

## PLACEBO THERAPY / IATROTHERAPY ( A Literary Review)

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### Introduction

The term "*Iatotherapy*" was coined by Feinstein<sup>48</sup> in 1972 while discussing the role of placebo in clinical practice in his famous work "Clinical Judgement". He holds the view that the curative effects of the placebo are due to the doctor's personal influence upon the patient's psyche and hence use of placebo as therapy is doctor induced, therefore, the term "*Iatotherapy*" should be preferred to placebo therapy. Whatever terms we use for the role of placebo therapy, it is known to the profession since antiquity in the form of charlatans or magic cure, although recognised later. Since the days of Hippocrates, it has been an accepted fact that medicines alone do not cure. Hippocrates put it as "*Nature performs her duty*". John Hunter (1728-1793) had testified the effects of placebo in a war field while treating the injured warriors. The Viennian physician, Joseph Skoda (1804-78) was so much impressed by the effects of placebo that he went on to denounce the theory of medical nihilism : i.e. *that the medicines are useless in the cure of a disease*. Houston. W.R.<sup>60</sup> (1938) emphasized the placebo effect of the "*doctor himself*" as the therapeutic agent in the article, "*The doctor himself as a therapeutic agent*" in Am. Int. Med - 11-1416-25. Although, similar thoughts have been reflected by the medical philosophers off and on, but the real momentum gained acceleration since the publication of "*Principles of Medical Statistics*"<sup>32</sup> in Lancet, Lond. 1937 by Sir Austin Bradford Hill and "*Introduction to Statistical Methods in Clinical Research*" in 1945 in which he introduced controlled clinical trials. Clinical trials carried out after the 50s studied the controls and found the effects of placebo. The medical literature got flooded up in two decades with amusing information about placebo-effects. The cure/relief rates achieved by the placebo became so much so that the medical philosophers and scientists like G.R. Forrer<sup>33</sup> (1964) went on to say that "*It is right to suspect*

*any report of research into a new drug which shows that it cannot relieve more than 40% of the patients*". Another scientist, Feinstein (1972) went on to say, "*there are many scientists in the academic or government advisory positions today who seem to prefer 5% improvement rate which is scientifically "pure" to a scientifically "impure" rate of 68%*". The effects of placebo were so overwhelming that one medical philosopher Schindel went on to suggest that the summarised placebo literature should form an indispensable part of undergraduate education in medicine.

It is in this context that the author has tried to bring forth the excerpts/literature on the topic in this article which may be of interest to the students, clinicians and research workers.

### Placebo : Meaning/definition of

It will not be out of place if we start right from the term "*Placebo*" itself instead of going outright into the details of our topic. To begin with, let us have a glimpse of what the word "*Placebo*" means and how it has cropped up in our medical literature.

In literature, "*Placebo*" has been defined etymologically, *placebo (Plaesi bou) (litrug) as vespers for the dead -xiii (Anensh) First word of the antiphon to the first Psalm in the office; "Placebo - Dominio in regions Vivorum (Psalm Cxiv-9)<sup>1</sup> "I shall please the lord in the land of living"*.

Placebo - "*a substance having no pharmacological effect but given to a patient or subject of an experiment who supposes it to be a medicine*".<sup>2</sup>

Placebo - "*A medicine given to humour or gratify a patient rather than to exercise any curative effect*".<sup>3</sup>

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Placebo - "an ineffective drug given solely to satisfy a patient's desire for medication".<sup>4</sup>

Placebo - "is the term used to describe a dose (or a pill) given to the patient not because it will have any definite action but because the patient will not be satisfied unless he or she received some active treatment".<sup>5</sup>

"Placebo are really little doses and symbols of faith. It does have, in fact, remarkable effect on a man when he knows that regularly three times a day, in water, after meals, he must take a particular dose. Many tests have shown what extraordinary effect can be produced by an inert pill plus belief and indeed, the effect may be so potent as to nullify trails of a new drug".<sup>6</sup>

On going through few of the definitions given above, we find that not only literature but a few of the medical dictionaries also express "Placebo" as merely a placebo i.e. "a substance of no established clinical/therapeutic efficacy". But, we find in Peer's Medical Encyclopaedia that "Placebos are more than an inert substance and that they can produce some results/effects of clinical importance".

## Placebo Effects

Now, let us see what authors of medicine, say about its effects:

"Evidence that placebo can have marked physiological effects have been afforded by demonstrations of their ability to heal certain kind of tissue damage, ... it is worth noting that a patient's expectation have been shown to effect the physiological responses so powerfully that they can reverse the pharmacological action of drugs".<sup>7</sup>

"Even if the source of pain is independent of the patient's emotional condition, like a surgical wound, the placebo can give relief".<sup>8</sup>

"In one study of patients with bleeding peptic ulcers, 70% showed "excellent results" lasting for over a period of one year when the doctor gave them an injection of the distilled water and assured them that it was a new medicine".<sup>9</sup>

"The Placebo effect is a most important therapeutic weapon in the hands of the modern physician as it utilizes the power of expectation".<sup>10</sup>

"Despite the fact that Chaucer connected placebo with psychopancy and Quincy's Lexicon in 1781, called placebos a common place medicine, the placebo effect is as potent today as it was during medical antiquity".<sup>11</sup>

"Placebo can show peak effects, carry over effects, cumulative effects and sometime habituation and addiction. They may also show varying efficacy and the response may be either positive or negative. They can exhibit all the attributes of an active preparation".<sup>12</sup>

"Many studies have shown again and again that symptoms of quite serious diseases can be greatly relieved in 30-40% of cases by Placebo and oddly enough that they are more effective in relieving severe symptoms than mild ones".<sup>13</sup>

"Placebo can produce observable side effects like rashes or a change in gastric secretion, but in general they are more effective in relieving subjective symptoms, and the high success of placebos have mostly been recorded in treatment of such symptoms as seasickness or anxiety, cough, post-operative wound pain, headache & in the common cold".<sup>14</sup>

"A large number of different conditions are seen to be susceptible to placebo therapy; these include post-operative pain, pain in the carcinomatosis, angina pectoris and rheumatoid arthritis".<sup>15</sup>

The foregoing excerpts about the opinion of the authors are suggestive of the fact that placebos are not merely an inert substance to please the patient but they may prove clinically effective. However, one author, Alan Norton<sup>14</sup> is of opinion that it alleviates subjective symptoms more readily than the objective ones.

The careful study of placebo effects during controlled clinical trials have verified that placebo therapy possesses both the positive and negative effects. However, the negative effects were found to be meagre ones in comparison with the positive effects. Some of these findings of different research workers are quoted below.

### Positive effects

- "Placebo in treatment of Angina Pectoris : 37.5% of the patients showed great or moderate improvement in their symptoms on a pla-



cebo, a higher proportion than any of the 16 drugs then in use for treating this condition"<sup>15</sup>.

"In 1950, Wolf, studied the gastric mucosa of Tom, a human subject with a large gastric fistula. He concluded that placebo effects could modify the pharmacological action of the active drugs or cause physiological responses to inert agents that simulated the active substances"<sup>16</sup>.

"In 1954, Lassang and his colleagues compared the efficacy of an injection of saline with that of 10 mg. of morphine for the relief of post-operative pain. In 12 patients who required two doses, 92% were relieved by morphine and 58% by placebo. In those requiring six doses, 61% were relieved by morphine & 40% by placebo"<sup>17</sup>.

"In a controlled trial of mild hypertension by Medical Research Council, England, the fall of blood pressure noticed by bendrofluzide 10 mg. daily or propranolol upto 240 mg. daily & identical placebo recorded showed reduction in systolic by 24 mm of Hg & diastolic by 13 mm by active drug against half of it by placebo. The difference at 3 months treatment between two groups was 10.5 mm over 5.5 mm of Hg by active drug & placebo respectively. The difference in a year showed not much difference"<sup>18</sup>.

"In a controlled trial in Psychiatry, the response of the placebo group was noted as much positive as received by the drug receiving group"<sup>19</sup>.

"In a double blind study carried out between 1972 & 1975 in Hong Kong, the effect of Placebo maintenance treatment of narcotics addicts on 50 patients was found to be more effective than those 50 patients who were on methadone - maintenance dose; After 10 weeks of treatment, only 10% of controls needed treatment against 76% of the drug group. At the end of 3 years, only 2% of control turned up for the treatment against 56% of the methadone subjects"<sup>20</sup>.

"In a study of a "Comparative trial of four preparations in the treatment of Gastric Ulcer" Berndt & Gutz found that preparations consisting of natural or modified liquorice combined with antacid produced a regression rate of about

70%, Gefranil, a rate of about 60% and placebo about 50%".<sup>21</sup>

### Negative effects

Placebo can produce observable side effects like rashes or a change in gastric functions but in general they are more effective in relieving subjective symptoms.

A few of the excerpts are mentioned below :

- In an experiment by Gruber (1956) the effects of placebo in comparison to that of tablets of d-1- propoxyphene 50 mg, acetylsalicylic acid 325 mg and codeine phosphate 32.5 mg; minor side effects were equally obtained and were directly proportional to the quantity of the dose of the active drug or the placebo.
- Godfrey (1973) reported that placebo effects upon exercise induced asthma was negligible against intravenous injection of saline and atropine which gave 83% relief.
- In a double blind controlled trial of an antibiotic in minor respiratory illness, Rothi S.B. has reported that side effects in G.I. tract were observed equally in active and placebo group. Complications appeared in 2.7% of placebo group against the active group.<sup>22</sup>

### Evolution of Placebo Therapy

The evolution of Iatrotherapy dated back to the prescientific era when magic cure was the common method of treatment of the sick. Since the days of "Thoth" and "Imhotep" of Egyptians and Greeks, placebo has been used either in the form of spell or as a drug with spell. The whole of the Mesopotamian medicine was magic spellbound. Even in the beginning of the scientific era, Hippocrates denounced that "*Nature performs her duty*" and confirmed thereby that in many of the cases medicine was not the instrument of cure. Later on, the effects of placebo was confirmed by John Hunter accidentally. Joseph Skoda was so much influenced by the effects of placebo that he proposed the hypothesis of medical nihilism. The word placebo in medicine became a subject of study since the publication of an article in 1936 in the Lancet by Sir Austin Bradford Hill. Some of



the excerpts on the topics are noted below.

*"The art of medicine, as opposed to the science of Medicine was developed long ago prior to the advent of scientific Pharmacology, the healer depended on art for his cures. Fortunately, for him, patients usually recovered despite such medicines as "flesh of vipers, spermatic fluid of frogs, horns of deer and animal excretion".<sup>30</sup>*

*In Egyptian medicine, the patron diety of Egyptian physicians was Thoth. The Ebers papyrus of Egyptian says "he gives to the physicians skill to cure."<sup>25</sup>*

*Isis was even invoked as a provider of magical cures.<sup>26</sup>*

*Giving of drugs alongwith some magical spell began during the Egyptian era and the empirical use of a number of drugs started diminishing as the effects of a few only in relieving the ailments was noticed.<sup>27</sup>*

*Like Egyptian medicine, Mesopotamia medicine was also magic and religious, and medicine was practiced by Priests. They were classified into three classes viz. (a) Diviners - who interpreted omens and foretold the course of disease, (b) Exorcists - who drove out the evil spirits which caused disease, and (c) Physician proper - who performed operations and administered drugs.<sup>28</sup>*

*Even during the best of the scientific approach in Greek medicine, the priestly practice of magic persisted on.<sup>29</sup>*

*Hippocrates studied the pattern of medical practice and noted that even without medicine there was healing. He noted the effects of placebo and went on to say "Nature performs her duty".<sup>23</sup>*

John Hunter (1728-1293), a Scottish surgeon is said to have testified the effects of placebo during a war field where he was attending to the injured warriors. Once the decoction/oil used for applications to the wound of the injured fell short and finding nothing in hand, John Hunter boiled oil whose efficacy was nil and applied it to the injured with suggestion that this was a new drug and to his horror he found that the rate of healing was much more than the schedule decoction officially recognised.

*Chaucer connected Placebos with psychophancy & Quincy's Lexicon in 1781 called placebo a common place medicine.<sup>31</sup>*

The word *placebo* was first used in connection with therapy at the end of the eighteenth century. In a Dictionary from 1787 placebo was said to be a *common place method or medicine, calculated to amuse for a time rather than for any other purpose*. And in Fox's New Medical Dictionary from 1803, it was defined as "*an epithet given to any medicine adopted more to please than to benefit the patients*".

Skoda (1804-78) was the exponent of the *Therapeutic Nihilism* prevailing at that time.

Evan W. and Hoyle. C. are said to have noted the effects of placebo in Angina pectoris and Houston W.R. (1983) emphasized the placebo effect of the doctor himself as the therapeutic agent in the article "*The doctor himself as a therapeutic agent*" in Am. Int. Med.11- 1416-25.

Following the publication of Sir Austin Bradford Hill's article in Lancet in 1936 followed by publication in a book form and its subsequent editions, there has been an increase in the use of statistically designed clinical trials in Medicine and the use of placebo became essential in a controlled clinical trials. Consequently, the effects of placebo were noted and given due importance in Medical Science. The controlled clinical trials were introduced by him in 1945.

During the decade (1950-60) many workers like Lassanga, Gruber, Wolf, Leslie, Beecher, Joyce and Knowels worked on placebo.

During (1960-70) Hinkoff, Schapira, Belinit and other's works were supplemented by Blackwell, Feinstein and Godfrey.

## How Placebo Works ?

How does the placebo work? This is a mystery and one is little farther forward in invoking "Suggestion" or more psychoanalytical effects.

*"The Placebo acts by symbolically supplying for the adult that which during infancy was supplied by the mother. That is milk".<sup>33</sup>*



*"It is likely that this mechanism is operative in part in any enthusiastically presumed therapeutic regime. It has been shown experimentally that the threshold of pain perception may be greatly raised by suggestion"*<sup>34</sup>

Chaucer - connected placebo with Psychopancy.<sup>35</sup>

*"Experiments have shown that bodily mechanism are responsive to the impulse arising in the cortex; impulses which are originally set in motion by language of symbols"*.<sup>36</sup>

*Even Freud wrote that "Expectations coloured by hope and faith is an effective force with which we have to reckon in all our attempts at treatment and cure"*.<sup>37</sup>

#### **Effects of change of colour, shape of placebo and cost of placebo**

Effects of placebo have been noted to change with change of colour, shape and form in which they were administered. Some of the observers have come out to express their opinion that all the effects of placebo are depending upon what is known as suggestion therapy used directly or indirectly by the physicians in rapport with their patients. Individual image of the physicians also have some influence in the effectiveness of the placebo depending upon the analogy of faith healing. The faith of the patient in the skill of the individual physician enhances the acceptability of the formulation prescribed by the physician. Some others think that in the modern society where economic status plays a role in image forming the high costs charged even for placebo helps the effectiveness of the placebo in the positive direction.

A few of the quotations are given below :

*"The high costs greatly potentises its effect"*.<sup>38</sup>

*"There is some evidence that symptoms respond particularly to green and depression symptoms to yellow tablets"*.<sup>38</sup>

Blackwell (72) reported an interesting class experiment for medical students who were given placebos consisting of either one or two pink or blue capsules. The students were conditioned to expect sedative or stimulant effects, but not told

which to expect with which capsule. 66% of those given the blue capsule felt less alert than 26% on the pink ones. Similarly, 72% on the blue capsules said that they felt more drowsy versus 37% on the pink.

Placebo effects are influenced by dose, in a study comparing d-1-propoxyphene 50 mg., acetyl salicylic acid 325 mg, codeine phosphate 32.5 mg, and placebo. Subjects were given either one or two tablets. The same minor side effects were seen on both active drugs and on placebo. And, there were more complaints when two tablets were been given than one, whichever regime was used (Gruber, 1956).

*"Expectation, Symbolism or Notion. Suggestion - stimulation interest involvement and participation"*.

*It is also worth noting that a patient's expectation have been shown to effect the physiological responses so powerfully that they can reverse the pharmacological action of drug.*<sup>39</sup>

*When a patient is in presence of the doctor, the contemporary image of the physician as a healer and authority figure is reinforced by certain culturally established symbols.*<sup>40</sup>

*Man has built in recuperative powers which can be seen at works when a cut heals without attention. This process can be speeded up by suitable stimulation. It seems that "suggestion" is an essential therapeutic instrument overdue for recognition.*<sup>41</sup>

*The major expected outcome of the interest called the "placebo effect in medicine" or the "Hawthorne effect" in the behavioural sciences, is increased satisfaction, satisfaction derived, both directly from the quality of interaction and indirectly from the effects of the involvement in identification of one's own needs and participating in one's own treatment.*<sup>42</sup>

*The Placebo effect is a most important therapeutic weapon in the hands of the modern physician as it utilizes the power of expectation.*<sup>43</sup>

*Witness the success of witch doctors and other present day practitioners of bizzare forms of healing, who add little more than suggestions to Nature's healing process.*<sup>44</sup>



The shamam, like the physician, tries to cure the patient by correcting the cause of illness. The shamam's role may involve aspects of physician, magician, priest, moral arbiter and representation of the group world view. His success often depends more on his ability to mobilize the patients hope, restore his morale and again his reacceptance into his social group rather than on Pharmacology.<sup>45</sup>

Hopelessness may retard recovery or even hasten death; for example the death rate of the aged shortly after admission to the mental hospitals is unduly high and with these people often no adequate cause of death is found at autopsies; raising the possibility that some of these deaths are due to lack of desire to live.<sup>46</sup>

It would be better to define the placebo effect as the therapeutic effect caused by the doctor-patient relationship :- Freud and co-workers have shown that the patient factor and the physician factor interact, and that the physician's confidence in the treatment he prescribes also has some importance.<sup>47</sup>

"Placebo effect" should be replaced by iatrotherapy as suggested by Feinstein.<sup>48</sup>

"Controlled therapeutic trials have shown that the patient doctor relationship greatly influence the therapeutic response".<sup>49</sup>

## Who Responds to Placebo

35% of the physically ill and 40% of mentally ill respond to placebo ..... Extrovert, sociable, less dominant, less self confident, more appreciative of their teaching, more aware of their autonomic function and more neurotics respond well to placebo.<sup>50</sup>

People who respond to placebo are equally of either sex and of average intelligence, but they tend to be older, more anxious and more preoccupied by their own bodily process than those who do not react.<sup>51</sup>

## Benefits of Placebo

"It is often wrongly, implied that Placebo responses are unquantifiable and unimportant".

"The belief that the patient has a part to play in the curing role should be encouraged. The placebo effect could be utilized as the Shamam used it, and it may in modern practice halt the use of and reliance on Drug Therapy".<sup>52</sup>

"Many new drugs and treatment which seem to present excellent results at first, later can prove disappointing as in the enthusiastic early hopes for "Cortisone treatment".<sup>54</sup>

"The wide spread popularity of the non-medical healers in the 20th century testifies to the fact that the physician needs to be more than a skilled technician if he is to cure successfully".<sup>55</sup>

As a control in scientific evaluation of drugs, placebo is of great benefit.

## Demerits

"The symbolic meaning of medication may not always be favourable as some patients fear and distrust doctors".<sup>56</sup>

The cost of placebo effect would in the long run be lack of confidence in the medical profession.

## Ethics and Placebo

### Placebo vs Semi - Placebo

"Those who have qualms of conscience about using pharmacologically useless medicines tend to use semi-placebos, such as vitamins in the vague hope that these may do some good. This is wrong for thereby the prescriber deceives himself as well as the patient, If deception, there must be, it must be whole hearted, unflinching and efficient".<sup>57</sup>

It seems a pity that those who use placebos are being obliged to the Drug Regulatory authorities to use substances such as ampicillin and chlordiazepoxide as the placebos of the modern era. The human aspect of the patient-doctor relationship and medical ethics also belong to the art of medicine and these topics must be considered specially in connection with analysis of the therapeutic decisions. Controlled therapeutic trials have shown that the patient-doctor relationship greatly influence the therapeutic response, and the ethical implication must be considered when the effects of new drugs are assessed in such trials.<sup>59</sup>



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