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Editorial

Role of Medical Ethics, Epidemiological Studies and Team-based Learning Approach in Medical Education in Improving Clinical Practice and Patient Care

Medical ethics is a systematic application of a set of moral principles that impart value to clinical practice and research. Once followed, these principles fulfill the expectations of the community and society (who is served and has diverse social and religious values) from the medical professionals within medical institutions. This approach consists of application of atleast seven basic principles: non-maleficence, beneficence, respect for person's autonomy, justice, proportionality, health maximization, efficiency, which are nonhierarchical (meaning no one principle routinely "trumps" another) and mutually exclusive, and may help one to fulfill their ethical obligations towards their patients or the subjects to be cared (1).

It appears that such principles in current usage in healthcare ethics are of self-evident value and can be clearly applied. It is generally held that these principles can be applied, even in unique circumstances to provide guidance in discovering our moral duties within those situations. For example, the principle that the physician "ought not to harm" any patient is on its face convincing to most people. The idea that the physician should develop a care plan designed to provide the most benefit to the patient in terms of other competing alternatives, seems both to be rational and self-evident. Further, before implementing the medical plan, it is now commonly accepted that the patient must be given an opportunity to make an informed choice about his or her care. Finally medical benefits should be dispensed fairly and proportionately so that people with similar needs and in similar circumstances will be treated with fairness, an important concept in the light of scarce resources such as solid organs and bone marrow transplants, expensive diagnostics, procedures and medications.

Intuitively, in the face of no other competing claims, we have a duty to uphold each of these principles (a *prima facie* duty). However, in the actual situation, we must balance the demands of these principles by determining which carries more weight in the particular case. Moral philosopher, WD Ross, claims that *prima facie* duties are always binding unless they are in conflict with other stronger or more stringent duties. A moral person's **actual duty** is determined by weighting and balancing all competing *prima facie* duties in any particular situation (2). Since principles are empty of contents, the application of the principle comes into focus through understanding the unique features and facts that provide the context for the case. Therefore, obtaining the relevant and accurate facts is an essential component of this approach to decision making (1).

The first paper in the present Issue of the Annals by Dr. Shridhar Sharma discusses some of the ethical dilemmas and their solutions when applied in dealing with the health of the subject in question, specially when this is an area of mental health (3). It has been argued that most ethical principles are still evolving and posing problems in every health care facility and are a challenge to every physician.

In this context, the Mental Healthcare Act (MHCA), 2017 is a historical intervention which, if implemented well, can prove to be a game-changer. Two specific features stand out. First, the act adopts a rights-based approach. It places obligations on mental health services and prescribes procedures that ensure that mental health professionals offer treatment in accordance with a person's will and preferences. The law provides for the right to make advance directives– a person may state how they wish to be treated (or not) in the eventuality that they have a mental illness and cannot make decisions for themselves at that point of time. Additionally, the law recognizes an entire gamut of rights relating to confidentiality, access to medical records, protection from cruel treatment and non-discrimination based on social markers, including sexual orientation. These rights are to be protected at all times when a person is undergoing mental healthcare and treatment as an admitted patient or otherwise. Two other Papers by Balhara *et al* (4) and Saimbi *et al* (5) are related to mental health issues of another kind, e.g. behavioural addiction and flower phobia and suggest the measures to treat them and how institutions like AIIMS, Delhi are making efforts to manage cases of behavioural addiction.

Following the multidisciplinary approach of the journal, the four other papers deal with three important aspects affecting the treating physicians (6-8) and medical educators (9). A number of research and review papers have shown the role of vitamin D (8) and gene therapy (6) in a variety of diseases including cardiovascular– myocardial infarction and stroke healing, diabetes mellitus– regeneration of beta-cells with pancreatic islets of Langerhans and psychosomatic disorders (7) as discussed in some of these papers are a few examples to cite. As the readers will find the claims for the success of these treatment modalities are many but the hard evidence in their favour is much meager. Regarding vitamin D, it is a misnomer. It is not a true vitamin (an amine as the group name suggests), but a hormone, because it can be synthesized endogenously through ultraviolet exposure to skin. This sunlight triggered reaction produces cholecalciferol in skin; liver then convert it to calcidiol (25-hydroxycholecalciferol/vitamin D2) which is then is converted by kidney to calcitriol (1, 25-dihydroxycholecalciferol/vitamin D3) – the active physiological form of the D-hormone in the body. It is, thus a sacosteroid hormone that exists in three forms, that are sequential metabolites produced by hydroxylases.

As a fat soluble hormone, vitamin D hormone metabolites have a special mechanisms for delivery in aqueous blood stream– endogenously synthesized forms are carried by a binding protein, whereas dietary forms are carried within lipoprotein particles. These two different carrier pathways lead to distinct biodistribution for endogenously-derived versus supplement-derived vitamin D hormones and may be the reasons for discrepancies observed when compared the physiological effects and various organ system studied after giving vitamin D hormone/supplementations. Same logic can also be applied when discrepent results are obtained when one studies physiological role of genes in growth and development as opposite to when gene therapy approaches are used for healing or regeneration of cells after they are lost due to degenerative or injurious nature of the disease process.

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Evolving Ethical Issues in Health and Mental Health

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ABSTRACT

Ethics is the Science of morals in human conduct. However, ethics and morals are not same. The ethics is based on certain principles, which include 'Respect for Person and Justice'. This principle is not in total conformity with Hippocratic tradition, where Physician is given a 'Position of Paternalism'. The basic idea of 'justice' is that all human beings are equally valuable. Similarly, the principle of liberty is the right to self determination but what is the use of this right that can not be fulfilled. These basic principles are evolving and are constantly posing problems in every health care institution and are a challenge to every Physician.

Keywords: Ethics, morals, justice, autonomy, informed consent, ethics in health research.

Introduction

Ethics is the science of morals in human conduct, a moral principle or code (The Oxford Dictionary). However, ethics and morals are not same (1). Ethics go far beyond moral beliefs and values. Ethics is sustained by a purpose higher than ones own self interest. So the word 'ethics' encompasses the entire spectrum of good human conduct. Ethics as a branch of philosophy, deals with distinctions between right and wrong - with the moral consequences of human actions. Traditionally, ethics in medicine is guided by Hippocratic Principles where physician is placed in a position of "paternalism" (2, 3). The patient had no say on the issues related to treatment and all related circumstances like diagnosis. Physician was considered a confident and guardian of the secrecy of patients and Physicians' duty was to keep secrecy of knowledge and procedures followed in the management of patient's diseases.

Historically, the limitation in research was the classic 'do no harm principles'. During the last two millennium, science has grown tremendously and there are certainly changes in value system in society. However, ethics has not kept pace with the growth of science. It has been said that Science does not advance linearly in an orderly fashion but it jumps in different directions according to the scientific developments and sometimes the thinking is completely different than that of existing knowledge. Kuhn (1962) in his classic work, "the structure of scientific revolutions" calls these new ways as "thinking paradigm" (4). These new paradigms act as scientific lanes, as they capture the imagination of scientists, channelize their investigations for a time, until they in turn are substituted for a new paradigm. Thus, science advances and regenerates itself. These new scientific paradigms constantly influence our health care system. Concomitant with this growth in our knowledge, there is

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*The modified and updated paper is based on NAMS Golden Jubilee Lecture delivered at the Maharashtra Institute of Mental Health and BJ Medical College, Pune on April 26, 2011.

another global development, which is taking place in the field of medical ethics. This new development was earlier synthesized by Ramsey (1970) in another classic work "The Patient as Person" (5). He advanced the proposition that "the physician-patient relationship" was lopsided towards the side of the physician and proposed that it should be the patient and not the physician, who should dictate the terms of the relationship in all the substantive matters. His proposition, completely opposed to the earlier Hippocratic tradition which dictated medical ethics. In fact, in the West, these ideas ushered in an 'ethical revolution' of bioethics (4-7). In the Hippocratic tradition, the physician was not only the healer and technician but also a custodian and guardian of the secrets of the patient (8, 9). In return for this power over the patient, the physician would undertake not to take advantage of the relative weakness of the patient and never to compromise his honour or that of his profession and respect the intrinsic value of human life. With the passage of time regretfully these values have slowly changed and diluted the ethical guidelines. A critical look on available ethical guidelines would reveal that today these refer more to professional etiquettes rather than the question of moral values. However, ethics go far beyond moral beliefs and values. Unlike moral values, the ethical codes are higher but constantly influenced by the changing sociopolitical situations and scientific advancements at a given time (5).

The basic principle in ethics includes "Respect for Person and Justice". This principle is not in total conformity with Hippocratic tradition, where Physician is given a position of paternalism (2, 3). The basic idea of 'Justice' is that all human beings are equally valuable. Yet it is a fact that people differ from one another and that such differences often justify unequal access to health care. Then there are other elements of justice which include equality, liberty and freedom. The principle of equality states that differences between individuals do not justify unequal access to healthcare due to their ability to pay, social status, cultural affiliation, education, place of residence and gender, etc. Similarly, the principle of liberty is the right to self determination but what is the use of this right when it can not be fulfilled (10). These basic evolving ethical issues are constantly posing problems in every health care institution and are a challenge to every physician involving the ideology of justice and healthcare (11).

But 'justice' also has a legal meaning which is especially relevant to Forensic Medicine, with its role "in conflict of interest". A respect for the individual's right of privacy and the maintenance of confidentiality are major concerns of the physicians performing forensic evaluations (12-13). The Physician maintains confidentiality to the extent possible given the legal context. Special attention is paid to any limitations on the usual precepts of medical confidentiality. An evaluation for forensic purposes begins with notice to the evaluee of any limitations on confidentiality. Information or reports derived from the forensic evaluation are subject to the rules of confidentiality as apply to the evaluation, and any disclosure is restricted accordingly. However, the ethical values are fast changing in globalized world in health field and every day we observe how they are violated.

Therefore, any system of ethical guidelines should evolve with time and the changing health care system. There is a growing global concern on the new ethical paradigm and the existing legal framework supporting its application to all disciplines of medicine. Some of the legal and ethical issues that is unable to keep pace with the rapid growth of science and technology in the changing socioeconomic condition, where "ideology of economy" is influencing every walk of human life. How the new ethical paradigms are evolving in the present environment of scientific and technological growth in a democratic society requires a careful evaluation. Similarly, what is the proper relationship amongest law, ethics and morality needs a careful attention. Ethics and codes of ethics are shaped by law but law is shaped by those codes to some extent and both

are influenced by philosophical ethics (14).

To be able to appreciate this position where you are at any point in time, we must acknowledge and learn from the past – good and bad – or, one is likely to repeat the same. In 1946, after World War II(1939-45), during the Nuremberg trials, the Nuremberg Code for ethical conduct of research involving human subjects was developed (15). The trials highlighted highly unethical medical research conducted by Nazi doctors on many captive prisoners in the concentration camps during World War II. Much knowledge was gained from these studies. Should we not use this knowledge because of how it was gained, e.g. information on hypothermia – how long a person can survive in cold water before dying?

Nuremburg Code-1946 was developed consequent to Nuremburg trials at the end of the Second World War and published in 1949 (15-16). It is one of the earliest codes of conduct and prescribes the ten basic principles for conducting research in human beings. One of the basic principles was voluntary consent.

The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, overreaching, or other ulterior form of coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him/her to make an understanding and take an enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration; and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment. The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the conduct of experiment or clinical study. It is a personal duty and responsibility which may not be delegated to another with impunity.

Later the World Medical Association (WMA) made recommendations guiding physicians for biomedical research involving human subjects. It was adopted by 18th WMA held in Helsinki in June 1964 (17). This was subsequently amended by the 29th, 35th, 41st, 48th, 52nd, 59th and 64th WMA held at Tokyo in October, 1965, Venice in October, 1973, Hongkong in September, 1989, Somerset West, Republic of South Africa in October, 1996, Edinburgh in October, 2000, Seoul in October, 2008 and Fortaleza, Brazil in October, 2013, respectively. It states that- it is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission. Subsequently the WMA Declaration of Geneva binds the physician with the words, "The health of my patient will be my first consideration", and the International Code of Medical Ethics declares that, "*A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient*". Recently, WMA has revised Geneva declaration on participation in Capital Punishment on October 14, 2017 in Chicago in WMA General Assembly which states that *"it is unethical for physicians to participate in capital punishment in any way or during any step of the execution process"* (18).

In spite of these international declarations, we saw another major ethical violation in USA. In 1974, after the debacle of the syphilis natural history study conducted by the US Public Health Service on the participants of 'Tuskegee study of untreated Syphilis in the Negro Male' that withheld appropriate treatment even after antibiotics became available, the US enacted the National Research Act which established a

National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research. In 1979, this commission presented the Belmont Report (19). The US President, Bill Clinton apologized on behalf of the US government, to the surviving black participants and their surviving relatives on May 16 1997. This was done 65 years after the study was started.

Internationally, the Council for International Organization of Medical Sciences (CIOMS) in collaboration with WHO further developed "International Ethical Guidelines for Biomedical Research Involving Human Subjects" (http://www.cioms.ch/publications/layoutguide2002.pdf) (20). These guidelines are updated regularly, the most recent updation has been undertaken in 2016 and published as "International Ethical Guidelines for Health-related Research Involving Humans" (21).

In 2005, UNESCO presented the Universal Declaration on Bioethics and Human Rights to further advance the principle of bioethics (21).

In view of the above and other related developments there is a need to explore issues related to value conflicts that have implications for ethical practice, which include:

a) Autonomy
b) Beneficence and Effectiveness
c) Non-Malfeasance
d) Confidentiality
e) Justice
f) Informed Consent
g) Information
h) Voluntarism

The principle of "autonomy of the person" and the principle of "beneficence and non-malfeasance" in prevailing environment of 'justice' have also changed our understanding of ethics. Apart from these, with the growing social consciousness in the present day egalitarian society the principle of "autonomy of the person" and the principle of "beneficence (to do right) and non-malfeasance (to avoid causing evil or damage)" in the prevailing environment of justice have also evolved the understanding of ethics, specially after the Nuremberg trials in Germany and Tuskegee experiments in USA.

Despite the moral weightage of these new ethical guidelines witnessed in the western world, it is probable that these principles would not have obtained a powerful and accelerated importance, without the legal activism of the courts, powerful lobby of some NGOs within and outside UN, and the ubiquitous world media.

The new ethical paradigms and all the legal structures supporting their application are similar in all branches of Medicine.

Autonomy

The word autonomy denotes both "an ideal and an obligation" has also changed in recent times. The case for a physician to act paternalistically is followed by a counter argument which revolves around the respect of autonomy.

Autonomy, as an ideal, centres on a person's capacity for deliberation and reflection. Principle of autonomy presumes that a patient has a right to control his or her body and is consciously aware of having the capacity to make a decision with a sense of control. In medical ethics the word autonomy is commonly used to refer to an obligation. Persons ought to have independence to be free from coercion and inducements. This implies an obligation on the part of the physician to try to find out what the patient wants to achieve. This value has several implications in practice. It involves patient's mental capacity to understand and appreciate his free power and the context and the situation which may vary in:

a) Therapeutic situation
b) Research field
c) Forensic settings, which may include
    i. Therapeutic situation
    ii. Diagnostics-like Narcoanalysis in

many criminal cases or in a recent case of DNA testing to prove paternity of a person.

Beneficence and Effectiveness

The principle of beneficence conveys an obligation to maximize benefits to an individual, community and minimize risk of harm in physical, psychological and social areas to a patient. This includes both a philosophical and scientific aspect (22). Recently Indian Council of Medical Research (ICMR) has published a comprehensive "National Ethical Guidelines for Biomedical and Health Research Involving Human Participants" and on related issues (ICMR, 2017) (22).

Consent

Consent is a decision making capacity of a subject or a patient and it should be assessed on a case by case basis but it has many contradictory elements. The case for the therapist to act paternalistically as enunciated in Hippocratic Oath is followed by the counterargument which revolves around the respect for autonomy of a person. A bridge between these two opposing positions is then offered which depends on viewing informed consent as a dynamic process. As part of this procedure it is made clear that while autonomy is the desired end-state, it is not the be-all and end-all of treatment. Autonomy includes Informed Consent after providing sufficient information without coercion. Capacity means to understand and appreciate consequences of participation.

Consent to Treatment

In Principle of autonomy, i.e. patient has the right to control his/her own body. It translates legally into assault, i.e. if 'medically touched' without consent (i.e. without consent to that touching). Informed Consent: practice of legal and ethical significance for persons living with illness.

Context of Informed Consent should include in Therapeutic situation, Research, and in Forensic setting.

Meaning of "informed consent" includes that in order to be fully legal, the patient's consent must be informed. Being informed implies cognition, willingness, consideration, intention and understanding. Opinion and choice cannot be final and acceptable unless they are based on knowledge and information provided before the choice is exercised. It supposes that no consent will be valid which does not depend on willingness.

Information must be communicated to the patient in a manner that is consistent with the patient's capacity to understand and in a form that maximizes such understanding. Consent is context-specific, i.e. it will be valid only if it has been given in respect of the relevant proposed treatment and diagnostic procedure and it is not a general consent.

Informed Consent on Diagnostic Assessment to Conduct Relevant Tests

Patient should be informed about the purpose, method, likely duration and expected benefit of diagnosis. Similarly, in therapeutic situation, patient should be explained about alternative modes of treatment, possible pain or discomfort, risks and side effects associated with each treatment modality. Patient has the right to refuse or stop treatment, except as provided in some situation. Patient shall never be invited or induced to waive the right to informed consent.

Consent includes - Competence to consent and it refers to patient's cognitive ability and mental capacity to process information. It is specific to a patient's ability at a given time, so that a patient may be competent to make a treatment decision at one time and not competent another time.

Consent does not always guarantee competence- consent to have a sex by a 16-year

girl or mentally sick patient is both legally and ethically wrong. Competence and rationality are not synonymous. Rationality is a characteristic of a person's decision making process and not of personal ability to make decisions. The informed consent of the subject of a forensic evaluation is obtained when possible. Where consent is not required, notice is given to the evaluee of the nature of the evaluation. If the evaluee is not competent to give consent, substituted consent is obtained in accordance with the laws of the jurisdiction. Consent is one of the core values of the ethical practice of medicine and psychiatry. It reflects respect for the person, a fundamental principle in the practice of medicine and forensic medicine. Obtaining informed consent is an expression of this request.

Consent in Justice System

It is important to appreciate that in particular situations, such as court ordered evaluations for competency to stand trial or involuntary commitment, consent is not required. In such a case, a physician should so inform the subject and explain that the evaluation is legally required and that if the subject refuses to participate in the evaluation, this fact will be included in any report or testimony.

Consent to treatment in a jail or prison or other criminal justice setting must be differentiated from consent to evaluation in general practice. Any physician providing treatment in these settings should be familiar with the judicial rules in regard to the patient's right to refuse treatment. There are some special situations like forced feeding in cases of hunger strike is ethically debatable. Similarly, sterilization of females in a mentally subnormal home is ethically unacceptable.

What Does Consent Mean?

We must all remember that there is no valid (ethical) consent without all elements satisfied but the question may be raised, how do we define each element? “There is no statutory statement but is taken to mean” capable of understanding in broad terms, the nature and purpose of the treatment. English law defines the elements in the following terms:

Competence

There is no 'statutory statement' but is taken to mean 'capable of understanding in broad terms the nature and purpose of the treatment'. Similarly, the element of information includes possible standards, 'Patient based': level of information necessary in order to allow patient to operate his/her autonomy or it could be 'Profession based': in that medical situation, based on 'duty of care'. It is necessary to distinguish fact of consent from evidence to consent, e.g. a complete Informed Consent Form (ICF) does not amount to the act of consent, only it is evidence as to consent. Implied consent cannot be used beyond that which is 'reasonable', implied consent (patient's consent 'unavailable' where reasonable man would consent), e.g. in case of unconscious patient. After a head injury or other medical conditions when the principle of necessity includes that doctor owes a 'duty of care'. For this, we must distinguish necessity/convenience. Today, in Emergency Department (ED) patient's attendants are continuing to rise in all hospitals and medical and nursing teams are working under considerable strain and their priorities are to save the life and limb of each patient. Sometimes this creates both administrative and ethical issues (23).

Consent to treatment includes the principle of autonomy, i.e. patient has the right to control his/her own body. Translates legally into assault, i.e. if 'medically touched' without consent. Collection of cerebro-spinal fluid without consent is an assault but collection of urine is not.

Confidentiality

The issue of confidentiality is another area

which needs attention. Physicians should take precautions to assure that none of the confidential information they receive falls into the hands of unauthorized persons and Media for cheap publicity and marketing. Similarly, physicians should be familiar with the institutional policies in regard to confidentiality. Where no policy exists, physicians should clarify these matters with the institutional authorities and develop working guidelines to define their role.

The forensic situation often presents significant problems in regard to confidentiality. The psychiatrist, in particular must be aware of and alert to those issues of privacy and confidentiality presented by the particular forensic situation. Notice should be given as to any limitations. For example, before beginning a forensic evaluation, a physician should inform the evaluee that although they are physicians, they are not the evaluee's "doctor." Similarly, treating doctor should indicate for whom they are conducting the examination and what they will do with the information obtained as a result of the examination. Being retained by one side in a civil or criminal matter exposes the forensic doctor to the potential for unintended bias and the danger of distortion of their opinion. This becomes important in the field of psychiatry. The forensic psychiatrist practices specialty at the interface of two professions, each of which is concerned with human behaviour and each of which has developed its own particular institutions, procedures, values, and vocabulary. As a consequence, the practice of forensic psychiatry entails inherent potentials for complications, conflicts, misunderstandings and abuses. In custody cases, honesty and striving for objectivity requires that all parties be interviewed, if possible, before an opinion is rendered. Treating physicians should generally avoid agreeing to be an expert witness or to perform evaluations of their patients for legal purposes. The impression that a physician in a forensic situation might distort their opinion in the service of the party which retained them is especially detrimental to the profession and must be assiduously avoided. Honesty, objectivity and the adequacy of the clinical evaluation may be called into question when an expert opinion is offered without a personal evaluation.

Confidentiality is the obligation of a professional to keep in confidence the information shared by the patient during the course of consultation or treatment, except in cases of specific permission. The problems related to confidentiality when working with a multidisciplinary team and sharing of information through the electronic health record are other relevant issues which need careful attention. The treating team as well as the consultants specifically called for the patient come within the circle of confidentiality, and therefore, any disclosure of the information amongst them is permissible and does not involve its breach (24).

Ethics and the Physician-Patient Relationship

Ethics and physician-patient relationship are very important. This is due to rising patient expectation in democratic setup. One of the most important factors for this is the increased literacy and general awareness. Patients demand drugs for their each and every symptom. Along with this there is greater dissemination of scientific knowledge among the patients through commercial advertisements and increased access to internet. Thus, the doctor-patient relationship has become untenable due to social pressure of the patient and his family. Another factor which is compounding this problem is that the concept of confidentiality is disappearing among the physicians. All these issues have been examined by Frankena in his book “Ethics” (25).

Ethical Issues in Health Research include the principles of respect for individual, autonomy, humanism, compassion, principles of “Do Good unto Others”, “Do no Harm”, “Confidentiality” and “Informed Consent” are essential.

If the patient is unable to give consent, the consent can be taken from the most appropriate person- guardian or legal authorities.

Legally incapacitated person may only undergo medical research where authorized and if permitted by legal representative or any authority or an individual authorized or designated under his nation's law. Legally incapacitated person may not undergo medical research unless it is expected to produce a direct and significant benefit to his health. By way of exception, national law may authorize research involving a legally incapacitated person which is not of direct benefit to his health when the person offers no objection, provided a research is to the benefit of persons in the same category and that the same scientific results cannot be obtained by research on persons who do not belong to this category. Pregnant or nursing women may not undergo medical research where their health and/or that of the child would not benefit directly even if this research is aimed at benefiting others.

Ethical Issues in Human Genome

Conflicts regarding legal and ethical ownership of the Human Genome is an emerging new area. Who should have access to personal genetic information and how, it will be used? Who will own and control genetic information and who will be benefited are the questions which need to be addressed (26).

Ethics Committee

Institutional Review Board (IRB) or Institutional Ethics Committee (IEC), review and approval are other issues in this area. Often IEC or IRB is present but not properly working. In this respect, ICMR and Drugs Controller General of India (DCGI) at the Centre for Drugs Standardization and Control Organization (CDSCO), Ministry of Health and Family Welfare, Government of India have developed some guidelines for biomedical research and drug-related clinical trials. IRBs and IECs protect the safety and welfare of human research participants. These bodies are responsible for providing an independent evaluation of proposed research studies, ensuring that the research does not proceed unless standards and regulations are met (22, 27).

It is important that membership of IRBs and IECs should include non-scientist, community representative, scientifically sound researcher, both by qualification and experience and a legal person. Similarly, Scientific Review Board should have both internal and external experts.

Other Issues

Euthanasia and Physician-assisted Suicide; participation in torture by physician and participation in legal execution of Death are all relevant but will need a separate paper for discussion.

Conclusion

In conclusion, it may be said that the ethical behaviour is based on the physician and individual sense of responsibility towards the patient. A physician should always keep in mind the boundaries of his relationship with his/her patient. He/she should be guided primarily by respect of patient's autonomy, justice and concern for his/her welfare and integrity.

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Service Development for Behavioural Addictions: AIIMS Experience

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ABSTRACT

The concept of behavioural addiction is relatively new. The growing recognition of the behavioural addictions globally and increasing clinical queries catalysed the ongoing deliberations on setting up services for addressing behavioural addictions at the All India Institute of Medical Sciences (AIIMS), New Delhi. This led to establishment of what is arguably the first Behavioural Addictions Clinic (BAC) in the country. The clinic is an initiative of the Department of Psychiatry and National Drug Dependence Treatment Center (NDDTC), AIIMS, New Delhi. The current article offers an overview of the BAC, AIIMS, New Delhi.

Keywords: Behavioural addictions, internet addiction, internet gaming disorder, public health.

Introduction

Addictive disorders have been identified as significant contributors to the global burden of disease (1). These are not only associated with the adverse health consequences such as increased morbidity and mortality, but also impact the familial, social, occupational, financial and legal domains of life. The adverse consequences associated with addictive disorders extend beyond the individual to the family and community.

Traditionally, addictive disorders have largely been attributed to the use of psychoactive substances. In fact, the terms addictive disorders and substance use disorders have been used interchangeably in literature. A psychoactive substance is a chemical that acts upon the brain, resulting in changes in perception, mood, consciousness, cognition, and/or behaviour. However, during the past two decades it has been increasingly realised that while certain addictive disorders are related to the use of psychoactive substances, there are other addictive disorders that do not include use of the psychoactive substances. These addictive disorders are known as behavioural addictions. Non-substance addictions, non-chemical addictions and process addictions are some other terms used to describe these conditions. Some of the commonly described and reported behavioural addictions in the literature include gambling disorder, internet gaming disorder, internet addiction and sexual addiction.

Prevalence of Behavioural Addictions

While the behavioural addictions have generated a considerable interest among researchers over the past few decades, there are only a few large-scale studies that have explored

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the prevalence of these conditions. There is a considerable variation in the reported prevalence of different behavioural addictions across studies. This difference in prevalence rates can be attributed to the differences in the study design, definition of behavioural addictions, diagnostic criteria, choice of screening instrument, and type of population studied among others. In an earlier report, the prevalence of adult gambling disorder has been found to vary from 0.1% to 2.7% (2). The proportion of persons with pathological gambling is relatively higher among college students (3). The prevalence of internet addiction among adolescents has been reported to vary from 4.0% to 19.1% (3). The reported range of internet addiction among adults is 0.7% to 18.3% (3). The prevalence rates for problematic video game playing among adolescents have been reported to vary from 4.2% to 20.0% across studies (3). There is limited literature on other behavioural addictions to make firm conclusions about their prevalence rates.

An Indian study in selected urban localities of Bengaluru reported prevalence rates of 1.3% for internet addiction (2% males and 0.6% females) and 4.1% for mobile phone overuse (5% males and 3.1% females)(4). A comparative study among medical students across three countries (including India) found 0.5 % of the students to score in the range of severe problematic internet use (5). A recent survey among the attendees of a trade promotion event found that 15% of the respondents endorsed five or more features (out of nine) of behavioural addictions related to use of mobile technology (6). Most of the Indian studies on problematic internet use have focused on the students. Table 1 presents the summary of Indian studies that have explored prevalence of internet addiction/problematic internet use among students (7-26).

Table 1: Summary of the Indian studies that have explored internet addiction/ problematic internet use among students

Authors	Year	Instruments	Prevalence/Status of Internet Addiction
Meena *et al* (7)	2012	Young's Internet Addiction Test	59% - average users 25% - occasional problematic behaviour 2 % - severe problems
Chathoth *et al* (8)	2013	Young's Internet Addiction Test	58% - mild 19% - moderate to severe
Goel *et al* (9)	2013	Young's Internet Addiction Test, Duke Health Profile	75% - moderate users 25% - possible addiction 0.7% - addiction
Yadav *et al* (10)	2013	Young's Internet Addiction Test, 21-item Depression Anxiety & Stress Scale	12% - addiction
Kawa and Shafi (11)	2015	Young's Internet Addiction Test (IAT), Kessler Psychological Distress Scale (K10) and Demographic Data Sheet	67% - mild 29% - moderate 4% - severe
Jain *et al* (12)	2014	Young's Internet Addiction Test	8% students overuse; 1% were addicted

Kodvanji *et al* (13)	2014	Young's Internet Addiction Test	19% were addicted
Sharma *et al* (14)	2014	Young's Internet Addiction Test	35% - mild 7% - moderate 0.3% - severe
Srijampana *et al* (15)	2014	Young's Internet Addiction Test	2% - possible addiction 0.4% - addiction
Vyjayanthi *et al* (16)	2014	Young's Internet Addiction Test	9% - total prevalence
Balhara *et al* (5)	2015	Young's Internet Addiction Test	9% - mild 11% - moderate 0.5% - severe
Chaudhari *et al* (17)	2015	Young's Internet Addiction Test	51% - mild 7% - moderate
Kakkar *et al* (18)	2015	Young's Internet Addiction Test, Mental Health Battery	5% students addicted with significant problems
Krishnamurthy and Chetlapalli (19)	2015	Young's Internet Addiction Test	34% - mild 8% - moderate
Mitra *et al* (20)	2015	Young's Internet Addiction Test	15% - problematic
Setty *et al* (21)	2015	Young's Internet Addiction Test	75% - moderate users 25% - possible addiction 0.7% - addiction
Sulania *et al* (22)	2015	Young's Internet Addiction Test	15.5% at high risk
Banjara and Bhukya (23)	2015	Young's Internet Addiction Test	65% - average users 12% - possible addiction 2% - addiction
Gedam *et al* (24)	2016	Young's Internet Addiction Test, Mental Health Inventory	1% - severe among medical students 2% - severe among dental students
Mahanty and Mishra (25)	2016	Problematic and Risky Internet Use Screening Scale	70% of students with mild addiction
Nath *et al* (26)	2016	Young's Internet Addiction Test	44% - average users 46% - possible addiction 0.5% - addiction

Nosological Journey

The concept of behavioural addiction, while relatively new, has been documented for quite some time in the medical literature. Gambling disorder, one of the most well researched and described behavioural addictions, was first introduced in the 3rd Diagnostic and Statistical Manual (DSM-III) in 1980 (27). However, it was listed as pathological gambling under impulse control disorder. This was a reflection of the earlier conceptualization of pathological gambling as a disorder on impulsive-compulsive spectrum rather than being a clear addictive disorder. It was retained in DSM III R, DSM IV and DSM IV Text Revision (TR) as impulse control disorder (28). The International Statistical Classification of Diseases and Related Health Conditions (ICD-10) also classified pathological gambling as a habit and impulse disorder.

However, the growing body of research over the past two decades fuelled the emerging consensus that pathological gambling is closer to the addictive disorder. The behavioural addictions have made a formal debut in the most recent version of 5th edition of Diagnostic and Statistical Manual, i.e. DSM 5 (29). In fact, the DSM 5 has witnessed a paradigm shift with relabelling of the category of 'substance-related disorders' as 'substance-related and addictive disorders'. Gambling disorder is the first disorder to be listed as a behavioural addiction under this category. The upcoming revision of ICD, i.e. ICD 11 is also likely to follow the suit and introduce the behavioural addictions (30). Lack of sufficient peer reviewed evidence on other behavioural addictions has been cited as the only reason for their non-inclusion in DSM 5.

Behavioural Addictions: Proximity to Substance Use Disorders

The current conceptualisation of behaviour addictions groups these disorders closer to psychoactive substance use related addictions. Research studies have found multiple commonalties between these two sets of disorders. The co-occurrence rate of behavioural addictions and psychoactive substance use related addictions has been found to be high in clinical as well as epidemiological studies (31-33). Rapid reward discounting, poor performance on decision-making tasks, and diminished performance on tests of inhibition, cognitive flexibility, and planning tasks are cognitive deficits shared by persons with behavioural addictions as well as psychoactive substance use related addictions (2). Neurobiological studies have implicated similar brain regions (e.g. reward pathway, dorsolateral prefrontal cortex) and neurotransmitters and related enzymes (e.g. dopamine levels, platelet monoamine oxidase B activity) in emergence of both behavioural addictions and psychoactive substance use related addictions. Also, genetic studies have reported higher rates of substance use disorders among first degree relatives of persons with behavioural addictions. Finally, similar treatment approaches (pharmacological as well as non-pharmacological) have been found to be beneficial for the two sets of disorders (2).

Despite these similarities, behavioural addictions differ from psychoactive substance use related addictions on multiple accounts. Many of the bio-psycho-social underpinning related to behavioural addictions still remains largely unexplored. It is likely that despite of many commonalities between behavioural addictions and psychoactive substance use related addictions, it shall be too simplistic to see the two as a unitary concept. A better understanding of behavioural addictions consequent to ongoing research should help settle this debate in future.

Management of Behavioural Addictions

The research on management of behavioural addictions is still in its infancy. However, there is published evidence that can be used to guide clinical management of these disorders. It is recommended to follow an

integrated approach that includes a mix of pharmacological and non-pharmacological interventions. The medicines that have been found to be effective in management of behavioural addictions have been summarised in Table 2.

Table 2: Pharmacological interventions found effective in management of behavioural addictions

Medicine	Type of study
Naltrexone	Double blind placebo controlled trials
Nalmefene	Double blind placebo controlled trials
Fluvoxamine	Double blind placebo controlled trials
Paroxetine	Double blind placebo controlled trials
Lithium	Double blind placebo controlled trials
Escitalopram	Open label trials/ case reports
N-Acetyl cysteine	Open label trials/ case reports
Memantine	Open label trials/ case reports
Amantadine	Open label trials/ case reports
Acamprosate	Open label trials/ case reports

The non-pharmacological interventions that have been explored for management of behavioural addictions include cognitive behaviour therapy, behaviour therapy, time management skills, solution focused brief therapy, and a combination of group and individual therapies. A meta-analysis on effectiveness of treatment modalities for internet addiction found psychological as well as pharmacological treatment to be beneficial in management of internet addiction (34). Indian Psychiatric Society has in recent past published guidelines on management of behavioural addictions (35). It is also important to identify and manage the co-occurring mental disorders and substance use related disorders among persons with behavioural addictions.

Addressing Behavioural Addictions in the Country: the AIIMS Initiative

The growing recognition of the behavioural addictions globally and increasing clinical queries catalysed the ongoing deliberations on setting up services for addressing behavioural addictions at the All India Institute of Medical Sciences (AIIMS), New Delhi. This led to establishment of what is arguably the first Behavioural Addictions Clinic (BAC) in the country that is aimed at addressing all types of behavioural addictions. While initiatives taken so far in this area have targeted a particular type of behavioural addiction, the BAC at AIIMS caters to all types of non-substance use-related addictive disorders. The clinic is an initiative of the Department of Psychiatry and National Drug Dependence Treatment Center (NDDTC), AIIMS, New Delhi.

The BAC is housed in the Department of Psychiatry at AIIMS, New Delhi. It is a weekly clinic, that is held in the out-patient setting on every working Saturday. The clinic is run by a team of mental health professionals that include faculty from psychiatry and clinical psychology. The clinic has witnessed a gradual but steadily increasing clinical consultations since its inception. The clinic offers comprehensive screening, assessment and management services for behavioural addictions. Another emphasis at the clinic is for assessment and management of co-occurring mental and substance use disorders among those with behavioural addictions.

The most commonly observed behavioural themes include excessive and problematic use of internet, social media platforms, internet-based games, online pornography and gambling. Almost all the cases presenting to us have experienced significant socio-occupational dysfunction. In fact, emergence of this dysfunction is the most important reason for help seeking. Some of the commonly observed dysfunctions include declining academic performance, discontinuation of studies, financial losses, and interpersonal conflicts. Presence of co-occurring mental and substance use disorders is another significant findings among these cases. While a few persons seek help on their own, majority attend the clinic on insistence and persuasion of care givers. They are mostly young school-/college-going adolescents who actively deny their internet/smartphone use as problematic or having addiction. However, majority of the patients are male youth with age ranging between 16 and 25 years. The clinic has also witnessed consultation concerning the controversial 'Blue Whale Challenge'.

Apart from setting up clinical service, the BAC has also taken certain public health initiatives on the behavioural addictions. These include a collaboration with South East District Delhi Police to spread awareness on safe and healthy use of internet. The BAC, AIIMS is a collaborating partner of Delhi Police in this initiative targeted at the school students. Also, the BAC has contributed to the media reports on behavioural addictions aimed at increasing awareness among general public about this issue and spreading the information about the availability of such services. Additionally, the BAC has also participated in screening camps in collaboration with other medical institutes, where the visitors of the camp have been screened for presence of behavioural addictions related to use of mobile technology. Apart from this, contributions were made to the first ever consultative meeting on public health implications of excessive use of the internet, computers, smart phones and similar electronic devices organised by the World Health Organization (WHO) (36).

The BAC is also engaged in carrying out research activities on the themes related to behavioural addictions. While some of these projects have been completed others are underway. The findings from these studies have been published in peer reviewed academic journals (5, 6, 37). The clinic proposes to conduct studies on prevalence, bio-psycho-social correlates, and awareness and attitude towards the behavioural addictions. This is in keeping with the current conceptualisation of behavioural disorders as having bio-psycho-social underpinnings.

Way Ahead

The BAC at AIIMS recognises and realizes that behavioural addictions are a growing problem of public health importance. There is a need to spread awareness on presence of the problem as well as existing services for taking care of the same. The BAC aims to extend the public health campaign to a wider section of population. Also, it aims to expand research on various domains of these disorders. The clinic also aims to bring out recommendations and guidelines on prevention, screening, assessment and management of behavioural addictions. Presently, the BAC is well prepared and well placed to assume the leadership role in this area with contribution and participation of various stakeholders.

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Gene Therapy in India- Current Status

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ABSTRACT

Gene therapy is being considered as a promising modality for more than two decades now. It has been used for a number of difficult-to-treat conditions and has shown good results in some of the conditions, but not that effective in some others. Overcoming the initially faced hindrances, the research in the field of gene therapy resurged. India is one the major Asian countries where gene therapy-related research and centers have shown remarkable growth, despite certain constraints faced by the researchers. Current article discusses the different types of gene therapy along with its clinical implications and its current status in Indian context.

Keywords: Gene therapy, India, children.

Introduction

Gene therapy is an attempt to treat diseases by replacing defective gene with healthy genes or repairing the defective genes in order to improve the function of genes. World was first introduced to gene therapy in 1995 almost two decades ago when Blaese *et al* published his initial trial results of T lymphocyte directed gene therapy in Adenosine Deaminase (ADA) deficiency associated Severe Combined Immunodeficiency (SCID) (1).

Hindrances to gene therapy started following three deaths which occurred just after clinical initiation of gene therapy. One was due to multiple organ failure as a consequence of severe immune response to the viral vector and other two children died of leukemia (2, 3). These deaths raised issues of ethical concern following gene therapy and lead to complete halt of the trials all over the world. After the initial set back, interest later renewed almost a decade later in the year 2008, when gene therapy restored vision in three young children suffering from Leber's congenital amaurosis (4). After these successful results of gene therapy, United States of America and Europe became the pioneers in gene therapy-related studies and clinical trials. In Asian continent, China and Japan have emerged as the forerunners in the stem cell research, with China launching Gendicine, an injectable gene therapy product (a replication-incompetent recombinant human p53 wild type protein particles combined with adenovirus serotype 5) approved by the China Food and Drug Administration (CFDA) in 2003 for head and neck cancer. Japan has introduced Retronectin reagent, which is a recombinant human Fibronectin Fragment and on injection, enhances retroviral (as well as lentivirus, a form of retrovirus)-mediated gene transfection and transduction by helping the co-localization of target cell and virions. The reagent can enhance

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retroviral-mediated gene transfer to target cells that express integrin receptors VLA-4 and/or VLA-5, thus making the gene delivery more specific as the gene will not be delivered to body cells which lack VLA-4 and/or VLA-5 integrin receptors.

Types of Gene Therapy

It becomes important to understand some of the terminologies and the types that are often used in relation to gene therapy. Alternative terms like genetic engineering, Deoxyribonucleic Acid (DNA)-based therapy and molecular therapy are often used by layman and biologists. Gene therapy is one of the tool of genetic engineering used with purpose to alleviate suffering from hereditary diseases. However, genetic engineering in wider term not only aims to alter genes to correct genetic defects but may also be involved in modifying the genes to enhance the capabilities of the organism beyond what is normal. The latter is a dangerous proposition of genetic engineering.

A. Gene therapy can be classified into somatic cell and germ cell types, depending upon the type of cells that are modified by the therapeutic genes (6, 7). All the gene therapies till date are directed towards somatic cells only.

Somatic Cell Gene Therapy

In this type, genetic changes are directed towards somatic cells. As these cells are non-reproductive, effect is not passed into future generations, making it safer. The disadvantage is short duration of effects of somatic cell therapy as most tissues will be replaced by new tissues.

Germ Cell Gene Therapy

This is the type of gene therapy, where germ cells, i.e. either sperm or ova are introduced with therapeutic gene, leading to the changes that are inheritable, i.e. changes in gene may affect future generations.

B. Based upon the technique of delivery of vectors to the target cell, gene therapy can be further classified into ex-vivo and in-vivo therapy.

Ex-vivo Gene Therapy

Ex-vivo gene therapy is where the defected cells are extracted out of the body and targeted with therapeutic gene. Once successfully modified, they are cultured ex-vivo and transferred back to the host, where now the corrected gene replicates.

In-vivo Gene Therapy

In this modality, a vector that is capable of carrying the therapeutic gene, is used to inject host cells with normal gene.

C. The type of change brought out in the faulty gene classifies gene therapy as either gene replacement or gene addition.

Gene Replacement

Gene replacement means replacement of defective gene with a corrected one.

Gene Addition Therapy

Gene addition means restoration of normal function of cell by addition of normal or functional copy of gene into genome. This concept is primarily used in various gene therapy related research on cancer.

Clinical Implications

Cancer

Gene therapy-related research and its clinical application have been mostly utilized in the field of malignancy. By the end of 2009, nearly two third of gene therapy-related research was concentrated on cancers (8). Oncolytic viruses are used to introduce genes into malignant cells, thereby causing death of

malignant cells. Another approach is to deliver p53 gene (tumor suppressor gene) and thereby induce oncolysis. Gendicine that was first approved anticancer drug which was based on this gene therapy principle. Suicide gene therapy is another attempt to treat tumor by delivering of gene coding for enzyme that metabolizes prodrugs into locally active chemotherapeutic drug moiety.

Single Gene Disorder

Gene therapy has a significant role in the treatment of single gene disorders like muscular dystrophies, cystic fibrosis, alpha-1-antitrypsin deficiency, Huntington's disease, lysosomal storage diseases, chronic granulomatous disease, ornithine transcarbamylase deficiency, junctional epidermolysis bullosa, haemophilia, etc. (8).

Immunodeficiency

Over the years with development of gene therapy first major progression has been seen since the first trial in early nineties. After the initial set back where two patients treated for X-linked severe combined immunodeficiency (X-SCID) using retroviral vectors died with leukemia there were clinical trials that had showed clear therapeutic benefits of gene therapy in treatment of both X-SCID and SCID caused by adenosine deaminase (ADA) deficiency. Besides primary immunodeficiency, secondary immunodeficiency states like Human Immunodeficiency Virus (HIV) infection has also evolved as potential candidate for gene therapy. Transgenes can be transferred into haematopoietic stem cells or into T-cells, for specific protection against HIV infection to these cells. They act by disabling HIV-1 protein, or making the milieu unsuitable for HIV-1 replication (8).

Eye Diseases

It was for Leber's congenital amaurosis that there was renewal of faith in gene therapy after the initial set back seen in SCID. Eye being a small organ, hence it is possible that we can transfect a large number of ocular cells. Potential ophthalmologic conditions for gene therapy are glaucoma, Leber's hereditary optic neuropathy, red-green colour blindness and macular degeneration (9). A phase I study is going on to show effects of antiangiogenic cytokine Pigment Epithelium-derived Factor (PEDF) in treating age-related macular degeneration (9). Mancuso *et al* has also shown significant improvement in producing trichromatic colour vision in adult red-green colour blind monkeys by subretinal injection of adeno-associated virus containing a L-opsin gene (10).

Cardiac Diseases

Cardiac diseases are multigenic in origin, hence difficult to treat. There have been trials where scientists have devised techniques to deliver genes for various growth factors like vascular endothelial growth factors (VEGF), Fibroblast Growth Factors (FGF) to promote vascular angiogenesis (11). Though their results did not show significant improvement in stress-induced myocardial perfusion but improved regional wall motion indicated a favorable anti-ischemic effect encouraging further research in the field.

Central Nervous System (CNS) Disorders

Unlike cardiac, in neurological disorders gene therapy has shown promising results to treat Parkinsonism (12) and Alzheimer's disease (13). There have been several trials on gene therapy in Parkinsonism which are still in phase 1 and phase 2 but are showing gene therapy to be safe, tolerable and potential candidate for in-vivo studies (12). Various approaches used are, transmitting the gene for glutamic acid decarboxylase into the subthalamic nucleus (12) or delivery of the gene for neurturin in putamen cell bodies (14). Similarly in Alzheimer's disease gene therapy is being attempted to deliver Nerve Growth Factor gene into the human CNS (13).

Intrauterine Gene Therapy

Prenatal gene therapy or otherwise known as intrauterine gene therapy to resolve the problems of various genetically transmitted diseases is the future of gene therapy. If successful, we can diagnose and treat certain genetic disorders before they manifest in a child. Animal studies have shown some success in the field (15).

Difficulties with Somatic Cell Gene Therapy

Multiple rounds of gene therapy are required due to its short lived nature depending upon the turn-over rate of cells replication. The rapidly dividing nature of many cells prevent the gene therapy from achieving long-term benefits. The therapeutic DNA that is introduced into the target cells must remain functional and stable for long duration. Gene therapy is particularly effective in single gene disorders, hence difficult to apply in multigenic disorders. However, Thalassemia and haemoglobinopathies, though amenable to gene therapy present technical challenges in gene regulation.

The other problem faced is with the mode and the type of vectors used for the gene delivery. Initially viral vectors were used to deliver gene but the problems of endogenous virus recombination, oncogenic effects and most importantly unexpected immune response as seen in the very first case of gene therapy remain the concerns (2).

Ongoing Research in the Field of Gene Therapy

Introduction of New Vectors

Various non-viral vectors that are presently being given consideration for gene therapy are naked DNA, oligonucleotides, lipoplexes and polyplexes dendrimers, etc. The advantages these vectors hold over viral vectors is low immunogenicity, rapid turnover and low toxicity. Most of these vectors are still in experimental stage and we are far from development of a perfect vector of gene therapy. Non-viral vectors can further be classified into those limited to in-vitro applications like calcium phosphate transfection which is the system of choice for transmitting plasmid DNA into variety of cell cultures. Another type of non-viral vectors are also there which have both in-vivo and in-vitro applications like cationic liposomes, etc.

Gene Therapy in India

In India though interest in gene therapy took some time but with financial assistance provided by different government agencies, the country has shown rapid improvement in gene therapy-related research placing India third among the major Asian countries having gene therapy laboratories (16). The main aim is to develop new institutions for gene therapy research, strengthening of existing institutions which have good expertise in this area in order to initiate work in molecular genetics for decreasing the burden of genetic disorders in the country. The pioneer of gene therapy-related research in India is Advanced Centre for Treatment, Research and Education for Cancer (ACTREC) where active work on gene therapy for head and neck cancer using synthetic vectors is being carried out (17). It is heartening to note that scientists in over dozen of labs in India are working hard with small steps in contributing towards gene therapy work as depicted in Table 1 (18-24). Hareendran *et al* (18) suggested that targeting specific host cellular proteins is helpful to attenuate the immune barriers which are a key obstacle in clinical application of adeno-associated virus mediated gene therapy. An alternate approach for treating Haemophilia; a using allogenic transplantation in liver where tolerance against donor antigens can be induced by in-vitro allo-antigen primed T-regulatory (Treg) cells has been studied by Kochat and her team. Shetty *et al* (19) have shown that naïve stemness of pluripotent cells can be generated by devising a transgenic method to express a human ortholog of protein Asrij, present on mouse

Table I: Indian Scientists work on Gene Therapy

Investigators	Study	Year (ref)	State
Kochat *et al*	Repression of PARP-1, a DNA damage response protein, improves the transduction of single-stranded AAV vectors both in vitro and in vivo in mice. Findings will help Hemophilia B patents.	2016 (18)	Tamil Nadu
Hareendran *et al*	Examined the role of donor major histocompatibility complex (MHC)-stimulated host CD4(+)CD25(+) regulatory T (Treg) cells in suppressing immune responses against allogeneic uncommitted (Lin(-)) bone marrow cells (BMCs) for correction of bleeding disorder in HA mice.	2015 (17)	Delhi
Shetty and Inamdar	Ectopically expressed Asrij in epiblast stage equivalent-human embryonic stem cells (hESCs) to test for induction of naive pluripotency in primed pluripotent cells. The construct pCAG-Asrij was introduced into hESCs by microporation. Ectopic expression of Asrij in BJNhem20 hESC line was performed by selecting for plasmid transfection, followed by stable cell line generation.	2016 (19)	Bangalore
Misra *et al*	Liposomal transfection mediated gene transfer for tumors expressing Sigma receptors.	2016 (20)	Bangalore
Vij *et al*	They reported an amphipathic peptide Mgpe9 that can penetrate the uncompromised skin, enter skin cells and deliver plasmid DNA efficiently as nano-complexes *in vitro* and *in vivo* without any additional physical or chemical interventions prevalent currently leading to efficient gene expression up to the highly proliferating basal layer of the skin without observable adverse reactions or toxic effects.	2016 (21)	Delhi
Hati Boruah *et al*	Knockdown of myostatin gene (MSTN), transforming growth factor-β superfamily, and a negative regulator of the skeletal muscle growth, by RNA interference (RNAi), has been reported to increase muscle mass in mammals.This could provide an alternative strategy of gene knockout and develop stable caprinefetal fibroblast cells. Furthermore, these stable cells can be used as a cell donor for the development of transgenic cloned embryos by somatic cell nuclear transfer (SCNT) technique.	2016 (22)	Madhya Pradesh
Kumar *et al*	siRNA could be used in cancer therapy if naked nucleic acid could be transported using a suitable carrier. The authors developed a nano-carrier system using mesoporouspolycaprolactone (hmPCL) and showed its efficacy in knocking down cancer cells. This approach may open another way of gene therapy.	2016 (23)	Telengana
Sarkar *et al*	A new Cancer Terminator Virus (CTV), Ad.tCCN1-CTV-m7 was developed which displayed dose-dependent killing of Carcinoma Prostate (CaP) without harming normal prostate epithelial cells *in vitro* with significant anti-cancer activity *in vivo* in both nude mouse CaPxenograft and transgenic Hi-Myc mice (using ultrasound-targeted microbubble (MB)-destruction, UTMD, with decorated MBs).	2015 (24)	Orissa

embryonic stem cells (mESCs) which is essential for maintaining pluripotency. Misra *et al* (20) are working on selective gene transfection as a possible strategy of interest for reducing off-target gene expression and toxicity. Vij *et al* (21) have used nucleic acid therapeutics as an effective topical delivery system to overcome the barrier posed by different layers of the skin in cutaneous disorders. Hati Boruah *et al* (22) showed Ribonucleic Acid interference (RNAi) based co-transfection method could provide an alternate route of gene knockout besides providing stable cells which can be used as a cell donor for the development of transgenic cloned embryos by somatic cell nuclear transfer technique. Alternative and efficient nucleic acid transportation has been demonstrated by Kumar *et al* (23). Sarkar *et al* (24) have studied therapeutic efficacy of combining a BH3 mimetic with a novel Cancer Terminator Virus for treating advanced carcinoma prostate.

Obstacles in Growth of Gene Therapy in India

After the initial work in late nineties, gene therapy remained at backseat for a long time as the government was uncertain whether to give priority to this technology. There is absence of the regulatory framework with inadequate exposure level of regulators who are still not updated with the international standards. Prohibitive cost involved in preparing reagents requiring cyclic guanosine monophosphate (cGMP) conditions is another major hurdle. As a result, researchers in India do not have the freedom to take risk in order to develop technology to save several lives. No established Indian guidelines are available on the preparation of clinical grade reagents for clinical trials. Centralized resources for production and distribution of clinical grade gene vectors are lacking. Laboratories or pharmaceutical companies catering to gene services are meager in number, further adding to the difficulties faced by the researchers. Most of gene therapy research is still lab based, preclinical and mostly limited to cancers.

Road Ahead

Despite the above road blocks, India is fast picking up with the rest of the world in developing research related to gene therapy. Adding impetus to further research in India is the release of revised "National Ethical Guidelines for Biomedical and Health Research Involving Human Participants, 2017" and the National Guidelines for Stem Cell Research, 2017 in October, 2017 by the Indian Council of Medical Research (ICMR). These guidelines would encourage research for somatic cell gene therapy for conditions for which it is the only therapeutic option available with due permission from Department of Biotechnology (DBT) for gene constructs (25).

Gene therapy has been theoretically very sound, but its utility will be demonstrated once it comes into clinical practice. Now with the “Make in India” being a popular mantra encouraged by the Govt. of India, we should not shy out from the active involvement in gene therapy research and trials. More funding for academic research, development of dedicated departments with scope for capacity building and training, integration between researchers and clinicians, increasing public awareness and finally and most importantly with the development of Indian guidelines for gene and cell therapy clinical research trials by the ICMR will help in the transition of gene therapy from infancy to adolescence.

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Relevance of Traditional Indian Medical Concepts in Psychosomatic Medicine

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ABSTRACT

Traditional medicine comprises of health related knowledge, skill and practices indigenous to different cultures. India has a rich heritage of traditional system of medicine that emphasizes the close link between mind and body like the psychosomatic medicine. The government of India has set up a department of AYUSH (Ayurveda, Yoga and Naturopathy, Unani, Siddha and Homoeopathy). The importance of life style, dietary and environmental factors in the development of various psychosomatic disorders has been emphasized in all the Indian traditional systems of medicine. Although studies have shown acceptability and beneficial role of traditional medicinal practices, efforts should be made to tease out and conduct research on the practices, which can help physicians in improving well-being of the patients. More rigorous research is required in the direction to generate evidence base for these practices so that their full potential can be realized.

Keywords: Traditional Indian systems of medicine, AYUSH, Ayurveda, ayurvedic medicine, psychosomatic disorders.

India is a country of great cultural diversity and has a rich heritage of traditional system of medicine, such as Ayurveda, Yoga, Siddha, Unani and Homeopathy. The Ayurveda, Yoga and Siddha originated in India with history going back to nearly five millennia while Unani and Homeopathy came later to India and got assimilated in Indian culture (1). These ancient systems of medicine have been described under the term traditional medicine that encompasses diverse health concepts and approaches. Traditional medicine comprises of health related knowledge, skill and practices indigenous to different cultures (2). It plays an important role in meeting health care needs of people, especially in developing countries. As per World Health Organization estimates, around 80% of the population in some of the countries in Asia and Africa seek help from traditional systems of medicine for their primary care (3).

The Indian system of traditional medicine emphasizes the close link between mind and body like the psychosomatic medicine. In both, it is important to understand the interaction between biological, psychological and social factors in the causation and treatment of a disorder. It is not only restricted to the field of psychiatry but is applicable to entire system of modern medicine (4). It is important to utilize the knowledge derived from traditional Indian medical concepts to enhance our understanding of psychosomatic medicine. The Government of India has also taken an initiative to establish the Department of AYUSH (Ayurveda, Yoga, Unani, Siddha and Homoeopathy) to promote the use and develop research in this potential areas of Indian systems of medicine (5).

In this article we will briefly discuss about the different types of traditional Indian medicine

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systems and their relevance to psychosomatic medicine.

Basic Principles of Indian Traditional Medicine

Ayurveda is the most ancient system of Indian traditional medicine. Ayurveda means the science of life and it is believed that, the Hindu God, Brahma gave the knowledge of healing to the sages who passed it to their disciples in form of oral recitations and writings (6). The four Vedic Hindu texts, *Yajur Veda, Rig Veda, Sam Veda,* and *Atharva Veda* formed the basis of ancient Indian medicine. The knowledge of all Vedas was compiled by Agnivesha, which was later edited by Charaka and called as *"Charaka Samhita"*. This book is considered as the foundation of Ayurvedic medicine. The teachings of Ayurveda are based on the concepts of philosophical (*Vaisheshika*) and logical thinking (*Nyaya*) (6). The basic difference between the teachings of the two schools lies in the process of making a plan for treatment. *Vaisheshika* school laid emphasis on inferences and perceptions obtained from patients whereas *Nyaya* school focused on prior extensive knowledge about the patient's and disease condition before starting any treatment. The former classified any matter into six categories: *Dravya* (substance), *Guna* (quality), *Karma* (activity), *Samanya* (generality), *Visesa* (particularity) and *Samavaya* (inherence). According to Ayurveda, the entire universe is composed of five elements referred to as *Pancha Mahabhoota* (i.e. prithvi-earth, jal-water, agni-fire, vayu-air and aakash-sky). The different combinations of these elements form three basic humors (*Tridoshas*, means three defects: body disorders due to air or gases, body disorders due to bile, body disorders due to phlegm or inflammatory exudates) of human body: *Vata dosha, Pitta dosha* and *Kapha dosha*, controlling the basic physiological functioning. The human body consists of seven tissues (*Saptadhatus*, means seven elements), which work, in coordination to maintain the functioning of the body. The accumulation of different waste products known as (*Tri Malas*, means three excretory products or toxicants) can lead to different type of infections. Another important concept is of *Trayo Dosa*. *Agni* is a biological fire of the body for all the metabolic functions. The balance between these elements of the body is essential to maintain a healthy body (7). There are four basic tenets of treatment in Ayurveda: physician, drugs, the attendant and patient. Physician offers thorough examination, medications and therapies. There are three types of therapies. *Yukti vyapashraya* (rational/ physical therapy) reduce three *doshas* and includes life-style practices, diet, herbs, and clinical methods. *Sattavajaya* (psychological therapy) increases sattva guna by the practice of yoga. *Divya chikitsa* (spiritual therapy) helps in removing karmic afflictions by rituals, mantra, gemstones, pilgrimage, asceticism and other esoteric practices (7).

Yoga is a Sanskrit word which means "the union of the individual self (*Jiva-atman*) to transcendental self (*Parama-atman*)" (8). *Yoga Sutras*, written by an ancient yoga teacher and sage, Patanjali, was an effort to define and standardize the practices of yoga (8); an eight fold path of yoga for better expression of true self. These are: *Yama* (removal of bad habits), *Niyama* (inculcating good virtues building a new moral behavior), *Asana* (postures for practicing), *Pranayama* (controlling breathing pattern), *Pratyahara* (isolating the mental activities from external world), *Dharana* (trying to focus on one single object), *Dhyana* (concentrated meditation focusing on the self) and *Samadhi* (transcendental super consciousness). The methodological alteration of one's consciousness results in liberation from ego successfully controlling the pathological expression of biological psychic and social parameters of illness (8). There are many variants of classical yoga defined in the Indian literature. In India, *Raj yoga, Hath yoga* and *Mantra yoga*, are most commonly practiced for treatment of psychosomatic disorders (8). In recent years, research has been carried out that has shown yoga to have multiple beneficial

effects on bodily functions and immunity (9). This has resulted in incorporation of different yogic practices in the management of non-communicable diseases and as part of stress relieving packages.

Siddha system of medicine is attributed to the great Siddha (Master), named Ayastiyar. *Siddha* comes from the word *Siddhi* (achievement) and *Siddhars* are people who practice it (10). They are believed to have achieved divine power by virtue of their knowledge. *Siddha* literature is in Tamil and is practised largely in Tamil speaking part of India and abroad. Some of the works by Ayastiyar are present in standard books of medicine and surgery in daily use among the *Siddha* medical practitioners (11). Like Ayurveda, its basic premise is that all objects in the universe including human body are composed of five basic elements (*Pancha Mahabhoota*, vide Supra) namely, *earth, water, fire, air* and *sky.* This system considers the human body as a conglomeration of three humours, seven basic tissues and the waste products such as faeces, urine and sweat. The equilibrium of humours is considered as health, and its disturbance or imbalance leads to disease or sickness. Minerals and metals are used as drugs in this form of medicine. The principle of using metals for treatment is based on the concept of preventing body from decomposing by using materials, which are difficult to decompose. There are 96 basic principles of *Siddha* (10, 11).

The Unani medicine has originated from Greece and is based on the teachings of Hippocrates and Galen further advanced it (1, 12). The composition of human body is constituted of seven constituents; elements, temperament, humors, organs, pneuma faculties and spirits. These components are required in correct proportions for well-being and are taken into consideration while formulating any treatment (12, 13). Important concepts in practice of Unani medicine are temperament (mizaj), heredity, complaints, signs and symptoms of the body, external observation, examination of the pulse (*nubz*), urine and stool, etc. Various treatments include venesection, cupping, diaphoresis, diuresis, Turkish bath, massage, cauterization, purging, emesis, exercise, leeching, etc.

Homeopathy medicine was developed by Samuel Hahnemann and derives its name from two Greek words Homoios (like) and Pathos (treatment). In Homeopathy, the therapeutic modality is developed with consideration that it will produce manifestations of a disorder when administered to any individual (14). The symptoms of disorder are considered as body's natural defense mechanism and the underlying principle is to strengthen it. Homeopathy is based on two main principles. The first principle is 'like cures like'. This means that for any disorder, the homeopathic remedy should be the one that produces similar disorder in a healthy individual. The second principle is based on the dilution of medication so that its minimum dose is used. A homeopathic remedy maintains its biological activity even at small dosage and works by stimulating 'vital force' of life (14, 15).

Although the various traditional systems of medicine in India differ in their underlying principles, they take a holistic approach in understanding of causation and management of diseases. The basic tenant of all the systems is that the mind, body and environmental factors act in unison to cause an illness. Hence, it is important to understand contribution of each system for treatment of a disorder.

Conceptualization of Psychosomatic Disorders in Indian Traditional Medicine

Many theorists propose that the psychosomatic approach to health and disease forms the basis of Ayurvedic medicine (16). The '*Purusha*' (man) in Ayurvedic science is treated as a psychosomatic entity and is constituted by the *satva* (mind), the *atman* (soul) and the *sarira* (body). The basic premise of healthy living in Ayurveda is to maintain a balance between mind, body and soul or consciousness. This balance

can be achieved by having understanding about basic concepts of Ayurveda. The various psychological factors (*Mansika-bhava*), like *kama* (luster), *krodha* (anger), *shoka* (grief), *bhaya* (fear), *irshya* (envy) can affect the different humors. It results in disturbed physiological functioning of the body that may cause different psychosomatic disorders. Value based qualities of living that can act as protective factor against ill health. Increase in humors (physical factors) can also affect the mental health of human beings (17). Few noteworthy examples mentioned include increase in *Vatika* humors resulting in *Anidra* (insomnia). Similarly, *Pittaviridhi* causes *murchha* and *Kapha vridhi* causes *Tandra* (sedation) and *Nidra* (sleep). Many examples of psychosomatic disorders can be found in Ayurvedic texts like a clinical condition called *Grahini roga,* which is similar to irritable bowel syndrome (IBS) (18). The imbalance between different *doshas* results in dysfunction of *Agni* (fire) and is believed to be the cause for development of IBS. The *mansik-bhavas* (mental feeling or thinking) like *kama* (luster) and *krodha* (anger) can affect the *doshas* that may result in IBS.

Yoga explains the origin of psychosomatic disorders through the concepts of *Pancha Klesha* (five psychological afflictions) (19). These are *Avidya* (failure to recognize ultimate reality leading to physical attributions), *Asmita* (misplaced sense of identification which can result in believing psychiatric symptoms as originating from bodily dysfunction), *Raga* and *Dwesha* (attraction and repulsion) and *Abhinivesha* (clinging to life due to fear of death). *Avidya* is major factor responsible for different *Kleshas* from time to time and results in stress that is the underlying cause for various psychosomatic disorders. In Siddha medicine, psychosomatic disorders find mention in the works of Yogi Chitamani (20). The book describes in great details about different neurotic and somatoform disorders. Several scholars in the field of Unani medicine have philosophized about various causes of hysteria and other psychosomatic disorders. The effects of psychological signs and systems on the body were elaborated by Ibn-e-Nafees (1210–1288 A.D.) in his book, Kulliyat-e-Nafeesi (Book on Fundamentals, written by Nafeesi) (21). He proposed that excess of black and yellow bile in body affects the mind resulting in negative emotions, which can lead to psychosomatic disorders. He suggested change in the environmental factors and use of relaxation techniques in resolution of symptoms.

These different systems have also proposed various therapies for treating psychosomatic disorders. For example, Ayurveda mentions Panchkarma as a therapy for these disorders. It is a Sanskrit word, which means five karmas (actions): Virechan (purgation), Vaman (induced vomiting), Basti or Anuvasana (use of medicated oil enemas), Rakta moksha (detoxification of blood) and Nasya (administration of medicines through nasal route). The underlying principle is to cleanse the body from disease causing factors (22). This helps in maintaining the balance between three doshas. Wide range of Ayurvedic medicinal plants are used in the management of various psychiatric disorders. In a systematic review (23), Rout *et al* have compiled a list of 78 drugs, which are either used in combination or as monotherapy. There is greater acceptance of these drugs amongst the patients due to their easy availability, affordability and minimum side effects even though there is lack of scientific evidence for the efficacy and safety profile of these medicines.

Relavance of Indian Traditional Medical Knowledge in Treatment of Psychosomatic Disorders

The Indian traditional systems of medicine have been used worldwide and are classified under the broad rubric of complementary and alternative medicine (CAM). In a systematic review, which included 16 studies, Fras *et al* found the use of CAM to be as high as 74.8% in some of studies (24). The use was higher amongst more educated middle aged women. It

was more commonly used for psychosomatic disorders like back pain or joint pains pathologic, depression, insomnia, severe headache or migraine, and stomach or intestinal illnesses. The study also found that medical students had most critical views about CAM when compared with other health care professionals. A National population-based survey done in Australia found that 68.7% of people interviewed had had at least one form of CAM in preceding 12 months and around 45% of them had visited CAM practitioner (25). Yoga was used by 12% of them. Meditation and homeopathy were used in 17.5% and 6% of the participants, respectively. In a similar survey done in England, lifetime and 12-month prevalence of CAM use were 44.0% and 26.3%, respectively. This study also reiterated that as a group, psychosomatic disorders were the most common reason for consultation (26). The higher cost and dissatisfaction with modern medicine, along with the belief that it offers more holistic care and is devoid of side-effects, can be possible reasons for higher rates of acceptance of traditional therapies (24). The authors suggested that the future physicians should be more aware of the basic principles of these therapies so that they can meet the requirements of patients.

These methods of treatment from traditional medicine are deeply rooted in the Indian culture, and are frequently used by the patients. In India, 65% of rural population uses Ayurveda and medicinal plants for their primary health care needs (2). The concept of illness as a result of bad karma helps in accepting the pain of illness. The relationship between doctor and patient is like Guru – chela and doctor is considered as elderly figure who has to be respected (27).

The importance of life style, dietary and environmental factors in the development of various psychosomatic disorders has been emphasized in all the Indian traditional systems of medicine. In Ayurveda, the beneficial effects of exercise have been mentioned in first section (*Sutra Sthana*) and in the chapter on 'Non suppression of natural urges' of the Charaka Samhita (28). Exercise as therapy has been described for at least twenty types of diseases like *Trpti* (anorexia nervosa), *Apakti* (indigestion), *Gurugatrata* (heaviness of the body) and other psychosomatic disorders. Short-low graded exercise has been shown to decrease pain perception and persons with better fitness show higher pain threshold (29). Decreased pain threshold has been implicated in a number of psychosomatic disorders; hence regular exercise can be one of effective treatment strategies for dealing with somatic pain symptoms. A Dutch longitudinal study showed that lack of physical activity and sedentary life style was significantly associated with functional somatic symptoms (30).

Similarly, yoga has beneficial effects in many psychosomatic disorders. Fibromyalgia syndrome is a functional disorder in which psychosocial factors play an important role in etiology and management (31). Eight weeks of yoga therapy improved pain, pain perception as well as increased pain acceptance and mindfulness in fibromyalgia (32). The improvement was accompanied with changes in salivary cortisol levels. In a multi-country survey conducted amongst more than 2500 patients with fibromyalgia with an objective to determine their engagement with yoga practices and the perceived benefits (33), around 80% of the participants used yoga, and the most commonly cited benefits were decrease in stiffness, relaxation, and better balance. Numerous studies have shown the biological underpinnings for the beneficial effects of yoga (34), used as both a top-down or bottom-up mind-body practice. Yoga increases parasympathetic stimulation that improves the balance of autonomic nervous system. The increase in vagal activity decreases psychophysiological arousal and stress response and increases antioxidant levels decreasing oxidative stress and decreases cortisol levels.

Traditional systems of medicine pay a

great deal of attention on quality and composition of the food. There is a common belief that some foods have 'hot', 'cold' or 'heavy' properties; these affect *gunas* and *doshas* like *pitta* and *kapha*; the resultant imbalance may produce a symptom or disease. Studies have shown that poor quality diets are often associated with depression and anxiety, which are common comorbid conditions in psychosomatic disorders (35). Although conclusive evidence is lacking in this field, it is possible that dietary modification plays an important role in management of psychosomatic disorders. For example, many guidelines for management of IBS have stated beneficial effects of dietary modification. The most common recommendations are to adhere to a regular meal pattern, reducing intake of insoluble fibers, alcohol, caffeine, spicy foods, and fat (36).

Although studies have shown acceptability and beneficial role of traditional medicinal practices, scientific community needs to take an open view while determining its utility. Every effort should be made to tease out the practices, which can help physicians in improving well-being of the patients. More rigorous research is required in the direction to generate evidence base for these practices so that their full potential can be realized.

Current Status of Traditional Medicine in India

The government of India has set up a department of Indian Systems of Medicine and Homoeopathy (ISM&H) in 1995 with aim of recognising the alternative or the indigenous systems of medicine and simultaneously controlling, promoting and developing them. The department was renamed AYUSH (Ayurveda, Yoga and Naturopathy, Unani, Siddha and Homoeopathy) in 2003. The Government of India created a separate ministry called Ministry of AYUSH in 2014 that is headed by a minister of state (37). A recent analysis of National Sample Survey data about utilization of services by all patients seeking out-patient care in previous 15 days reported that only 6.9% of the study participants received treatment from AYUSH (38). The lower rates of utilization could be due to focus only on therapeutic use of AYUSH, thereby ignoring its use in disease prevention or health promotion. The government of India aims to promote research to generate evidence base for AYUSH through collaborative efforts and by giving financial assistance.

Conclusion

The traditional systems of medicine have a rich history and co-exist with the contemporary practice of modern medicine. Modern medical sciences have recognized the importance of mind-body interaction in genesis of psychosomatic disorders and suggest life style and dietary modification in their management. This is in tune with ancient wisdom that has always realized importance of these factors in maintaining healthy life. The very fact that these traditional medical practices are accepted by a large number of individuals worldwide should motivate systematic research in this direction. The evaluation of efficacy of these practices by modern research techniques can elucidate important facets of traditional systems of medicine.

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Association of Vitamin D and Diabetic Retinopathy in Patients with Type 2 Diabetes Mellitus

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ABSTRACT

Objective: To assess the association of vitamin D (VD) and diabetic retinopathy (DR) in patients with type 2 diabetes mellitus (T2DM).

Method: Literature search was conducted for studies assessing the association of VD and DR. Total 9 studies have a sum total of 1741 patients were included for final analysis.

Results: The concentration of VD in controls ranged from 17.5±3.6 to 31.9±12.9 ng/ml, while for T2DM patients without retinopathy it ranged from 11.94±4.21 to 23.10±6.12 ng/ml. T2DM patients with retinopathy had the lowest concentration, ranging from 10.02±5.61 to 19.25±7.86 ng/ml. A higher percentage of T2DM patients without (50.7% to 68.80%) and with (31.2% to 79.63%) retinopathy had VD deficiency (VDD).

Discussion: An inverse association between VD levels and DR was observed. The concentration of VD decreases as the stage of DR advances. VD seems to be an easily modifiable risk factor for DR. Thus, VD supplementation should be encouraged in population at higher risk for diabetic complications.

Keywords: Vitamin D, cholecalciferol, retinopathy, vitamin D deficiency, diabetic retinopathy, diabetic complications, type 2 diabetes, systematic review.

Introduction

With the rapid increase in the incidence of diabetes mellitus (DM) in recent years, the complications related to diabetes have become a larger health problem. Inadequately controlled diabetes precipitates various long-term microvascular (blindness, neuropathy and nephropathy) and macrovascular (cardiovascular and stroke) complications (1, 2) which form the leading cause of morbidity and mortality in diabetic patients worldwide (1). Diabetic retinopathy (DR) being one of the most prevalent complication of diabetes, is considered as a major culprit of blindness globally (1, 3). DR is also the most common cause of non-traumatic visual loss in the working-age population. It has been estimated that the worldwide prevalence of DR was 93 million (35%) and the prevalence of vision-

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threatening DR was 28 million (10.2%) among diabetic patients in 2010 (4). World Health Organization estimates that throughout the time DR accounts for approximately 5% of the worldwide prevalence of blindness, the prevalence rises sharply to 15-17% in developed countries (3).

There are various risk factors that have been suspected in the pathogenesis of DR, like hypertension and hyperglycemia. Although, hypertension and hyperglycemia have demonstrated strongest association, interventions directed at improving these factors have shown moderate success. Thus, the interactions among neural and retinal vascular dysfunction and the mechanisms leading to retinal pathology including neovascularisation have been questioned recently (3).

In addition to the classical role in skeleton and bone health, vitamin D (VD) has been identified to exert non-classical pleiotropic effects such as anti-inflammatory, antiangiogenic, antiproliferative, and immunomodulatory properties (5). It is also considered to positively regulate hypertension and blood glucose levels (6). Moreover, it has been established that maintaining VD at adequate levels can be a useful technique to prevent type 2 diabetes mellitus (T2DM) (7). T2DM and VD deficiency (VDD) have been considered as pandemic diseases with a number of health consequences. Furthermore, VDD is known to be more common in patients with diabetes (5). VDD has an established role in developing the risk of diabetic complications as VD is considered to affect the risk for retinopathy, due to its immunomodulatory properties (3). However, the effect of low levels of VD on causation of type 1 DM (T1DM) is well established, the association between VDD and T2DM is not consistent. Evidences collected from many epidemiological studies, indicate that most of the T2DM cases are attributable to manageable habits and lifestyle changes. Therefore, the identification of easily modifiable risk factors is crucial for the prevention of diabetes and its complications (1). Since, the evidence regarding the association of vitamin is limited (8), and, the prevalence of VDD is contentious in T2DM patients (9), this systematic review has been conducted to establish or refute the association between VD and DR.

A recent PubMed search (till March 31, 2017), with the use of terms “vitamin D” and “retinopathy,” yielded only 159 publications. Thus, few studies have addressed the question of the potential implication of VD in the pathogenesis of DR. Among these studies there were only 9 publications that met the inclusion criteria. The aim of this study was to collect available evidence on the association between VD and DR, and to summarize the results by performing a systematic review of published studies according to Meta-analysis of Observational Studies in Epidemiology (MOOSE) group recommendations (10). The primary objective of this review is to assess whether there is an association between VD status and DR in T2DM.

Methods

Criteria for Considering Studies for the Analysis

All the studies which were retrieved from different search sources based on search terms were screened according to the predefined inclusion and exclusion criteria. Cohort/cross-sectional/case control studies assessing the association between VD and retinopathy in T2DM patients were included in this systematic review. Studies on T1DM, not related to DR, not assessing VD levels, pediatric studies, retrospective studies, studies reporting combined result on both T1DM and T2DM, studies reporting combined data on complications of diabetes and studies with insufficient data were excluded.

Data sources and searches

We conducted an electronic literature search strategy for different PUBMED (till September 2016) for English language to identify studies on retinopathy. We further searched for additional trials in http://www.clinicaltrials.gov and http://ctri.nic.in. The search terms used were vitamin D and retinopathy. Full-text articles were retrieved and reviewed for performing systematic review.

Data extraction and analysis

Data extraction from the selected studies was conducted. Standard Excel spreadsheets were used for the data extraction. The following data were collected from the included studies: first author, year of publication, number of participants, mean age, duration of diabetes, HbA1c levels, body mass index, insulin therapy, total cholesterol, triglycerides, high density lipoprotein and low density lipoprotein.

Results

Search Results

The literature search results are summarized in the flowchart below (Fig. 1). After application of the inclusion and exclusion criteria, predefined in the study protocol, a total of 9 randomized controlled trials (RCTs) were included in the final systematic analysis. Amongst the nine studies included in the systematic review, six studies compared the VD levels in controls and in T2DM patients with DR

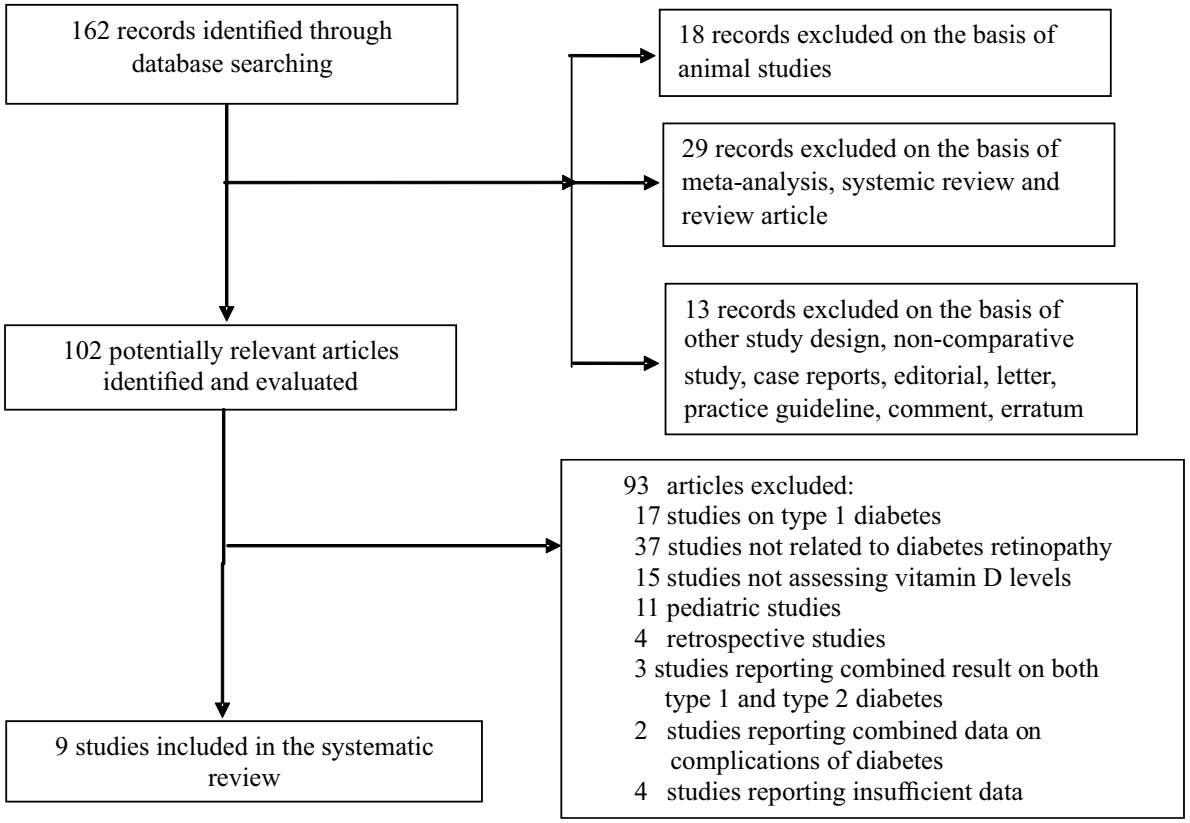

Fig. 1: Flow diagram of the literature search strategy. Number of studies identified and rejected at each stage are described.

(1, 9, 11-14), and 4 studies demonstrated the difference between controls and T2DM patients without DR (1, 11-13), one study demonstrated the difference in the levels in T2DM patients with or without DR, and further with Grade 1 or Grade 2-4 DR (8), one study compared the VD levels in patients without DR with non-sight threatening DR (NSTDR) and sight threatening DR(STDR) (15), two studies demonstrated the difference between control, T2DM patients with proliferative DR(PDR) (9, 14) and one study compared the VD levels in controls, T2DM with PDR and non-proliferative DR (NPDR) (16).

Clinical Characteristics of Study Participants

A total of 9 studies were included, analyzing 1,741 diabetic patients. The mean age of controls ranged from 50.7±13 to 60.1±10.9 years, for diabetics without retinopathy the age ranged from 53.22±0.867 to 58.28±11.39 years, while for diabetics it ranged from 52.85±8.26 to 61.6±11.5 years. Mean duration of diabetes in diabetics without retinopathy ranged from 7.2±5.5 to 11.24±5.34 years, whereas, for diabetics with retinopathy the duration ranged from 5.34±3.09 to 13.9±7.3 years. In the diabetics without retinopathy the HbA1c levels ranged from 7.3±1.2% to 10.36±0.65%. However, in diabetics with retinopathy the levels ranged from 7.7±1.4% to 10.88±0.55%. The mean duration of diabetes in patients with PDR was 22.0±10.5 years, while for NPDR it was 18.9±11.1 years. For patients with NSTDR and STDR, the mean duration of diabetes was 10.31±7.05 and 11.68±7.26 years, respectively, while the HbA1c level was 8.94±2.17% and 8.95±2.30% for patients with NSTDR and STDR, respectively (Table 1).

Vitamin D Concentration and Diabetic Retinopathy

The mean concentration of VD in controls ranged from 17.5±3.6 to 31.9±12.9 ng/ml, while the mean concentration of VD for T2DM patients without retinopathy ranged from 11.94±4.21 to 23.10±6.12 ng/ml. T2DM patients with retinopathy had the lowest concentration, ranging from 10.02±5.61 to 19.25±7.86 ng/ml. The VD level in T2DM patients with NPDR was 23.6±10.3, whereas, for PDR the concentration ranged from 11.62±5.69 to 21.10±10.5 ng/ml. Patients without DR had the highest levels (20.5±8.1 ng/ml) as compared to patients with Grade 1 (20±9 ng/ml) and Grade 2-4 DR (18.6±11 ng/ml). Similarly, patients without DR had the highest levels (18.86±7.12 ng/ml) as compared to patients with NSTDR (17.44±6.19 ng/ml) and STDR (15.36±4.81 ng/ml) (Table 2).

Prevalence of Vitamin D Deficiency and Diabetic Retinopathy

Prevalence of VDD ranged from 34.61% to 53% in controls. A higher percentage of T2DM patients without retinopathy and with retinopathy had VDD, which was in the range of 50.7% to 68.80% in the former and 31.2% to 79.63% in the latter, respectively. Twenty-one percent T2DM patients with PDR had VDD, whereas, 18.5% T2DM patients with simple retinopathy had VDD. Percentage of T2DM patients having VDD was higher in Grade 2-4 DR (67.1%) vs 55.6% with Grade 1 DR. Prevalence of VDD was higher in patients with STDR (85.24%) as compared to NSTDR (70.18%)(Table 3).

Discussion

DM being the most common endocrine disorder with its increasing prevalence every year needs to be addressed urgently (17), as the complications of diabetes may become larger health problem. As evident by many epidemiologic studies, most T2DM cases are attributable to modifiable habits and lifestyle factors. Thus, the recognition of easily malleable risk factors is crucial for the prevention of diabetes and its complications (1).

Inadequately controlled DM precipitates various long-term microvascular (blindness, nephropathy, and neuropathy) and macrovascular (cardiovascular and stroke) complications (1, 2), which forms the leading cause of morbidity and mortality in patients of

Table 1 : Clinical characteristics of study participants

First author	Study design	Groups	N	Male %	Female %	Age (yrs)	Duration of diabetes (yrs)	HbA1c level (%)	BMI (kg/ m^2)	Insulin therapy (%)	TC (mg/dl)	TG (mg/dl)	HDL (mg/ dl)	LDL (mg/dl)
Reddy *et al*, 2015* (1)	Cross-sectional case control	NDC	99	55	45	54.26± 0.743	NA	5.77± 0.20	25.02 ±5.16	NA	151.72 ±10.90	153.81 ±17.54	31.76 ±2.20	104.51 ±5.23
		DR	82	58	42	57.46± 0.913	10.69± 6.10	10.88± 0.55	24.39 ±4.51	NA	182.73 ±10.77	169.36 ±13.12	27.99 ±1.29	120.26 ±6.20
		DNR	82	57	43	53.22± 0.867	11.24± 5.34	10.36± 0.65	24.14 ±4.34	NA	171.47 ±15.24	185.94 ±17.22	26.02 ±1.68	121.16 ±4.90
Ahmadieh *et al*, 2013 (11)	Cross-sectional	Cases	136	38.7	61.3	59.2± 11.4	8.6±7	7.9±1.6	30.9± 5.2	NA	NA	NA	NA	NA
		Controls	NA	39.2	60.8	60.1± 10.9	NA	NA	28.8± 4.5	NA	NA	NA	NA	NA
Alcubierre *et al*, 2015 (8)	Observational case control	NR	144	51.38	48.62	58.1± 10.3	7.2±5.5	7.3±1.2	31.2± 5.2	NA	181.6± 37	137.4± 82.4	48.6± 10.9	111.6± 30.9
		R	139	51.08	48.92	60.3± 8.9	13.9±7.3	8.3±8.4	31.8± 5.4	NA	185.1± 36.5	140.5± 122.7	52.2± 15.6	106.4± 30.2
He *et al*, 2014 (15)	Cross-sectional	NDR	625	50.72	49.28	58.28± 11.39	8.29± 6.92	8.85± 2.69	24.28 ±3.52	NA	4.72± 1.01	1.71± 1.39	1.08± 0.29	2.79± 0.83
		NSTDR	562	50.88	49.11	58.90± 11.42	10.31± 7.05	8.94± 2.17	24.44 ±3.54	NA	4.83±1. 28	1.85±1. 95	1.09± 0.27	2.79± 0.87
		STDR	333	51.05	48.95	60.66± 12.47	11.68± 7.26	8.95± 2.30	24.24 ±3.52	NA	4.68± 1.26	1.62± 1.42	1.11± 0.31	2.71± 0.83
Bajaj *et al*, 2014 (12)	Cross-sectional case control	Cases	158	60.12	39.88	52.85± 8.26	5.34± 3.09	NA	NA	NA	NA	NA	NA	NA
		Controls	130	61.25	38.75	51.87 ± 6.43	NA	NA	NA	NA	NA	NA	NA	NA
Longo-Mbenza *et al,* 2014 (13)	Case control	NDNR	45	21	53.3	50.7± 13	NA	5±0.6	22.4± 2.9	NA	174.2± 141	75.6± 7.4	56.3± 14.5	63.1± 27
		All T2DM	150	65	56.7	55.2± 13	NA	9.3±4.1	25.8± 5.0	NA	203.2± 56.2	131.8± 45.5	45.3± 27.5	86.7± 45.7
		T2DM without DR		39	53.6	56.6± 12.4	NA	9.8±4.3	26.3± 5.0	58.3	205.1± 54.6	125.2± 45.6	46.6± 118.8	86.2± 42.8
		T2DM with DR		26	66.6	53.4± 13.6	NA	9.8±4.3	25.2± 5	59.1	200.8± 58.6	137± 45.1	43.5± 35.8	47.3± 49.5
Aksoy *et al*, 2000 (14)	Cross-sectional	Controls	20	40	60	56.6± 5.14	NA	NA	NA	NA	NA	NA	NA	NA
		NDR	20	60	40	57.1± 9.41	4.3±5.17	NA	NA	NA	NA	NA	NA	NA
		BDR	15	46.66	53.33	56.9± 9.83	7.4±6.20	NA	NA	NA	NA	NA	NA	NA
		PrePDR	14	50	50	57.1± 5.81	9.7±4.54	NA	NA	NA	NA	NA	NA	NA
		PDR	17	52.94	47.05	58.8± 6.07	12.1± 4.62	NA	NA	NA	NA	NA	NA	NA
Suzuki *et al*, 2006 (9)	Case control	Cases	581	54.56	45.43	61.6± 11.5	11.8±8.6	7.7±1.4	24± 3.9	NA	NA	NA	NA	NA
		Controls	51	49.01	50.98	58.2± 10.6	NA	4.8±0.6	22.0± 2.8	NA	NA	NA	NA	NA

Payne *et al*, 2012 (16)	Cross section-al	ND or OD	NA	53	NA	62.0± 11.6	NA	5.8±0.5	27.9± 6.1	NA	NA	NA	NA
		ND and OD	NA	45	NA	59.8± 13.3	NA	5.8±0.3	28.7± 8.0	NA	NA	NA	NA
		No BDR	NA	51	NA	62.4± 11.3	7.4±7.8	7.5±2.0	31.7± 9.8	24	NA	NA	NA
		NPDR	NA	53	NA	68.3± 10.0	18.9± 11.1	7.4±1.2	31.2± 6.7	73	NA	NA	NA
		PDR	NA	50	NA	59.8± 12.0	22.0± 10.5	8.1±1.9	33.1± 6.7	74	NA	NA	NA

Data are mean±standard deviation.
*Data in mean±standard error.
DR: diabetic retinopathy, DNR: diabetic without retinopathy, NDC: non-diabetic controls, ND: non-diabetic, OD: ocular disease, NR: non-retinopathy, R: retinopathy, NDR: no diabetic retinopathy, NSTDR: non-sight threatening diabetic retinopathy, STDR: sight threatening diabetic retinopathy, BDR: background diabetic retinopathy, NA: not available, BMI: body mass index, LDL: low-density lipoprotein, TC: total cholesterol, TG: triglycerides, HDL: high-density lipoprotein.

Table 2 : Vitamin D concentration and diabetic retinopathy

Author	Vitamin D levels (ng/ml)										P value
	Controls	T2DM with DR	T2DM without DR	T2DM with PDR	T2DM with NPDR	T2DM with simple DR	Grade 1 DR	Grade 2-4 DR	NSTDR	STDR	
Reddy *et al*, 2015 (1)	23.25±61.03	17.12±1.05	16.71±0.97	NA	NA	NA	NA	NA	NA	NA	<0.05*
Ahmadieh *et al*, 2013 (11)	22.5±12	21.8±13.7	12.3±5.5	NA	NA	NA	NA	NA	NA	NA	<0.001*
Alcubierre *et al*, 2015 (8)	NA	19.2±10.1	20.5±8.1	NA	NA	NA	20±9	18.6±11	NA	NA	<0.05**
He *et al*, 2014 (15)	NA	NA	18.86±7.12	NA	NA	NA	NA	NA	17.44±6.19	15.36±4.81	< 0.01#
Bajaj *et al*, 2014 (12)	27.19±9.36	23.10±6.12	19.25±7.86	NA	NA	NA	NA	NA	NA	NA	=0.0001*
Longo-Mbenza *et al*, 2014 (13)	30.85±6.81	15.22±4.4	10.02±5.61	NA	NA	NA	NA	NA	NA	NA	<0.0001*
Aksoy *et al*, 2000 (14)	24.28±6.71	11.94±4.21	NA	11.62±5.69	NA	NA	NA	NA	NA	NA	<0.001*
Suzuki *et al*, 2006 (9)	17.5±3.6	17.6±6.6	NA	15.1±8.0	NA	16.5±6.4	NA	NA	NA	NA	<0.05##
Payne *et al*, 2012 (16)	31.9±12.9	NA	NA	21.1±10.5	23.6±10.3	NA	NA	NA	NA	NA	<0.001*

Data are mean±standard deviation.
T2DM: type 2 diabetes mellitus, DR: diabetic retinopathy, PDR: proliferative diabetic retinopathy, NPDR: non-proliferative diabetic retinopathy, NSTDR: non-sight-threatening diabetic retinopathy, STDR: sight-threatening diabetic retinopathy, NA: not available.
* cases vs control.
** grade 2-4 retinopathy vs no retinopathy.
# NSTDR and STDR vs without DR.
PDR vs no DR.

Table 3 : Prevalence of vitamin D deficiency and diabetic retinopathy

First Author	Prevalence of VDD (%)										P value
	Controls	DM without retinopathy	DM with retinopathy	DM with PDR	T2DM with simple DR	T2DM with NPDR	Grade 1 DR	Grade 2-4 DR	NSTDR	STDR	
Reddy *et al*, 2015 (1)	45	66	63	NA	NA	NA	NA	NA	NA	NA	<0.05*
Ahmadieh *et al*, 2013 (11)	53	68.8	31.2	NA	NA	NA	NA	NA	NA	NA	NA
Alcubierre *et al*, 2015 (8)	NA	50.7	61.9	NA	NA	NA	55.6	67.1	NA	NA	<0.05**
He *et al*, 2014 (15)	NA	63.61	NA	NA	NA	NA	NA	NA	70.18	85.24	<0.01#
Bajaj *et al*, 2014 (12)	34.61	NA	79.63	NA	NA	NA	NA	NA	NA	NA	=0.0001
Suzuki *et al*, 2006 (9)	NA	60.3	NA	21.0	18.5	NA	NA	NA	NA	NA	NA

Data are mean±standard deviation.
T2DM: type 2 diabetes mellitus, DR: diabetic retinopathy, PDR: proliferative diabetic retinopathy, NPDR: non-proliferative diabetic retinopathy, NSTDR: non-sight-threatening diabetic retinopathy, STDR: sight-threatening diabetic retinopathy, NA: not available.
* cases vs control.
** grade 2-4 retinopathy vs no retinopathy.
# NSTDR and STDR vs without DR.

diabetes worldwide (1). DR being one of the most prevalent microvascular complications is considered as a major culprit of blindness globally (1, 3). Various risk factors have been implicated in the pathogenesis of DR. Although, hypertension and hyperglycemia have demonstrated strongest association with the DR, interventions directed at improving these have shown moderate success. Thus, the interactions among neural and retinal vascular dysfunction and the mechanisms leading to retinal pathology including neovascularisation have been questioned recently (3).

VDD has been associated with increased risk of chronic diseases, such as cancer, T2DM, cardiovascular disease, and autoimmune diseases including T1DM and multiple sclerosis, as evident from epidemiologic studies (1, 8, 18). Moreover, a wide prevalence of VDD and DM has been observed across all ages, socioeconomic conditions, races, and

geographic regions. Despite, the well-established effect of hypovitaminosis D on causation of T1DM, the relationship between VD insufficiency and T2DM is inconsistent (1).

Nutritional status, particularly micronutrients, might influence the risk for DR by affecting the biochemical mechanisms underlying DR (1, 3). Moreover, studies have suggested that VD might influence the risk for diabetes and its complications (1). VD has shown pleiotropic effects such as, suppression of cell-mediated immunity, regulation of cell proliferation, stimulation of neurotropic factors like nerve growth factor, glial cell line-derived neurotrophic factor, neurotropin, suppression of renin–angiotensin–aldosterone system, reduction of albuminuria, immunomodulatory effects (12), anti-inflammatory effects, anti-angiogenic, and anti-fibrotic properties (12, 19) and therefore all these VD effects may provide a potential link between VDD and diabetic complications (3) including DR, as there are rising evidences that, inflammation and angiogenesis are involved in the initiation and propagation of DR (19). Findings from some recent studies show a significant inverse association between 25-hydroxyvitamin D [25 (OH)D] levels and the prevalence of diabetic microangiopathy, thus suggesting that VD and microvascular complications are strictly inter-related. Nonetheless, whether lower levels of VD are the cause or result of the microvascular complications are currently unknown (2). Moreover, the possible role of vitamins in the pathogenesis of diabetic complications is of much interest (8).

In a study conducted on T2DM patients low blood VD concentrations were found to be associated with an increased risk of macro- and microvascular disease events (18). Additionally, a study found an inverse relationship between 25(OH)D and the severity of DR, thus concluding that, lower 25 (OH)D status strongly correlates with a higher prevalence of microvascular complications in T2DM patients (2). Another study including both T1DM and T2DM patients, showed an association between the severity of DR and prevalence of VDD (20). An inverse association of 25 (OH)D levels with DR was demonstrated only in men. However, the sex-related variation in the relationship between 25 (OH)D levels and DR is uncertain (19). Furthermore, a meta-analysis demonstrated that VDD is more prevalent in diabetic patients, and that VD supplementation may delay or prevent diabetic complications (21).

In contrast to most reports, serum 25-OH VD concentrations did not differ between subjects with or without diabetes in a retrospective study (21). Another study conducted retrospectively including both T1DM and T2DM patients, found no association between serum 25(OH)D and the presence and severity of DR (3). Thus, the evidence behind the association between VD and retinopathy is non-confirmatory, hence, this systematic review was performed.

The VD levels were found to be inversely associated with the presence of DR. The controls had the highest levels as compared to T2DM patients with or without DR. Additionally, T2DM patients without DR had higher levels than the patients with DR. Moreover, VDD has been found to be associated not only with the presence of DR but also with severity of DR. The concentration of VD decreased at advanced stages. Patients with Grade 2-4 DR had the lower concentration as compared to Grade 1, whereas, patients without DR had higher levels than Grade 1 patients. Similarly, patients with STDR had lower concentration than patients with NSTDR, while patients without DR had highest concentration. Controls had highest concentration as compared to T2DM patients with simple PDR, NPDR and PDR, with PDR patients having the least concentration. All the studies included in this systematic review showed a significant association between the VD levels and DR.

VDD was highly prevalent in the T2DM patients. However, two studies demonstrated that, the prevalence of VDD was higher in patients without DR than in patients with DR (1, 11), suggesting the prevalence of VDD irrespective of the presence of DR, whereas, one study demonstrated a higher prevalence of VDD in T2DM patients with retinopathy as compared to without retinopathy (8). An increased prevalence of VDD was observed in advanced stages of DR. The prevalence of VDD was higher in patients with PDR as compared to simple DR (9). A higher percentage of patients with Grade 2-4 had VDD that patients with Grade 1 DR. Prevalence of VDD was higher in patients with STDR than in NSTDR (15).

Despite, the scarce evidence behind the association of VD and DR, this systematic review suggests an inverse association between the two. However, the question on the potential role of VD in the pathogenesis of diabetic retinopathy is yet to be answered (8). Given previous research indicating possible anti-inflammatory and antiangiogenic properties of VD, the connection between VD and DR warrants further studies (20).

Conclusion

Through this systemic review, it was observed that there is an inverse association between the VD levels and DR. Additionally, the concentration of VD decreases as the stage of DR advances. Moreover, the prevalence of VDD is higher in T2DM patients as compared to controls, which further increases in the advanced stages of DR. Based on the results, it is advisable that VD levels should be routinely monitored in T2DM patients, as VD seems to be an easily modifiable risk factor for DR. VD supplementation should be encouraged in population at higher risk for the diabetic complications.

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Introducing the Team Based Learning as an Approach to Reviving Interest in Biochemistry amongst Undergraduate Medical Students-An Exploratory Study

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ABSTRACT

Introduction: Much emphasis has been given to different approaches to active learning. Our primary objective was to elicit interest amongst students in the areas of neglected, difficult topics in Biochemistry. Encouraging team building and developing team spirit by roping in all students in the exercise was the secondary objective of our study.

Methods: It was a single blind controlled interventional study. A Team Based Learning (TBL) Module was developed for First Professional MBBS students of 2015 batch. The topics selected were of high difficulty level. Ten groups were formed by random allocation. Study materials and reference sources were displayed and distributed two weeks prior to the initiation of TBL sessions. Each TBL session consisted of pre-test preparation (through didactic lectures and self-study), MCQ-based pre-test, application of concepts, Problem Based Questions (PBQs), reviewing and post-test. This was followed by administration of feedback questionnaire. The data obtained were analysed using SPSS version 21.

Results: When the pre-test and post-test marks were compared, significant improvement in the students' performance was observed ($p<0.05$). According to students' feedback, the learning exercise was innovative, beneficial, helped in better comprehension of difficult topics, increased in-depth knowledge on the topic, fun-filled and relaxing, eventually leading to better learning. Students were able to analyse and give rational and logical responses to complex PBQs. There was an increase in interest towards reading and referring in detail about the topics allotted to them. Library usage and issue of reference books as seen in the logbook increased rapidly. They were more confident in Biochemistry after conducting a series of TBL sessions. While comparing the performance marks after the TBL sessions with that after classroom didactic lecture method, students were of the view that TBL was better than lectures. The difference in scores obtained by two groups (2016 vs. 2015) was significant. The groups who were exposed to TBL had far better scores than those exposed to lectures in the same topic.

Conclusion: The focus these days is on self-directed learning for medical students to become self-regulated, independent learners, which is essential for acquiring competencies and TBL appears to be one such modality.

Keywords: Active learning, team-based learning, problem-based questions, student-centric learning, feedback questionnaire, self-directed learning.

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Introduction

Biochemistry as a subject in the MBBS course is difficult and seems quite intangible to the new medical students. In addition, lack of motivation to learn the subject further adds to the already existing poor attitude towards the subject. To overcome these pitfalls and to generate interest in this basic medical subject, one must come up with innovative ideas of teaching and learning, hence knowledge acquisition through interaction by team-based learning (TBL) or small group discussions is advocated. Of late, much emphasis is being given in active learning approaches for difficult subjects (1, 2). Active learning is a teaching-learning process in which students are actively engaged in various learning activities, such as reading, conceptualizing, discussion, or problem solving that promote analysis, synthesis, and evaluation of lecture contents (1-3). Team learning is an approach to large-group teaching that combines the assets of small-group interactive learning with facilitator-motivated content delivery (4). Team learning is being used effectively in professional disciplines other than medicine. We hypothesise that TBL has the potential to enhance the knowledge and improve the attitude and skills of large number of students and not a handful as does a small group discussion. This would ultimately result in better ways to learn the difficult aspects of Medicine. More so, it is not a well-tested method of teaching in Indian context especially in Biochemistry. Some endeavour in Pharmacology (5), Dentistry (6, 7) and Microbiology (8) has been initiated lately. Keeping the aforementioned concerns, we planned the TBL module to change the classroom experience from acquiring course content and concepts in a lecture-based format (teacher-centric learning) to applying course content and concepts in a team format (student-centric learning) and to make difficult topics easier to all.

Rationale of this study: the increasing student/teacher ratio enormously results in a large group that do not comprehend the knowledge imparted. More so the use of power point presentations for large group lectures fades off much of the interest in the topic. So, how much the students support the conventional teaching method as didactic lectures is itself a big question. Hence, TBL was introduced with the aim to prepare students for active, collaborative learning within a similar cohesive group.

Methods

After obtaining approval from the Scientific Review Committee and the Institute Ethics Committee to carry out the project, the present study was conducted with the First MBBS students in the Department of Biochemistry at our institute. The students were explained about the project in detail and a written informed consent was taken. Ninety nine students participated in the study. The topics selected for TBL were already covered in the form of didactic lectures and were provided two weeks before the pre-test. Study material distribution and the sources for the topics were also provided. The steps of TBL were adapted from the work done by Haidet *et al*, 2002 and the outline is given in Table 1 (9).

We designed the study by a comprehensive preparation of a Module on the Unit "Biological Catalysis". MCQ based pre-test was conducted on Enzymology after delivering didactic lectures on the topics. TBL exercise was planned as a 5 hours' session starting with students completing assigned pre-readings or other advanced preparation. Ten teams of 10 students each were formed, except the one team where only nine students were included. According to the group dynamics, each group had a leader, scribe, a reporter and a timekeeper. Orientation and query answering regarding the exercise was undertaken.

Each team made a presentation on the assigned topic followed by discussion on problem-based questions (PBQs.) It was

Table 1: Steps of Team Based Learning (TBL), adapted from Haidet et al, 2002 and modified according to the situational needs

1st year undergraduate medical students N=99
Didactic lecture on topics from a specific unit
Pre-test on the unit
Team formation and their orientation
Allocation of subtopics and Problem Based Questions (PBQ)
Formation of faculty review panel (constituted by the faculty and senior resident of Biochemistry)
Presentation and PBQ discussion by the students
Post-test on the same topic
Administration of feedback questionnaire

conducted during the class session and involved the individual, the teams, and the entire class. During the problem-solving process, students were given a worksheet that contained a series of questions to be answered in solving a particular problem. The students worked through the entire worksheet, and then using the simultaneous reporting the facilitator revisited each question and had the student teams to discuss, defend their best choice and analyse their solutions to the questions. The module got to the end with a short instructor-led review and closure activity. It was followed by post-test on the same topic.

Thereafter, post-class reflection was obtained through feedback questionnaire. All 25 items in the Questionnaire set were affirmative. Faculty feedback was also taken using a validated questionnaire.

Validation of the questionnaire set was achieved by the following method. A structured questionnaire was developed and administered to 50 students who were quizzed to gain feedback on the overall suitability of the questionnaire. According to them, the questionnaire was suitable in terms of length and language clarity and did not require any correction. Cronbach's coefficient was 0.65, suggesting internal reliability of the questionnaire. Mean Content Validity Ratio (CVR) was 0.84 based on the opinions expressed by fellow faculty members.

Statistical analysis was performed using the Graph Pad Prism 5 (Graph Pad Software, Inc., San Diego, California) and SPSS 21 (SPSS Inc., Chicago, Illinois). Kolmogorov-Smirnov test was conducted to assess for normalcy of MCQ scores. The mean and standard deviation of marks obtained was calculated and pre-test and post-test scores were compared using Mann-Whitney U-test. A $p<0.05$ was taken as statistically significant. We recorded the

responses of the feedback questionnaire on a Likert scale. The students completed the survey during class time in the presence of the tutors. Anonymity was maintained. Feedback responses of the 99 students in both the groups were recorded and satisfaction index for each item was calculated.

Example of a Module Undertaken

Allocation: Ten groups were randomly allocated and each was assigned a module. We had reframed a module to exemplify one such module here. One of the group was assigned the subtopic Enzyme Kinetics. The topics were announced two weeks in advance, study materials and other sources provided.

Presentation: It was made by the group leader using chalk and blackboard. No power point presentation was allowed. Time given for the presentation was 12 ±3 minutes each.

PBQs-related to estimation of V_{max} and K_m of prostaglandin endoperoxide synthase by inspection. Prostaglandins are a class of eicosanoids, the fatty acid derivatives with a variety of extremely potent actions on vertebrate tissues. They are responsible for producing fever and inflammation and its associated pain. Prostaglandins are derived from the 20 carbon fatty acid arachidonic acid in a reaction catalysed by the enzyme prostaglandin synthase. This enzyme, a cyclooxygenase, uses oxygen to convert arachidonic acid to PGG_2, the immediate precursor of many different prostaglandins.

a. The kinetic data given below are for the reaction catalyzed by prostaglandin endoperoxide synthase. Focusing here on the first two columns, determine the V_{max} and K_m of the enzyme.

Arachidonic acid	Rate of formation of PGG_2	Rate of formation of PGG_2 (with 10mg/ml ibuprofen/min)
0.5	23.5	16.67
1.0	32.2	25.25
1.5	36.9	30.49
2.5	41.8	37.04
3.5	44.0	38.91

b. Ibuprofen is an inhibitor of prostaglandin endoperoxide synthase. By inhibiting the synthesis of prostaglandins, ibuprofen reduces inflammation and pain. Using the data provided, determine the type of inhibition that ibuprofen exerts on prostaglandin endoperoxide synthase (10).

Results

Mean marks scored by the students in the pre- and post-tests of specified unit are given in Table 2. The marks scored following TBL were significantly higher than the marks scored prior to this exercise ($p<0.05$).

Mean scores of students in Part Examination in the same Unit (Enzymology) of 2015 Batch (not exposed to TBL sessions) as compared to 2016 Batch (exposed to TBL exercises) was significantly higher ($p<0.05$).

Table 2: Mean marks scored by the students in the pre- and post-tests of specified unit

N=99	Mean marks scored (MM-15)	Mann Whitney U-Test p value
Pre-test	10.37 ± 1.99 (CI: 9.98 - 10.77)	< 0.05
Post-test	11.70 ± 2.01 (CI:11.30 - 12.10)	

The feedback from the students on this teaching-learning method activity on a Likert Scale is shown in Table 3.

The average rating was 3.1, minimum (1.78) for item 11, which specified that the activity helped in overcoming shyness and hesitation in the class. A maximum mean score of 3.57 was obtained for item 7, which specified that self-study, discussion and team work are the activities that helped in realizing in better understanding of the topic. The Satisfaction Index for each item was calculated using the following formula:

$$\frac{[(n_1*1) + (n_2*2) +(n_3*3)+(n_4*4) + (n_5*5)]*20}{(n_1+n_2+n_3+n_4+n_5)}$$

Where, n is the total number of students gaining the score mentioned in the subscript for that particular item. It was highest (90.1) for item 3 and lowest (75.4) for item 4 on a 1–100 satisfaction index scale. All 10 items showed Satisfaction Indexes of 75. Most of the students found sessions interesting, according to them, it helped them in better comprehension, in better orientation during didactic lectures on the topic and in improving their analytical ability. Satisfaction Index as calculated from the above-mentioned formula is given in Table 3.

Discussion

In this study, we carried out a student-centric active teaching-learning exercise, TBL. We observed that the marks scored in the test following TBL sessions were higher than the marks scored after didactic lectures. Students' feedback revealed that they were satisfied by this teaching approach, and their knowledge, comprehension and interest on the topic increased after the activity. They found the group discussion on difficult aspects very useful and interesting. They appreciated the MCQ-based assessment and viewed coming up for presentation as an opportunity to open and demonstrate their knowledge and communication skills.

TBL exercise is an active learning plan that teaches students to collaborate and work as a team to achieve a common learning objective, thereby increasing individual's strength (11). Prior to conducting TBL, students acquire the required information and concepts by means of conventional didactic lectures, and then they work as team to solve various PBQs. Inspite of working as a team in TBL, each team member is responsible for his own learning outside the class.

Numerous studies have shown the benefits of this mode of active learning as a powerful tool to ingrain in-depth knowledge and increase comprehension of the topic (12, 13). Vasan in his study on TBL in Anatomy and Embryology concluded such sessions improve student commitment towards course content. In the study, according to the students' feedback, TBL along with didactic lectures enhanced their understanding of course content and belief that it will help in better performance in their examinations (14). Similar to our findings, Wolff *et al*, found that TBL sessions lead to increased learning by delivering essential knowledge, contextualizing content, and explaining difficult concepts (15). Mcinerney stated that this way of teaching has a powerful impact on student learning but a significant contribution from facilitators is required for implementing and conducting it properly (16). This mode of teaching-learning is useful not just for the basic sciences but also for acquisition of clinical skills and workshop sessions (17).

Like the responses to feedback, others have also documented that in TBL, students feel actively involved, and it helps them in their learning and in developing team work and communication skills as well (18).

One of the noticeable advantage of TBL is overcoming shyness and developing communication skills by the students not only when one acts as a presenter but also when one is among the audience and articulates the question and participates in the discussion. During the sessions, it was perceived that the students, who

Table 3: Feedback responses of the 99 students and satisfaction index of each item

S .No.	Items	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree	Satisfaction Index
1	Team Based Learning was an innovative way of T/L Method	0	2	24	55	5	80.3
2	The Team Based Learning Exercise was useful /beneficial to me	0	2	8	60	15	82.9
3	I can now rationalize better when asked a question	0	2	23	55	6	80.6
4	The Difficult concepts /graphs in this unit have become vivid and clearer by the self-directed learning	0	3	28	50	4	79.3
5	The exercise helped me get some novel ideas for research project	0	12	44	26	2	69.0
6	I would advise the junior batches to go for TBL	1	3	9	47	25	84.2
7	I realised that self-study, discussion and teamwork help in better understanding of the topic	0	0	9	45	30	88.0
8	The study material given was sufficient and fool proof for the detailed study for the topic	2	5	28	38	11	78.2
9	I saw the whole process as valuable and not a waste of time and resources	0	4	4	29	10	80.9
10	I have you learnt and acknowledged the importance of Peer Learning	0	0	8	60	18	84.6
11	The activity helped in overcoming shyness and hesitation in the class	2	4	14	24	6	75.6
12	I have developed better rapport with my teacher	0	6	20	50	14	80.6
13	I have attain the depth of knowledge of the topic covered and can solve any difficulty level questions from this topic	0	5	27	44	15	81.6
14	I received enough emotional support by the faculty before and after (positive criticism) my presentation in front of the class	0	1	24	42	17	85.0
15	I want this T/L exercise to be conducted in other departments also	0	1	22	43	19	85.4

usually do not interact with their teachers or peers, were motivated to participate in the activity with full zest. In addition, as teams work together and compete with other teams, sense of responsibility and loyalty to the team develops among the team members.

In the Indian context, the academic culture in most Medical Schools is to encourage the established conventional approach as pedagogy. But the paradigm is now shifting as fresh recruited teachers have joined in and have incorporated TBL and small group learning as part of the teaching learning exercise (19). Working effectively as a team in TBL method where every member shoulders equal responsibility has been well recognised by the Western medical educators as competence-based (20, 21).

The study shows that TBL requires much hard work from both, the teachers as well as the students, hence it is difficult to incorporate this method for all the topics. We suggest that it would be a good practice to conduct such sessions at the final stage of each professionals, focussing on the more difficult topics. The evaluation through feedback questionnaire helped us in knowing the students' perception with regards to TBL. It also aided us in identifying potential problems related to pre-class assignments, team dynamics, student-faculty relations, and overall learning. This would be helpful in improving the subsequent TBL sessions.

Study Limitations

There were time constraints and not all department faculty and residents could attend all the sessions. Not all doubts of the participants could be clarified in the assigned time duration. The whole TBL was tailor made according to our needs and resources; exhaustive study if desired can only be done when TBL is taken into account with all the steps planned meticulously and incorporation of flawless MCQs.

Conclusion

TBL is a learner-centred instructional strategy for both the instructor and the students, providing students with regular opportunities to learn how to collaborate with the peers. It is the need of the hour for learning modern medicine as it emphasises on accountability, decision making and collaboration with peers; all of which are essential for adult learning and developing competencies for healthcare professionals. Our study shows that TBL method may also be applicable in contexts beyond Western ones, that it is also suitable in cultures that mostly employ 'traditional' approach to teaching and learning.

We conclude that TBL can be used as a complement to didactic lectures for difficult topics in Indian medical schools and strategically be used for promoting the development of cognitive, psychomotor as well as affective domains. MCI vision 2015 document states that there should be Competence Based Education in Medicine and TBL is one such method.

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Conflict of Interest

None.

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Case Report

A Curious Case of Flower Phobia: Anthophobia

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ABSTRACT

Fears, anxieties and specific phobias are classified as internalizing behavior problems. The development of specific phobias may result from the pairing of a specific object or situation with the emotion of fear. Flowers are usually perceived as pleasant stimulus, producing a relaxing effect on our mind and body, but here we present a rare case, wherein flowers are perceived as a malevolent stimulus and producing phobic anxiety in an eleven-year old boy, leading to avoidance behaviors and much interference in normal functioning. He was diagnosed to have Specific Phobia of natural environment type with Somnambulism and treated with SSRI (escitalopram) and Behavior Therapy (systematic desensitization). Over a period of eight months his symptoms remitted completely and he maintained the remission for now one year with no further intervention.

Keywords: Childhood fear, phobias, anxiety, behavior therapy, flowers fear.

Introduction

Experiencing fear and anxiety is normal and healthy in the course of child development and emotional growth. These emotions can even be looked upon as adaptive and as impressive markers of increasingly complex cognition and abstract thought processes (1, 2). However, when these fears linger and become more intense, a different type of developmental event may be signaled - the development of a specific phobia.

A specific phobia diagnosis as per International Classification of Diseases, 10th Edition (ICD-10) should be considered when there is marked fear of a specific object or situation not included in agoraphobia or social phobia or shows marked avoidance of such objects or situations. Experiences symptoms of anxiety in the feared situation at some time since the onset of the disorder with significant emotional distress due to the symptoms or the avoidance, and recognizing these as excessive or unreasonable. The symptoms are restricted to the feared situation or when thinking about it (3).

Further childhood phobias may result from terrifying or frightening experiences; they may also be due to observing or through reading about it or hearing about fears and phobias in others.

Some childhood phobias apparently have no obvious environmental cause, direct or indirect, and reportedly 'have always been present' in the child.

In general, when a specific event is paired with an emotional experience the person is susceptible to a permanent emotional association between feared object and fear or anxiety. Avoidance behaviors in children often take the form of tantrums, crying, and shying away. Often the child is brought in for treatment not because of the fear itself but due to severity

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of the disruption to the family's daily routine as a result of avoidance and distress-related behaviors (4).

Flowers are usually perceived as pleasant stimulus, but extreme irrational fear of flower is called Anthophobia; a Greek connotation for flower. It is in this light, we present a case of flower phobia, little is known about it in scientific literature, so far only one case has been reported in Indian literature. In this case they treated the child alone with behavior therapy (5).

Case Report

Master X, an eleven-year old boy, class seventh student, was a scholar at school. He was the only child of his parents, living in a joint family and had cordial relation with all. He was born at full term with normal delivery and no developmental delays. There was no history of psychiatric illness reported in the family.

He took treatment for bronchitis at one-year of age. By five years of age he was noted to be getting out of bed during deep sleep, walking around unaroused with a blank look on face, unaffected by environmental stimuli, if guided back to bed would sleep, wake up next day with no memory of it. He had no history of past psychiatry treatment.

Temperamentally he was shy, with a slow to warm up temperament, quick learner, an avid book reader, loved scientific activities, played cricket and badminton.

On his first visit to psychiatry OPD, he appeared guarded, made less eye contact. Gradually warmed up and complained of having sudden anxiety at the sight or thought of flowers, interfering in his daily functioning. Mother described the child would get flushed, scream, cry, turn sweaty, shiver, frantically run about, turn angry at times, become numb and curl-up in himself, at the sight of flowers or in their vicinity.

Anamnesis revealed the first time he was ever noted to show his fear was on his third birthday, where he screamed and cried when he was given flowers. Later by eight years of age, the fear became prominent even in school and other social situations like flower arrangement activity at school and during picnics at park. His family noticed him avoiding situations and places that had flowers, both real and unreal, to pictures in book and television, to even not allowing flowers at home. Parents or patient couldn't give history of any specific event or stressor for onset of phobia. There was no history of other anxiety disorder or mood disorder.

Recently as he experienced severe anxiety and displayed sudden anger at a social event where he became difficult to manage, his parents got worried and brought him for his first consultation.

A dual diagnosis of specific phobia (F40.2) with non-organic sleep disorder somnambulism (F51.3) was made according to ICD-10 (3).

He was investigated to rule out medical comorbidities. Magnetic resonance imaging of brain revealed an arachnoid cyst measuring 15x20x45cm with well-defined margins in the midbrain, posterior fossa in retrocerebellar location and communicating with the fourth ventricle. No seizure activity or slowing was noted on electroencephalography.

An initial psychological assessment was also done that revealed an IQ of 112. Children's Apperception Test (CAT) showed difficulties in interpersonal relationships with parental figures conflicts between need for achievement and disapproving environment leading to anxiety reactions.

Background of the Case

Dynamic exploration revealed that the child was ambivalently attached to his mother, he showed less attachment towards his father as he was insensitive towards his emotional needs.

At home there were interpersonal and family conflicts. The family showed too much attention and concern towards his fear.

During explorative sessions, mother revealed that she had described the child one of her own fears to flower as a child, where she got bit by a bee while trying to touch it. The fears were reinforced later by watching a man in a serial who displayed a terrifying behavior at the sight of flowers. Our patient described he feared the nectar and the pollens of a flower as it attracts the bees and they bite that causes pain. He also feared the petals, leaves and big flowers specifically like marigold and tuberoses. The child so far has never had a personal bee biting experience but he appears to have role modeled his fears from his mother and the television character, leading to avoidance behaviors.

Treatment

Treatment was started with escitalopram and gradually increased to 10 mg along with clonazepam 0.25 mg. Psychological management was started with free association and relaxation training exercise.

Relaxation was followed by systematic desensitization. We started in-vitro exposure with imagery and then in-vivo exposure to artificial and real flowers, simultaneously cognitive restructuring was also started. Initial few sessions were interactive using creative therapies like drawing and writings following which his interactions with therapist improved. By the sixth session the child appeared comfortable to touch and even hold artificial flowers in hand, first small then big flowers; slowly his proximity with real flowers was reinforced and by the ninth session he could come to holding them in his hands. A total of 12 sessions were conducted.

His mother was enrolled into therapy as a co-therapist that helped him to cope better at home. Once he mastered control over fears and anxieties he was taken to the garden where he displayed fear to hibiscus and sunflowers but could endure it with reduced anxieties, showed no terrifying response.

During Cognitive Behavior Therapy (CBT) sessions he was explained the mechanism of learning the fear and how it was being maintained. Therapy was focused on giving him alternative explanations to challenge his fears, avoidance behaviors and attempts were made to substitute it with more adaptive beliefs and responses. He was given homework(s) like reading about flowers, noting facts, watering flowers, making small bouquets at home, etc.

Treatment Outcome

By the end of eight months the child showed marked improvement in his overall symptoms, that is when other aspects of his personality were brought into therapy for which social skill training were regularly conducted. Currently patient and his family have reported improvement in anxieties and also in his sleep behavior. He was gradually tapered down to 5 mg dose of escitalopram and CBT maintenance sessions were continued.

Discussion

Specific phobias are the most prevalent anxiety disorders according to nearly all epidemiological studies of the general population (6,7). There is research suggesting that the typical age of onset for specific phobia is between ten and thirteen years of age (8).

Environmental factors like trauma, vicarious learning, genetic factors, temperamental predispositions, parental psychopathology, parenting practices, contribute to development and maintenance of childhood phobias, thus emphasizing need to address these multiple dimensions during treatment (6, 9).

Excessive fears leading to anxiety disorders affect the neuronal circuitry and can

induce lasting structural change in synaptic connectivity and plasticity. Successful treatments with pharmacological agents like selective serotonin reuptake inhibitors are thought to be safe in children with evidence of improving neuronal plasticity in recovery (10), which is why we preferred using escitalopram. Such benefits are known to be augmented when coupled with psychotherapy.

Most commonly exposure therapy is used, however studies show techniques like counterconditioning, extinction, habituation, change in catastrophic cognitions, development of coping skills, increased self-efficacy, emotional processing, and changes in perceptions of dangerousness are even helpful (11, 12).

Children usually enjoy flowers but here we attempted in highlighting the phobic avoidance that the child developed which is rarely seen or identified. We aimed to provide the child a holistic treatment involving the family and correcting his environment. It is seen that the families either do not know how to handle their child's fears, think it will go away after a "phase" or "stage", or have just grown to accept the fear and have altered their lives to live with it. In this case an intelligent and cooperative child and parent, regularity of CBT sessions, understanding of diagnosis, psychoeducation were the key for success of therapy and recovery.

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