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Research Article

The Early Use of Blinding in Therapeutic Clinical Research of Neurological Disorders

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Abstract

We sought to identify early uses of blinding in therapeutic clinical trials of neurological disorders by multiple search methods. A 1784 report by Benjamin Franklin and others described the evaluation of the use of Mesmerism to treat neurological and other syndromes including headache and epilepsy, using blindfolds and screens. This report demonstrated the usefulness of blinding to reduce bias in clinical research, yet despite this early discovery, blinding was not widely accepted or routinely used until the 20th century. Blinded clinical trials began to be used for various neurological syndromes in the 1950s, sporadically at first and then increasing in frequency in subsequent years. The reason for this delay is unclear, but we propose several hypotheses.

Keywords:
neurology; research; clinical trial; blind; placebo

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Introduction

Background

Blinding/masking the allocation of subjects to treatment groups in therapeutic clinical research is now a well-established method to reduce the chance of bias and erroneous conclusions about safety or efficacy.[1] A single-blind design, where subjects are unaware of their group assignment, can lessen the influence of the placebo effect on outcomes. A double-blind design, where the investigators are also unaware of subject group assignment, can minimize observer expectation bias. Both the placebo effect and observer expectation bias are likely to be significant confounders in therapeutic clinical trials of neurological syndromes, because outcomes of interest to both patients and investigators often include a substantial subjective component. Despite the benefits of blinding, the general timeframe for its introduction to therapeutic clinical research of neurological disorders, however, is unclear. We sought to identify early examples of the use of blinding for this purpose.

Methods and Materials

Books and articles covering the history of neurology and the history of clinical research were reviewed for the likely timeframe of introduction of blinding.[1,2,3,4,5] We searched PubMed, Google Scholar, and Project MUSE in early 2011 with combinations of the terms “neurology,” “treatment,” “blind,” and “placebo.” During initial searches we identified 10 neurological disorders that appeared to be the most likely candidates for the earliest use of blinded trials, and repeated the searches substituting the name of each of these disorders for the term "neurology." We then reviewed articles from these searches from the 1950s and 1960s to find the earliest examples of blinding for each disorder, and reviewed the references of the included articles. For an estimated timeline, PubMed was then searched using the limit of "clinical trial" with the terms of each of the 10 neurological disorders, “treatment,” and “blind” to determine the number of publications matching these search criteria for each decade after the 1950s; all the matching studies reported in the 1950s are discussed below. After the 1950s, only the initial reports for the 10 neurological disorders that had not already been reported are discussed below.

Results

We found one report from 1784, then a handful of reports from the 1950s, with a subsequent accelerating pace of reports as discussed below and estimated in Table 1.

The first example that we could find of the use of blinding in a therapeutic clinical research study of any medical condition, which also included neurological disorders, is the 1784 report by Benjamin Franklin and others describing the evaluation of the techniques of Franz Anton Mesmer.[6] Mesmer was a German physician who gained fame and a popular following for his unorthodox method of healing in the 1770s. Hypothesizing the existence of an imperceptible fluid, which he called “animal magnetism,” that connected every element of the universe, including human bodies, Mesmer argued that disease resulted from an imbalance of this fluid within the body. Cures required the redirection of the fluid through the intervention of a physician who used his hands as a conduit through which the fluid could pass from the universe into a patient’s body. Mesmer claimed his method could treat many conditions, including neurological ones like headache and epilepsy, because the animal magnetism insinuated itself into the nerves and “may itself cure nervous disorders.” Mesmer’s treatments took place in a dim room with “a circular vat, made of oak & raised a foot… from which protrude bent, flexible metal rods.” The patients sat in rows around the vat, with one of the metal rods given to each person to apply directly to the afflicted part of his or her body. In the corner sat a piano, on which music was played, sometimes

Table 1. PubMed returns for the searches "(condition name) treatment blind" with the limit of clinical trials.

Disorder	1960s	1970s	1980s	1990s	2000s
Headache	12	114	427	928	1333
Parkinsonism	9	101	173	238	376
Multiple Sclerosis	5	20	141	237	451
Cerebral Palsy	1	4	11	29	69
Stroke	1	34	310	839	1416
Neuropathy	1	4	73	176	194
Muscular Dystrophy	1	4	31	31	35
Epilepsy	7	40	155	313	307
Sciatica	1	10	21	18	29
Amyotrophic Lateral Sclerosis	0	3	23	41	48

with additional sounds and voices. The combination of light, music, and incantations from Mesmer resulted in a form of hypnotism that became popularly known as "mesmerism."

Mesmer's process was powerful enough to cause some patients to go into convulsions and lose consciousness. He achieved impressive results with many of his patients and inspired a devoted following, including among members of the French court. As Mesmer's fame spread, though, controversy followed.

Many physicians questioned the effectiveness of his techniques and the very existence of animal magnetism. King Louis XVI of France, who was not quite as taken with Mesmer as other members of his court, commissioned the French Academy of Sciences to investigate Mesmer and his therapeutic claims. The Academy appointed several prominent citizens to the committee, including Benjamin Franklin, who was living at the time in Passy near Paris, as well as Antoine Lavoisier, Joseph-Ignace Guillotin, and other medical and scientific luminaries of France.

To test the veracity of Mesmer's claims, the commission set up a series of experiments. In an early experiment, seven patients known to be sensitive to animal magnetism were brought to Franklin's home for a demonstration. There "they were magnetized in front of him & in front of the other Commissioners… and felt nothing." They also magnetized Genevieve Leroux, a nine year old who was subject to convulsions and "a disease similar to what is called chorea sancti Viti." Based on their initial findings, the commissioners asked, "Why did this agent produce no effect upon Genevieve Leroux, who was in a perpetual state of convulsions?"

The next experiment was done on one of the members of the commission itself. Struck by a migraine, the unnamed commissioner was magnetized by Mesmer's disciple M. Deslon for thirty minutes. "One of the symptoms of this migraine is excessive coldness in the feet. M. Deslon brought his foot close to that of the patient, the foot was not warmed, the migraine lasted its usual length, & the patient after sitting down by the fireplace felt the salutary effects that heat has always provided, without having felt during the day or the next night any of the effects of magnetism." At this point, the commissioners had already begun to draw early conclusions, articulating their understanding of one component of the placebo effect, which is the wish of the patient to please their physicians.

"Let us take the standpoint of a commoner, for that reason ignorant, struck by disease & desiring to get well, brought with great show before a large assembly composed in part of physicians, where a new treatment is administered which the patient is persuaded will produce amazing results. Let us add that the patient's cooperation is paid for, & that he believes that it pleases us more when he says he

feels effects, & we will have a natural explanation for these effects; at the least, we will have legitimate reasons to doubt that the real cause of these effects is magnetism."

They then discussed the role of skepticism on the placebo effect.

"These facts permitted the Commissioners to observe that magnetism has seemed to be worthless for those patients who submitted to it with a measure of incredulity; that the Commissioners, even when those with jittery nerves deliberately focused their attention elsewhere, having been armed with philosophical doubt that ought to accompany every examination, did in no way feel the impressions felt by the three lower-class patient, & they must have suspected that these impressions, even supposing them all to be real, followed from an anticipated conviction, & could have been an effect of the imagination."

From this idea, they designed their next set of experiments using blinding to "determin[e] up to what point the imagination can influence feelings & establishing whether it can be the cause of all or part of the effects attributed to magnetism."

The Commissioners chose next to examine a woman known to be sensitive to Mesmerism: for her, "it was only a question of protecting her from her imagination, or at least getting it out of the way." The Commissioners blindfolded her so they could observe her reactions to the magnetization experiment without her knowledge, and they observed that the phenomena no longer corresponded to the places where the magnetism was directed. They then removed the mesmeriser, M. Jumelin, but told the woman that she was still being magnetized. "The results were the same, even though nothing was done to her from near or afar; she felt the same heat, the same pain in her eyes & ears; she also felt heat in her back & loins." They then signaled to M. Jumelin to magnetize her over her stomach. This time "she felt nothing, the same thing with her back. Sensations diminished instead of increasing. The headache remained, the heat in the back & loins came to an end." Based on this experiment, they wrote, "It was natural to conclude that these sensations, true or false, were determined by the imagination."

After this landmark initial experiment using blinding of both true treatment and placebo, the Commissioners replicated their findings with additional subjects. They found the same results in similar experiments "on a blindfolded man & a woman with eyes uncovered; it was clear that their answers were determined by the questions that were posed."

They now sought to demonstrate a lack of effect with the opposite approach, "as facts are more conclusive than reasoning & provide more striking evidence." The Commissioners wanted to test how magnetism would work when the imagination was not at work. They set up an apartment with rooms adjoined by a door. The door itself was removed and covered with paper. They then invited a seamstress "whose sensitivity to magnetism was known" to come over but did not tell her that they had another test for her. The woman was seated in a chair by the paper-covered doorframe. The Commissioners stood in the other room while one magnetized the seamstress through the paper. For half an hour, they watched as she was magnetized, with no apparent effect on the seamstress. "During all this time, Mlle. B** was conversing cheerfully; asked about her health, she answered freely that she felt quite well," read the report. From this experiment, the Commissioners concluded that "Ones sees therefore that the imagination alone produces all the effects attributed to magnetism; & when the imagination does not act, there are no more effects."

These tests proved to the commissioners that animal magnetism did not exist. Instead, it was "imagination" that likely caused the effects seen with treatment, presenting, in clear and prescient language, their understanding of what we now call the placebo effect:

"This agent, this fluid does not exist, but as chimerical as it is, the idea of it is not new…Magnetism therefore is only an old error. This theory is being presented today with a more impressive apparatus, necessary in a more enlightened century; but it is not for that reason less false. Man seizes, abandons, takes up again the error that gratifies him. There are errors which will be eternally dear to humanity. How many times has astrology not reappeared upon the earth! Magnetism draws us to return to it. The desire has been to link it to the celestial influences so as to make it more captivating & attract men with the double hopes that touch them most, the hope of knowing their futures, & the hope of prolonging their days."

The Commission's report, while discrediting Mesmer in the scientific community, did not diminish popular interest in Mesmerism. Magnetic healing continued to be practiced in the 19th century and even experienced resurgence in England in the late Victorian era.

While the report did not state who came up with the idea of blinding, there is evidence that Lavoisier primarily designed the experiments.[7] Lavoisier and Franklin continued to collaborate and discuss many scientific issues until Franklin's death in 1790. Four years later, in 1794, Lavoisier was beheaded by a machine popularly known by the name of their fellow commissioner, Guillotin.[7]

Despite the commission's widely-disseminated findings and methods,[7] not to mention the fame of the Commission members, the next instance of blinding in a clinical study for a neurological disorder does not appear to have come for another 169 years. In 1953, a report from Los Angeles, California, of a trial evaluating ergot derivatives for "hypertensive headaches" reported that the drug's effect was "compared with those obtained with placebos... of the same size, color, and shape... for many months, the placebos being given at the same intervals."[8] The author reported good efficacy of the study drug, and stated that they felt that the effects seen were not "psychogenic" due to "the absence of complete relief in any patient receiving placebos." The single investigator of the study was not blinded. This study appears to be the first of what became a slowly increasing use of blinding in neurology trials.

In 1954, a second single-blind study was reported from a private neuropsychiatric practice in Milwaukee, Wisconsin, evaluating the treatment of headache with ergotamine-caffeine suppositories.[9] Aware of the placebo effect, the authors stated that "An objective, non-directive approach was used in handling these patients...as the author was aware of the possible psychological effect brought about by the use of suppositories in anal erotic patients who frequently have headaches as a presenting complaint. This factor was carefully evaluated in the procedure and was checked with placebo suppositories." It appears that the placebos were not given to concurrent control patients, but as a check on patients responsive to active treatment, "In instances where excellent results were obtained, the placebo suppositories were substituted." When placebo medication was used, "patients invariably called soon after starting on the new medication and complained that the new suppositories were no longer effective and that the headache had returned or no longer was relieved by the suppository."

A third single-blind study was the 1954 report of a four-way crossover study of artane, panparnit, hyoscine, and placebo for Parkinsonism.[10] In this study, "All medicaments, including placebo, were prepared in identical capsules which were not distinguishable in appearance... by the use of the placebo any tendency to respond because of the psychologic factors involved in treatment rather than the specific pharmacologic properties of the drug could also be evaluated."

Blinding in an epilepsy trial made its appearance in the 1955 report of a single-blind study of five drugs for "petit mal epilepsy," where each group was crossed-over with placebo.[11] That same year a report appeared of the first double-blind neurology trial we could find of a new compound for Parkinsonism.[12] In an effort to reduce the placebo effect, all subjects were given "inert tablets resembling" the study drug, and "Patients who had responded to previous therapy but were no worse on the inert tablets could not be regarded as having derived benefit from active treatment. In order to minimize the dilution of the final figures they were eliminated from the trial. The one patient from the not responded group who was better on the inert tablets was also eliminated for similar reasons." The investigators gave the remaining subjects the study drug and graded their responses. They then divided the "improved" group in two, and described their method to achieve the double-blind. One investigator divided the group with a written index: "This index, together with correspondingly coded bottles of tablets, was handed to a third party, who dispensed the tablets. Whether a given patient received active or inert tablets was unknown to either the clinician or the person dispensing the tablets." Interestingly, in their discussion the authors gave a rather mixed review of "the double-blind test," stating that "Methods of statistical control, although highly desirable, should not interfere with the clinician's freedom of action" while at the same time stating that "The essential requirement is that neither the clinician nor the patient shall know whether the tablets are active or inert." These opposing statements perhaps suggested the tension of recognizing the need for blinding while also feeling discomfort at giving up control during the course of the trial.

In 1956, a double-blind study was reported of cortisone therapy for headache after pneumoencephalography.[13] In this study, the investigators performed the "complete" technique of removing all the cerebrospinal fluid and replacing it with an equivalent quantity of gas. In analyzing their data, they found that, "When the patients were divided into those having psychogenic conditions and those having organic diseases, it was found that those in the psychogenic group responded best to the placebo." They did not state how the psychogenic versus organic determination was made. These results led them to conclude that "regardless of the treatment used, those patients whose symptoms are entirely on a psychogenic basis will respond erratically." Commenting on the purpose of blinding in their study, they discuss the observer expectation bias and their attempt to mitigate it: "It is exceedingly difficult to make a consistently accurate evaluation of a factor as subjective as a headache... An attempt was made in this study to set up a situation in which the usual criticisms of an evaluation of the effectiveness of a form of medication could be avoided…The natural and unavoidable tendency of observers to be influenced by knowledge of the treatment given each patient was avoided by distribution of the potent medication and the placebo in a random manner as unknowns." This was the earliest study we found to clearly articulate the principle of the observer expectation bias.

In 1957, a study was reported of the use of digestive enzymes for multiple sclerosis that was, for the most part, double-blind.[14] "The A. H. Robins Co. helped in setting up a double blind experiment by supplying Entozyme and also placebo tablets identical in appearance to the active preparation. These were prescribed as Entozyme A and Entozyme B and the clinician evaluating the patients neurologically did not know which one contained the medication until the study had been going on for approximately twenty months." The total study length was 24 months, and the authors did not state why the blind was broken prior to study completion.

It is probable, although rarely stated, that patients in these early studies were not informed that placebos were used. A 1958 report of a crossover study of benactyzine in patients with "violent tempers" and Parkinsonism stated that "No patients ever discovered that some of the tablets they were receiving were blanks."[15] It was not stated, however, how the authors knew this to be true. Knowledge of the placebo effect on both safety and efficacy outcomes was clearly expressed: "Once again this minor investigation shows that inert substances produce the same effects as drugs with pharmacological properties; they are useful to patients who believe they will get benefit from them, and they cause undesired side-effects; and the side effects may be present only with the inert tablets and not with the actual drug."

In the same issue of the British Medical Journal, another report appeared of a new compound tested with a placebo-controlled crossover design in patients with post-encephalitic Parkinsonism.[16] This report was notable for being the first we found that described the effectiveness of the blinding procedure for both subjects and investigators, while also hinting of early struggles and ethical issues encountered during blinded trials:

"It was decided to stop all current therapy for a day before the trial began. When this decision was taken it was not expected that withdrawal symptoms would be so troublesome. Actually they were severe in three cases... One of the three patients threatened suicide unless he was put back on his previous treatment. In other cases these symptoms may have prejudiced the patients against the new tablets... There was a slight difference in appearance between the two tablets, so that some of the doctors knew which was genuine and which dummy on the first day. It is doubtful if any of the patients recognized the difference in appearance between the two tablets... In two cases withdrawal symptoms were severe, and the dummy tablet had to be discontinued and previous treatment reinstituted."

In 1962, there was a single report of two double-blind, placebo-controlled trials of carisoprodol for cerebral palsy, with one trial for "athetoids" and the other for "spastics."[17] The language of this report demonstrates the continued development in the understanding of the placebo effect and observer expectation bias by investigators:

"By sheer suggestion, these children felt better, and their functioning at all levels improved, when they were on either the drug or the placebo... In nearly every case there was a favourable response to the mere giving of a tablet, because of the expected and hoped for improvement... We feel this must be partly the psychological effect of extra attention... The trial illustrates the difficulties of carrying out a double-blind trial on a group of severely handicapped children where all those concerned - child,

parent, physiotherapist, speech therapist, occupational therapist and teacher - are actively looking for improvement, and the first two, at least, are emotionally involved... The net result appears to be that merely giving tablets, with the added increased attention of assessment and record-taking, unleashes a psychological urge to improve. One wonders if some factor in the everyday treatment of these children has failed to stimulate this urge."

Similar to one of the studies discussed above, the authors of this study are critical of the design they chose, or at least of the additional difficulty entailed: "Doubt can be felt about the assessment of a drug with the rigidity of a double-blind trial, where the timing, dosage and length of observation cannot be varied... A double-blind trial lasting several months is not an easy undertaking, if in a sufficiently large number of children, accurate records are to be kept and no untoward events are to occur. These final arguments rather beg the question as to the value of the overriding verdicts given by short double-blind trials and suggest that some regard must be given to clinical judgement over a long period." These studies had followed an open-label trial of the same drug in the same patient populations, where benefit had been found. Perhaps the diminished enthusiasm for blinding was influenced by the refutation of their previous positive findings in the unblinded study.

In 1963, carisoprodol was studied in a double-blind, placebo-controlled trial of multiple types of musculoskeletal disorders, including patients with sciatica, which appeared to also use randomization: "Patients were admitted to the trial sequentially and were allocated to treatment with the drug or placebo by a system of randomized selection, adhered to throughout."[18] A double-blind stroke trial was also reported in 1963 of intravenous plasmin for thrombolysis of presumed ischemic stroke, a decade prior to computed tomography.[19] To avoid enrolling patients with hemorrhagic stroke, the subjects were "treated within seventy-two hours of the onset of symptoms... In every case, the cerebrospinal fluid was crystal clear and... the blood pressure on admission was below 180 mm Hg... to minimize the risk of inadvertently including cases with hemorrhagic infarction in the series." Also in 1963, another report appeared of a double-blind trial of a vitamin B preparation and glutamic acid to prevent peripheral neuropathy in patients receiving high-dose isoniazid for pulmonary tuberculosis.[20]

A 1964 report described a double-blind trial of Duchenne muscular dystrophy patients given a mixture of nucleotides and nucleosides intravenously and intramuscularly.[21] The authors noted the difficulties of assessing a therapy for this condition, due to the “enthusiastic response of a parent, distressed by the progressive disability seen in his child.” In this study, the placebo group was given oral calcium lactate pills, but they were "not given inert intravenous infusions and intramuscular injections as it was felt that this was hardly justifiable; a similar plan was adopted by the Streptomycin in Tuberculosis Trials Committee of the M.R.C. (1948); it was discussed and approved by Bradford Hill (1963)... The patients were assessed in pairs, and, in case local bruising might reveal which patient had received the intravenous therapy, both children had their arms covered with dressings." This interesting reference to epidemiologist and statistician Bradford Hill, and the landmark randomized clinical trial he participated in, which is considered the first modern trial of this type, suggests the early intersection of the clinical trial method advances of randomization and blinding, which now dominate therapeutic research.[1,22]

In 1971, a double-blind study was reported of isoprinosine for amyotrophic lateral sclerosis.[23] The authors stated a common ethical concern with the use of placebo control groups, "Since the disease is progressive and the pathology presumably irreversible, moral issues were involved in a double-blind study. If some participants did not receive the medication, they would not derive benefit from the study." To address this, the investigators enacted a compromise solution: "The study was, therefore, set up that any patient who felt that the medicine he was taking was ineffective would be placed on the other one after a minimum of ninety days. This guaranteed that each participant would receive the true medication if he continued to get worse. The patient would not know whether, on a given trial, he had been receiving a placebo or the isoprinosine, but he would be sure he had had a trial of isoprinosine one of the two times.” The study ended up analyzing only the first drug period because the “motivation of the patients differed in the two trial periods. When a patient was given the first drug, he was not biased either way. It was to his advantage to be very critical. If he was not getting worse or was improving, he should obviously continue with the medication. If he was certain that he was getting worse, it was to his advantage to change to the other pill as soon as possible... Motivation in the second trial was quite different. The patient had already rejected the first pill, thinking that it must have been the placebo.

There was no advantage in giving up the second pill quickly, since the patient usually felt that this was the real medicine, in contrast to the hope that it was in the first trial." Subjective, but not objective, improvement was seen "in two patients, both receiving placebo, and the degree of improvement noted was impressive. One decided he no longer needed a cane and began brushing his teeth again. He was convinced the medicine caused a miracle. The other patient gave a long list of aspects in which he thought he had improved within two weeks after changing from isoprinosine to the placebo. He noted increased neck strength, speech improvement, better walking, and so on. He clearly had not improved in any of these parameters, and the examiners were surprised by the strength of his conviction which did not correlate with the obvious facts. These 'improvements' are easy to understand in terms of the great psychological stress the patients were under and the hope that a potentially new medicine offered."

There appeared to be an accelerating rate of publication of therapeutic clinical trials using blinding for the 10 neurological conditions included in our search after the 1950s (Table 1).

Discussion

In 1940, Israel Wechsler, one of the most respected neurologists of his time, reported the results of an unblinded and uncontrolled trial of vitamin E for patients with amyotrophic lateral sclerosis.[24,25] He reported that "11 out of the 20 cases showed varying degrees of improvement. Two patients seem to have recovered, 4 showed marked degrees of improvement and 5 moderate degrees." One subject stands out:

"Case 4. - L. G., male, age 36, began to have weakness of the legs in March, 1939. For 1 year before the onset of the illness he lived on a restricted diet poor in vitamin E because of gall bladder disease. Weakness of the hands soon followed and generalized fibrillations appeared in June, 1939. When first seen on January 27, 1940, he had marked spasticity in both lower extremities, universally increased deep reflexes with bilateral Babinski reflexes and clonus, generalized fibrillations, weakness of the shoulder and arm muscles and almost complete paralysis of the hand muscles, atrophy of the supra- and infraspinati, deltoids, pectorals and all the small muscles of the hands. Treatment was begun in February and has continued to date. The fibrillations have practically disappeared, walking is somewhat improved and some power has returned in both thumbs. The case may be regarded as definitely arrested and somewhat improved."

It is now known that Case 4 was Lou Gehrig, by whose name the disease is commonly known in the United States. Despite the reported results, other sources confirmed that his disease was progressive until it eventually killed him in 1941.[24] It seems that the temptation to believe and the desire to see positive results are hard to overcome for even the most seasoned investigators in their field.

In 1994, Noseworthy and others reported their analysis of a novel feature of a trial of several immunomodulatory drugs for multiple sclerosis: "Each clinical assessment was performed consecutively by both a blinded (evaluating) and unblinded (treating) neurologist at 6-month intervals throughout the study."[26] They found that the unblinded neurologists found a treatment benefit on their clinical evaluations at multiple time points, whereas the blinded neurologists did not find evidence of benefit. This study provides evidence that observer expectation bias can lead to erroneous conclusions of a clinical trial in neurology.

If Benjamin Franklin and his group understood the usefulness of blinding for therapeutic clinical research, and clearly communicated their findings, why did so much time pass until its reintroduction in neurology? The cause of this is unclear, and we can only offer conjecture.

While not stated in the report, there is reason to believe that Franklin's commission saw their mission as disproving, rather than proving, the efficacy of Mesmer's treatments. Franklin, for one, wrote seven days after the commission was created:

"As to animal magnetism, so much talk'd of, I am totally unacquainted with it, and must doubt its existence till I can see or feel some effect of it. None of the cures saide to be perform'd by it, have fallen under my observation; and there being so many disorders which cure themselves and such a disposition in mankind to deceive themselves and one another on these occasions; and living long having given me frequent opportunities of seeing certain remedies cry'd up as curing everything, and yet so soon after totally laid aside as useless, I cannot but fear that the expectation of great advantage from the

new method of treating diseases will prove a delusion. That delusion may however in some cases be of use while it lasts. There are in every great city a number of persons who are never in health, because they are fond of medicines and always taking them, and hurt their constitutions. If these people can be persuaded to forbear their drugs in expectation of being cured by only the physicians's finger or an iron rod pointing at them, they may possibly find good effects tho' they mistake the cause."[7]

Physicians with ideas for new treatments, however, were the usual investigators in clinical trials, and were understandably interested in proving what they already believed to be true: that the new treatment was beneficial. Could it be that rigor of scientific evaluation, including blinding, naturally increases when trying to disprove what one believes to be false, than in trying to prove what one believes to be true?

Throughout the 19th century, as alternative medical systems like homeopathy, Thomsonism, and phrenology vied for medical dominance in the United States, mainstream doctors put forth streams of studies and arguments disproving these systems.[27] Oliver Wendell Holmes, for instance, called homeopathy a “kindred delusion” and set about systematically taking down each of its beliefs and tenets.[28] Could it have been that mainstream medicine in the 1950s finally felt confident enough in their marginalization of alternative healers that they were willing to admit the possibility of their own susceptibility to bias?

Perhaps the explanation was simply the accelerated pace of the introduction of new treatments, which likely led to the common occurrence of conflicting results produced by multiple studies of the same question. Exasperated with contradictory information, investigators may have increased the rigor of their trials in hopes of finding more reliable answers to therapeutic clinical questions.

Possibly the growing influence of statisticians in clinical research played a role, as this group had a deep understanding and ability to quantify experimental bias.[2] The cooperative movement in clinical research that developed during, and particularly after, World War II may also have contributed. Perhaps simply having groups of investigators collaboratively developing protocols led to proposals with increased rigor including blinding.[2] Another possible explanation is that a regulatory framework was developing during the mid-twentieth century that may have imposed blinding on reluctant investigators.[2] This could explain some of the critical comments about blinding in several of the articles we found.

We believe that the studies we found are among the earliest therapeutic studies using blinding for neurological conditions. Headache, in particular, was likely to have been one of the earliest uses of blinding for any medical condition, as it is almost entirely a subjective disorder with strong psychological interplay. However, our research has several limitations. We relied on databases rather than hand searching of all clinical trial reports of the several centuries in question, and because the indexing on these databases is inconsistent and incomplete, we could have missed even earlier blinded studies. Our understanding of the reason for the timing of the development of blinding is limited, primarily by the brief mentions of its justifications in the reports we found. Our quantification of the time course of blinded therapeutic clinical trials for the 10 neurological conditions we explored is likely representative, though not a complete picture, of the accelerating pace of publications of interest.

Conclusions

We found evidence that blinding in therapeutic clinical research for neurological disorders was discovered and well-reported in the 18th century, but did not appear to enter modern trials until the 1950s, with increasing use in each subsequent decade. The cause for this delay is unclear. Perhaps, among so many other things, the neurologist Hughlings Jackson was correct when he said: “It takes 50 years to get a wrong idea out of medicine, and 100 years to get a right one into medicine.”[29]

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