulation in the United States*. Cambridge: Harvard UP; 1980.
2. Beecher H. The powerful placebo. *JAMA* 1955; 159: 1602–1606.
3. Taussig H. The thalidomide syndrome. *Sci Am* 1962; 207: 29–35.
4. Sjöström H, Nilsson R. *Thalidomide and the Power of the Drug Companies*. Harmondsworth: Penguin; 1972.
5. Shapiro A, Shapiro E. *The Powerful Placebo: from Ancient Priest to Modern Physician*. Baltimore, MD: Johns Hopkins UP; 1997.
6. Lasagna L. A comparison of hypnotic agents. *J Pharmacol Exp Therap* 1954; 111: 9–20.
7. Shorter E. A brief history of placebos and clinical trials in psychiatry. *Can J Psychiatry* 2011; 56: 193–197.
8. Ironically enough, thalidomide was marketed in many countries in combination with secobarbital as Noctosediv.
9. Lasagna L. Thalidomide – a new nonbarbiturate sleep-inducing drug. *J Chron Dis* 1960; 11: 627–31.
10. Greiner T, Gold H, Cattell McK et al. A method for the evaluation of the effects of drugs on cardiac pain in patients with angina of effort. *Am J Med* 1950; 9: 143–155.
11. Kuhn R. The treatment of depressive states with D-22355 (imipramine hydrochloride). *Am J Psychiatry* 1958; 115: 459–464.
12. Höhn R, Gross G, Gross M et al. A double-blind comparison of placebo and imipramine in the treatment of depressed patients in a state hospital. *J Psychiatric Res* 1961; 1: 76–91.
13. Laties V, Weiss N. A critical review of the efficacy of meprobamate (Miltown, Equanil) in the treatment of anxiety. *J Chron Dis* 1958; 7: 500–519.
14. Lasagna L. A study of hypnotic drugs among patients with chronic diseases. *J Chron Dis* 1956; 3: 122–133.
15. Brown W. A comparative study of three hypnotics: methyprylon, glutethimide and chloral hydrate. *Can Med Assn J* 1970; 102: 510–511.
16. Healy D, Mangin D, Applbaum K. The shipwreck of the singular. *Soc Stud Sci* 2014; 44: 518–523.
17. Ban T, Schwarz L. Comparative clinical study of three hypnotic drugs. *Can Med Assn J* 1961; 84: 1259.
18. Lasagna L. The controlled clinical trial: theory and practice. *J Chron Dis* 1955; 1: 353–367.
19. Murdoch J, Campbell F. Antithyroid activity of N-phthalyl glutamic acid amide (K 17). *BMJ* 1958; 1: 84–85.
20. Florence AL. Is thalidomide to blame? *BMJ* 1960; 2: 1954.
21. Fullerton P, Kremer M. Neuropathy after intake of thalidomide (Distaval). *BMJ* 1961; 2: 855–858.
22. Willman A, Dumoulin J. Distaval (thalidomide) and foetal abnormalities. *BMJ* 1962; 1: 444.
23. Speirs A. Thalidomide and congenital abnormalities. *Lancet* 1962; 279: 303–305.
24. Rodin A, Koller L, Taylor J. Association of thalidomide (Kevadon) with congenital anomalies. *Can Med Assn J* 1962; 86: 744–746.
25. Larsen A, Hole L, Mackenzie B. Congenital deformities associated with the use of thalidomide during pregnancy, British Columbia, 1961–62. *Can J Pub Health* 1963; 54: 505–508.
26. Vanderbes J. *Wonder Drug: the Secret History of Thalidomide in America and Its Hidden Victims*. New York, NY: Random House; 2023.
27. McFadyen R. Thalidomide in America: a brush with tragedy. *Clio Medica* 1976; 11: 79–93.
28. Nulsen R. Trial of thalidomide in insomnia associated with the third trimester. *Am J Obstet Gynecol* 1961; 8: 1245–1248.
29. Taussig H. Thalidomide. *Circulation* 1963; 27: 321–322.
30. Ling G, Dolman C, Boyd J. Drug-induced (thalidomide) malformations. *Can Med Assn J* 1962; 87: 1259–1262.
31. HG W, EF D. The use of placebos in therapy. *NY State J Med* 1946; 46: 1718–1727.
32. Sheskin J. Thalidomide in the treatment of lepra reactions. *Clin Pharm Ther* 1965; 6: 303–306.
33. Sheskin J, Convit J. Results of a double blind study of the influence of thalidomide on the lepra reaction. *Int J Leprosy* 1969; 37: 135–146.
34. Vargesson N, Stephens T. Thalidomide: history, withdrawal, renaissance and safety concerns. *Exp Opin Drug Saf* 2021; 20: 1455–1457.